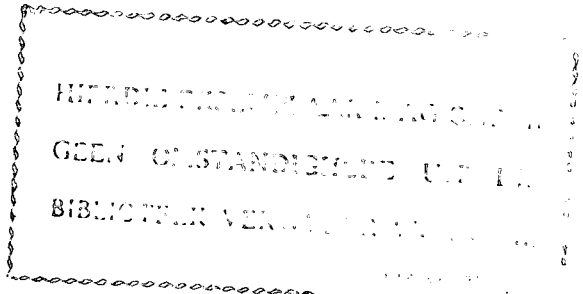

AN INVESTIGATION INTO THE INFLUENCE OF CIMETIDINE ON THE BIOAVAILABILITY AND PHARMACOKINETICS OF NIFEDIPINE AND THE IMPORTANCE OF METABOLIC POLYMORPHISM ON THIS INTERACTION

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Dedicated to my parents

So little done, so much to do.

- Cecil John Rhodes

C O N T E N T S

C H A P T E R 1

INTRODUCTION, OBJECTIVES AND LITERATURE SURVEY

1.1 INTRODUCTION

Nifedipine is a calcium channel blocker and has been shown to be an effective and relatively well-tolerated treatment for stable, variant and unstable angina, mild to severe hypertension and Raynaud's phenomenon (Sorkin et al., 1985).

Disposition of nifedipine after oral administration is dependent on rate and extent of absorption, first-pass hepatic metabolism (Waller et al., 1984) and oxidative phenotype of the subject (Kleinbloesem et al., 1984d).

Cimetidine is a third generation H_2-receptor antagonist. Its ability to block histamine-induced gastric acid secretion is attributed to an antagonistic effect on parietal cell H_2-receptors. It should be noted that cimetidine contains an imidazole nucleus long regarded as essential for H_2-receptor blockade (Gerber et al., 1985).

Cimetidine has also been shown to interact with the microsomal cytochrome P-450 linked monooxygenase system, thus inhibiting drug metabolism (Taylor et al., 1978; Pelkonen and Puurunen, 1980; Puurunen et al., 1980; Henry et al., 1980; Borm et al., 1981; Röllinghof and Paumgartner, 1982). It does not impair glucuronidation mediated by glucuronyl transferase (Gerber et al., 1985; Röllinghof and Paumgartner, 1982). It may thus be possible to separate the inhibitory effect of cimetidine on specific enzyme systems in the liver from its gastric H_2-receptor antagonising effect.

Because of nifedipine's extensive metabolism in the liver by oxidation and hydroxylation (Kleinbloesem et al., 1984) and cimetidine's inhibition of the oxidative pathway (Hansten and Horn, 1987; Somogyi and Gugler, 1982), it could be expected that cimetidine would increase plasma concentrations of nifedipine when given concurrently, as supported by Smith et al. (1987). Their results could not support any influence of gastric acidity on nifedipine bioavailability (Raemsch and Sommer, 1983).

1.2 OBJECTIVES

The objectives of this study were to investigate the influence of cimetidine on the bioavailability and pharmacokinetics of nifedipine as well as the importance of metabolic polymorphism on such an interaction, should it exist.

1.3 LITERATURE SURVEY

1.3.1 Histamine$_2$ antagonists

Histamine-blocking activity was first detected by Bovet and Staub in 1937 in one of a series of amines with a phenolic ether function synthesized by Fourneau. This drug, 2-iso-propyl-5-methyl-phenoxyethyldiethylamine, was too toxic for clinical use. Pyrilamine maleate, one of the derivatives proven to be acceptable, was described by Bovet and his colleagues in 1944 and is still one of the most specific and effective histamine blockers of this category.

By the early 1950s, diphenhydramine and many other compounds with histamine-blocking activity had been described, but none of them blocked all of the many effects of histamine. They effectively blocked the responses to histamine which were later to be ascribed to the H_1-receptors (Ash and Schild, 1966), but they all failed to inhibit gastric acid secretion which involves H_2-receptors (Finkelstein and Isselbacher, 1978). It was thus of considerable interest when Black and colleagues described the H_2 blocking agents in 1972.

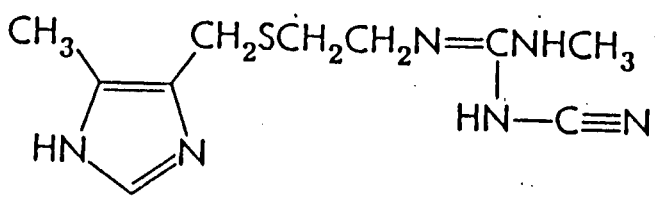
All of the available antagonists are reversible, competitive inhibitors of the actions of histamine. Only the H_2 blocking agents will be reviewed further with special reference to cimetidine.

The discovery and introduction of H_2-receptor blocking drugs were most welcome because of clinical evidence that hypersecretion of gastric acid and peptic ulceration account for as many as 4 million hospital days per year in the United States of America alone. This group of drugs has provided an effective therapeutic approach to the treatment of these conditions (Douglas in Goodman and Gilman, 1985).

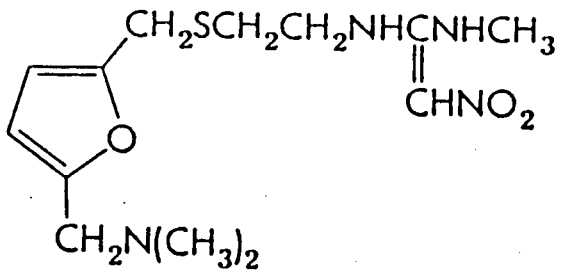
1.3.1.1 Chemistry

The synthesis of H_2 antagonists was achieved by stepwise modifications of the histamine molecule. Some 200 compounds later, the first highly effective drug with potent H_2-blocking activity, burimamide, resulted (Black et al., 1972). Because of unacceptable levels of toxicity and side effects of burimamide, cimetidine (N-cyano-N'-methyl-N''-(2-[(5-methylimidazol-4-yl)methylthio]ethyl)-guani-dine) was synthesized and became the first H_2 blocker to be introduced for general clinical use. Cimetidine and many other drugs of this group retained the imidazole ring of histamine but had much bulkier side chains. However, this ring structure is not essential: ranitidine possesses a substituted furan ring and is also an effective H_2 blocking agent. Other ring structures appear in other highly effective agents (see Ganellin, in Ganellin and Parsons, 1982). The precise structural requirements for H_2-receptor recognition are uncertain. The H_1-receptor antagonism is determined by an ammonium group and these agents do not have an imidazole or furan ring (Freston, 1982a).

Figure 1.1



Cimetidine



Ranitidine

1.3.1.2 Pharmacological properties

The H_2-blocking agents are highly selective in their action and are virtually without effect on H_1-receptors and receptors for other autacoids or drugs. Although H_2-receptors are distributed widely in the human body, H_2 blockers have very little influence on physiological functions other than gastric secretion, which implies that the extragastric H_2-receptors are of minor physiological importance.

The ability of H_2 blockers to suppress responses to histamine, acetylcholine (ACh) and gastrin makes them potent inhibitors of all phases of gastric acid secretion. They reduce both the volume of gastric juice secreted and its hydrogen ion concentration. They inhibit basal (fasting) secretion as well as nocturnal secretion and also that stimulated by food, sham feeding, fundic distention, insulin or caffeine and all other known gastric acid stimuli (Henn et al., 1975; Pounder et al., 1976a; Cano et al., 1976; Pounder et al., 1976b; Richardson et al., 1976). Because of a reduction in volume of gastric juice, output of pepsin is also reduced as the two generally fall in parallel (Binder and Donaldson, 1978). Although there is also a reduction in the secretion of intrinsic factor, absorption of vitamin B_{12} is adequate even during long-term therapy with H_2 blockers (Binder and Donaldson, 1978; Douglas in Goodman and Gilman, 1985). These blockers have no consistent effect on the rate of gastric emptying, lower oesophageal sphincter pressure or pancreatic secretion (Freston, 1982a).

The mechanism by which gastric acid secretion is inhibited, is unknown. One of the more acceptable theories is based on the observation that isolated parietal cells have specific receptors for the classical three secretagogues, namely histamine, gastrin and ACh (Finkelstein and Isselbacher, 1978; Freston, 1982a; Douglas in Goodman and Gilman, 1985). Each secretagogue may stimulate acid secretion independently. A background concentration of histamine potentiates the actions of the other two secretagogues. According to this theory of "potentiating interactions", H_2 antagonists inhibit acid secretion by blocking the effects of histamine on its receptor and eliminating the potentiating effect of histamine on gastrin and ACh.

1.3.1.2.1 Absorption, fate and excretion

Cimetidine is rapidly and almost completely absorbed by the oral route (Burland et al., 1975; Finkelstein and Isselbacher, 1978). Absorption is little impaired by food or antacids. Plasma peak concentrations are reached in about 1 to 2 hours (Finkelstein and Isselbacher, 1978; Freston, 1982a) and hepatic first-pass metabolism results in a bioavailability of about 60%. According to Bodemar and colleagues (1981), the bioavailability of cimetidine measured as the ratio between the areas under the plasma concentration vs time curves (AUC) after oral and intravenous administration was 76%. They also found that the relative bioavailability of cimetidine does not appear to be dose-dependent.

The elimination half-life is about 2 to 3 hours (Burland et al., 1975; Freston, 1982a) increasing with age (Somogyi et al., 1980). The volume of distribution at steady-state was about 80% of body weight decreasing with age (Somogyi et al., 1980). Cimetidine is primarily eliminated by the kidneys and 70% or more may appear unchanged in the urine (Burland et al., 1975; Finkelstein and Isselbacher, 1978; Taylor et al., 1978), decreasing with age (Somogyi et al., 1980); much of the rest is excreted as oxidation products with 10 to 15% being a sulphoxide metabolite (Taylor et al., 1978; Mitchell et al., 1981). Patients with renal failure may therefore require decreased frequency of dosing (Ma et al., 1978; Larsson et al., 1981). About 15% is metabolized in the liver (Freston 1982a; Pelkonen and Puurunen, 1980). Approximately 10% of cimetidine is recovered in stools (Griffiths et al., 1977).

1.3.1.3 Adverse reactions and side effects

Millions of people having been treated with cimetidine explains the long list of adverse reactions. However, it is evident that the incidence of these reactions are low, probably under 5%, and are generally minor (Burland et al., 1975; Freston, 1982b). (See Table 1.1) The side effects include headache, dizziness, malaise, skin rashes, pruritis, galactorrhea, gynecomastia, loss of libido, impotence and reduction in sperm count (Delle Fave et al., 1977; Bateson et al., 1977). Gynecomastia and afore-mentioned sexual dysfunctions are encountered because of binding of cimetidine to androgen receptors.(Douglas in Goodman and Gilman, 1985). Cimetidine also stimulates secretion of prolactin and elevated levels of this hormone have been seen during intravenous administration of the drug as well as during chronic oral treatment. The mechanism by which cimetidine stimulates prolactin release is not known (Delle Fave et al., 1977; Carlson and Ippoliti, 1977).

Cimetidine also binds to the haeme moiety of cytochrome P-450 and thereby diminishes the activity of the hepatic microsomal mixed-function oxidases (Wilkinson et al., 1974, Rendic et al., 1979; Pelkonen and Puurunen, 1980; Puurunen et al., 1980). Various other drugs may thus accumulate during treatment with cimetidine. Cimetidine also tends to reduce hepatic blood flow which can slow the clearance of drugs and contribute even more to the possible toxicity of drugs taken concomitantly with cimetidine (Douglas in Goodman and Gilman, 1985).

Cimetidine can also lead to various central nervous system disturbances particularly in elderly patients and in those with hepatic or renal disease (Schentag et al., 1981). These include slurred speech, somnolence, lethargy, restlessness, confusion, disorientation, agitation, halluci-nations and seizures (McGuigan, 1981). Somogyi and co-workers (1980) have shown that older patients clear cimetidine more slowly than younger patients, suggesting that the older patients may have sustained higher blood concentrations of cimetidine on a standard dosage regimen. This may have contributed to the appearance of above-mentioned disturbances in elderly patients.

In rare cases cimetidine has been associated with thrombocytopaenia, granulocytopaenia and hepatotoxicity (McGuigan, 1981). According to McGuigan (1981) there is no evidence of renal insufficiency as a consequence of cimetidine treatment. A rise in serum creatinine has however been reported (Haggie et al., 1976; Burland et al., 1977; Kruss and Littman, 1978). Cimetidine has been noted to enhance some cell-mediated immune responses (McGuigan, 1981). When given by rapid intravenous infusion, profound bradycardia and other cardiotoxic effects have been noted occasionally (Douglas in Goodman and Gilman, 1985).

The resulting hypochlorhydric stomach when on cimetidine treatment may lead to the formation of bezoars and the survival of bacteria. The latter may explain rare cases of candidal peritonitis (Douglas in Goodman and Gilman, 1985).

Table 1.1 Most frequently reported adverse effects in 9907* and 2182# cimetidine-treated patients

Adverse Reaction	Patients	
	%*	%#
Diarrhoea	1.0	1.8
Nausea and vomiting	0.8	
Rash,hives,pruritis	0.4	1.2
Dizziness	0.3	1.3
Headache	0.2	
Epigastric pain	0.2	
Gynaecomastia	0.2	
Constipation	0.2	
Flatulence	0.2	
Drowsiness	0.2	1.3
Dry mouth	0.1	
Muscular pain	0.1	
Tiredness		1.7
Miscellaneous	1.8	

* Based on a survey of Gifford et al. (1980) with calculations by Freston (1982b)
# Burland, 1978

1.3.1.4 Therapeutic uses

More or less a 50% inhibition of acid secretion is achieved with cimetidine plasma concentrations of 800ng/ml. Nocturnal acid secretion is inhibited by about 70% (Douglas in Goodman and Gilman, 1985). In a study by Finkelstein and Isselbacher (1978), it was found that a 300mg dose of cimetidine reduces both nocturnal and basal acid secretion by 90 to 95%. According to Freston (1982a), an oral dose of 300mg raises basal gastric pH to at least 5 for more than 2 hours. More than 90% inhibition of acid secretion occurs for 4 hours after administration. Nocturnal basal gastric acid pH was raised to 5 or more for 3 to 4 hours and acid secretion was inhibited by a mean of about 90% for 7 hours by the same dose. The same dose before a standard meal raises the mean gastric pH to 3 to 4 for three hours and to about 6 after 4 hours. Cimetidine is therefore used in the following clinical hypersecretory states: peptic ulceration, Zollinger-Ellison syndrome, reflux oesophagitis, stress ulcers, preanaesthetic use in emergency operations (prevention of the acid aspiration syndrome/Mendelson's syndrome) (Freston, 1982a), short-bowel syndrome and hypersecretory states associated with systemic mastocytosis or basophilic leukaemia with hyperhistaminaemia (McGuigan, 1981).

1.3.1.5 Drug interactions

Several interactions have been reported of which only the clinically significant will be mentioned. Three principal mechanisms by which cimetidine administration may affect the pharmacokinetics and therapeutic action of concurrently administered drugs, are suggested: (1) effect on drugs of which absorption is related to gastric pH; (2) effect on oxidative metabolism of drugs by hepatic microsomal enzyme systems, especially the cytochrome P-450 system; and (3) effect on hepatic blood flow (Gerber *et al.*, 1985). Drugs affecting the pharmacokinetics of cimetidine will also be considered.

1.3.1.5.1 Effects of cimetidine on absorption of other drugs

Several drugs are unstable in the acid milieu of the stomach (e.g. benzylpenicillin and erythromycin) and are formulated so as to overcome acid degradation (e.g. enteric-coated tablets, ester salts) (Somogyi and Gugler, 1982). Drugs said to be gastric irritants are formulated as enteric-coated tablets to negate this side effect (e.g. theophylline, valproic acid, prednisolone). Because disintegration of some tablets and the dissolution of many drugs are dependent on the pH of gastric fluid, alterations in gastric pH may reduce the amount of drug absorbed (Somogyi and Gugler, 1982).

Sodium benzylpenicillin (600mg) was investigated in 5 healthy volunteers and it was concluded that increased absorption of acid-labile substances can occur in some patients taking cimetidine (Fairfax et al., 1978).

Reports on tetracycline are conflicting. In some the absorption of tetracycline was reduced (Fisher et al., 1980) while in others no reduction in absorption could be proven (Garty and Hurwitz, 1980). These discrepancies may be due to failure to standardise food intake, which has a marked effect on the absorption of tetracycline (Welling et al., 1977). Tetracycline is also metabolised in the liver and because of the effect of cimetidine on liver enzymes, this may have masked interaction at the level of drug absorption. It can only be concluded that cimetidine has no clinically significant effect on tetracycline absorption (Somogyi and Gugler, 1982).

Khoury et al. (1979) reported that the absorption of aspirin as measured by serum salicylate, is impaired in the presence of cimetidine when intragastric pH rises above 3,5. No firm conclusions can be drawn from this study due to a short sampling period, as well as the possibility of an interaction involving salicylate metabolism (Somogyi and Gugler, 1982).

Ibuprofen is a weak organic acid and its solubility thus increases with increasing intragastric pH. Pretreatment with cimetidine thus increases both the rate and extent of absorption of ibuprofen (Parrott and Christensen, 1984).

No significant alterations in the disposition of ampicillin and co-trimoxazole by cimetidine could be proven (Rogers et al., 1980).

In a study with prednisolone, Morrison et al. (1980) found that cimetidine had no overall statistically significant effect on prednisolone absorption. A large interindividual variation may however have masked any possible interaction. Three subjects who received placebo treatment first, developed lower plasma prednisolone concentrations than those who received cimetidine first. This was attributed to 'poor absorbers', but the results could also be interpreted as being due to inhibition of prednisolone metabolism in the group receiving cimetidine first (Somogyi and Gugler, 1982).

Cimetidine attenuates ketoconazole's absorption. This apparently clinically significant interaction probably occurs because of the latter's poor solubility in water. This can be avoided when ketoconazole is given in an acid solution (Van der Meer et al., 1980).

The studies on drug interactions with cimetidine related to drug absorption appear to be contradictory and inadequately designed. Except for ketoconazole, where the interaction seems to be of importance, cimetidine does not alter the extent or rate of absorption of other drugs to a predictable or clinically significant degree (Somogyi and Gugler, 1982).

1.3.1.5.2 Effects of cimetidine on elimination of other drugs

Because of cimetidine's inhibiting effect on microsomal drug metabolism (Puurunen and Pelkonen, 1979; Puurunen et al., 1980; Henry et al., 1980; Borm et al., 1981, Röllinghoff and Paumgartner, 1982; Ruffalo and Thompson, 1982), it reduces the systemic clearance of several drugs including warfarin (Serlin et al., 1979), diazepam (Klotz and Reimann, 1980a), desmethyldiazepam (Klotz and Reimann, 1980b), chlordiazepoxide (Desmond et al., 1980), phenytoin (Bartle et al., 1982,1983; Frigo et al., 1983), theophylline (Wood et al., 1980; Reitberg et al., 1981; Roberts et al., 1981; Weinberg et al., 1981), carbamazepine (Telerman-Toppet et al., 1981), imipramine (Miller and Macklin, 1983; Abernethy et al., 1984) and caffeine (Broughton and Rogers, 1981). Lorazepam and oxazepam are not affected because of their limited hepatic biotransformation (Patwardhan et al., 1980; Klotz and Reimann, 1980b). Klotz and Reimann (1980b) concluded that benzodiazepines which are metabolized by phase I reactions (hydroxylation) are impaired by cimetidine but those which are eliminated by conjugation to form the glucuronide (phase II reaction) are not impaired. The inhibition of hepatic drug metabolism by cimetidine seems to be unrelated to its action on H_2-receptors, but the presence of an imidazole ring may well play a vital role as ranitidine and tiotidine, which do not contain these ring structures, do not cause the same effect (Henry et al., 1980; Henry and Langman, 1981).

Daneshmend and co-workers (1984) found that the cimetidine associated hepatic enzyme inhibition appears to persist with prolonged treatment (200mg three times daily and 400mg at night for four weeks). Patients on chronic cimetidine therapy, thus appear to remain vulnerable to certain drug interactions.

Jackson (1981) and Mitchell et al. (1981) have demonstrated that cimetidine protects against acetaminophen (paracetamol) hepatotoxicity in rats and man by preventing the formation of the toxic metabolite. The action of cimetidine appears to delay the development of toxicity and it is therefore suggested that cimetidine may be a useful adjunct to N-acetylcysteine for the treatment of massive acetaminophen overdoses. This was supported by Kadri and colleagues (1988) in a case report.

Bodemar and colleagues (1981) did a study on the pharmacokinetics of cimetidine after single doses and during continuous treatment. They concluded that cimetidine does not appear to induce or inhibit its own metabolism during treatment.

1.3.1.5.3 Effects of cimetidine on hepatic blood flow

Charbon and co-workers (1980) concluded after a study on anaesthetised dogs, that H_2-receptors were present in the left gastric and common hepatic vascular beds. Cimetidine could therefore reduce to a small extent, total liver blood flow by its reduction of flow in the hepatic artery (Somogyi and Gugler, 1982).

Reduction in hepatic blood flow by cimetidine was first reported by Feely et al. (1981) in relation to propranolol clearance. They found that cimetidine acutely reduced liver blood flow during fasting by almost 25%, as measured by indocyanine green clearance. Chronic cimetidine therapy (300mg four times daily for seven days) reduced the flow by 33%, as measured over eight hours by calculating the relative disposition of oral and intravenous propranolol. They thus recognized the major therapeutic implications for numerous other drugs of which the systemic clearance is largely dependent on hepatic blood flow, given concurrently with cimetidine. These include morphine, lidocaine, pentazocine, meperidine and certain beta-adrenergic blockers (Feely et al., 1982; Lam and Clement, 1984; Knapp et al., 1983; Wing et al., 1984; Bauer et al., 1984).

It was, however, found by Daneshmend and colleagues (1984), that chronic cimetidine treatment (200mg three times daily and 400mg at night for four weeks) does not reduce apparent liver blood flow. As they did not examine the effects of a single dose or of a short course of cimetidine on apparent liver blood flow, they concluded that it was possible that there may have been some reduction in apparent liver blood flow at the start of the treatment which had disappeared after four weeks of treatment.

Propranolol clearance is also reduced by cimetidine by means of inhibition of hepatic enzymes and not only by reduced hepatic blood flow (Charbon et al., 1980; Feely et al., 1981; Duchin et al., 1984). Labetalol, chlormethiazole and metoprolol were found to interact similarly with cimetidine (Daneshmend and Roberts, 1981; Kirch et al., 1982a,b).

According to the venous equilibration model of hepatic elimination (Rowland et al., 1973; Wilkinson and Shand, 1975), the rate of blood flow into the liver is the chief determinant of clearance of intravenously administered drugs with a high hepatic extraction ratio, whereas the principal determinant of oral clearance for drugs of this class is the activity of the enzymes responsible for drug metabolism in the liver. Cimetidine is capable of altering the clearance of high-extraction-ratio drugs (ratio > 0,7) whether given orally or intravenously. (Hepatic extraction ratio is the fraction of a drug removed from the blood during a single transit through the liver.)

With regard to the time course of the interaction, it was shown that one day's treatment with cimetidine produced maximal inhibition of chlordiazepoxide clearance which did not decrease further with 30 days' cimetidine treatment. Two days after discontinuing cimetidine, the clearance of chlordiazepoxide had returned to the control value. A rapid onset and offset of inhibition of drug metabolism was thus indicated as well as the fact that the interacting agent was cimetidine itself rather than a metabolite (Patwardhan et al., 1981).

In studies done by Klotz and Reimann (1980a,b), considerable inhibition of diazepam and desmethyldiazepam metabolism was found lasting more than 90 hours after the last dose of cimeti-dine. Considering that cimetidine has an elimina-tion half-life of about 2 hours, most of the drug should be eliminated after approximately 10 hours, implying that the time course of inhibitory effect may differ according to the interaction between cimetidine and/or its metabolite and the different forms of cytochrome P-450.

It has also been reported that the degree of inhibition of drug metabolism by cimetidine is more pronounced in patients who already have impaired liver function (Röllinghoff et al., 1981).

1.3.1.5.4 Drugs affecting the pharmacokinetics of cimetidine

Most studies concentrated on the effect of cimetidine on the pharmacokinetics of other drugs, but the reverse can also be important for cimetidine therapy.

In a study of Fisher et al. (1980) on cimetidine and tetracycline interaction, it could not be concluded that tetracycline alters the disposition of cimetidine. A study of Morrison et al. (1980) suggests an interaction of prednisolone on the disposition of cimetidine.

Gugler et al. (1981) found that an antacid (aluminium plus magnesium hydroxide) significantly reduced absorption of cimetidine. In the same study, it was found that metoclopramide had a tendency to shorten the time to peak cimetidine plasma concentration. This was confirmed by a study of Kanto et al. (1981). Kanto et al. (1981) also showed that propantheline delayed the time to peak cimetidine plasma concentration and reduced the AUC by an average of 23%. Although probably not significant, the interactions of metoclopramide and propantheline with cimetidine confirm the notion that the rate and extent of cimetidine absorption is dependent on gastric motility (Somogyi and Gugler, 1982). In a study of Somogyi et al. (1981), it was proven that some induction of cimetidine hepatic metabolism by phenobarbitone took place, but impaired absorption and enhancement of gastrointestinal metabolism by phenobarbitone could not be totally ruled out.

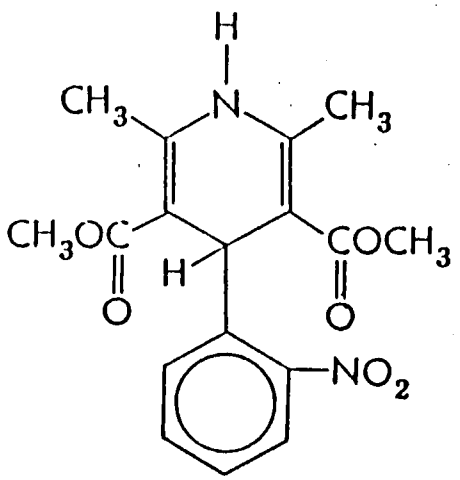
1.3.2 Calcium channel blockers

In 1962, it was reported that verapamil, a coronary vasodilator, possessed negative inotropic and chronotropic effects that were not seen with other, apparently similar vasodilator agents, such as nitroglycerin. The mechanism of action was originally thought to be due to coronary vasodilatation and blockade of myocardial ß-adrenergic receptors. Fleckenstein suggested that the mechanism of action was related to inhibition of the movement of calcium ions into the cells with resultant inhibition of excitation-concentration coupling. He termed such agents calcium antagonists. Although these agents were termed calcium antagonists, they do not directly antagonize the effects of calcium. They inhibit the entry of calcium into cells and have thus been termed calcium channel blockers (slow channel blockers, calcium entry blockers). Nifedipine is an example of this class of drugs (Needleman *et al.* in Goodman and Gilman, 1985).

1.3.2.1 Chemistry

Nifedipine is a dihydropyridine derivative (4-[2'-nitro-phenyl]-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxcylic acid dimethyl ester) and is soluble only in organic solvents such as alcohol or polyetylene glycol.

Figure 1.2



Nifedipine

1.3.2.2 Pharmacodynamic properties

1.3.2.2.1 Haemodynamic effects

(a) Effect on blood pressure

Nifedipine decreases mean arterial blood pressure at rest and after exercise by 20% or more. Significant reductions ($p < 0.001$) in blood pressure occur within 30 minutes after administration of both the oral and sublingual dosage forms (Bonaduce et al., 1983), and may last up to 5 hours (Banzet et al., 1983). Significant decreases in blood pressure (up to 34%) were seen in patients with hypertension, coronary artery disease or hypertrophic obstructive cardiomyopathy after 1 to 4mg of intravenous nifedipine (Murphy et al., 1982; Pfisterer and Burkart, 1982; Schanzenbächer et al., 1982). Nifedipine produces a greater reduction in blood pressure in patients with hypertension compared to normotensive individuals (Emanuelsson et al., 1984; MacGregor et al., 1983).

(b) Effect on heart rate

Kleinbloesem and co-workers (1984c) showed that the administration rate of nifedipine is an important determinant of its effects. Since the increase in heart rate after vasodilatation is mediated by baroreflex (Lederballe Pedersen and Mikkelsen, 1978), these findings imply that this reflex can be avoided by slow rates of drug input. It may thus be possible to dissociate the effects of nifedipine on blood pressure and heart rate by administering the drug so that it is absorbed at a relatively low rate (Kleinbloesem et al., 1984c), which may include giving the drug with meals (Hirasawa et al., 1985).

Heart rate was increased in cardiac patients and normal volunteers after acute administration of sublingual nifedipine (Lederballe Pedersen and Mikkelsen, 1978). Increases in heart rate have ranged between statistically non-significant and 28% and have been shown to be due to a baroreceptor-mediated increase in ß-adrenergic tone secondary to systemic vasodilatation.

No significant increases in heart rate were found after acute or long term (up to 12 months) oral administration of nifedipine capsules (Littler et al., 1983; Olivari et al., 1984; Saadjian et al., 1984). However, oral administration of nifedipine tablets in doses of 20 to 60mg in hypertensive patients has been associated with increases in heart rate between 29 and 38% (Banzet et al., 1983)

The intravenous and intracoronary administration of nifedipine has increased heart rate significantly for 5 to 15 minutes in healthy subjects and in cardiac patients both at rest and during exercise (Amende et al., 1983; Kleinbloesem et al., 1984a; Murphy et al., 1982; Pfisterer and Burkart, 1982, Schanzenbächer et al., 1982).

1.3.2.2.2 Effects on hepatic blood flow

Feely (1984) showed that 10mg nifedipine administered sublingually, significantly ($p<0.05$) increased apparent liver blood flow in 6 healthy volunteers as estimated by the indocyanine green method. There was also a positive correlation between the decrease in arterial blood pressure and the percentage increase in liver blood flow. It was suggested that the increase in liver blood flow was due to arterial vasodilatation produced by nifedipine. Additionally, oral nifedipine increased hepatic blood flow and decreased hepatic vascular resistance in patients with congestive heart failure (Leier et al., 1983,1984).

1.3.2.2.3 Concentration/effect relationship

Although therapeutic serum concentrations of nifedipine are not known, several studies have intimated that plasma nifedipine concentrations may correlate significantly with changes in blood pressure, heart rate and other hemodynamic parameters known to be influenced by nifedipine (Banzet et al., 1983; Kleinbloesem et al., 1984a; Taburet et al., 1983). However, in other investigations, no relationship was found (Lederballe Pedersen et al., 1979,1980; Reves et al., 1983)

It has been suggested that since individual sensitivities to nifedipine's clinical effects may vary markedly, routine plasma concentration measurements would not be advantageous (Reves et al., 1983; Stern et al., 1984).

1.3.2.3 Pharmacokinetic properties

Few well designed studies have been performed that adequately describe the pharmacokinetic properties of nifedipine. Possible reasons are that until recently no parenteral dosage form was commercially available and furthermore that nifedipine is very light-sensitive, breaking down rapidly on exposure to daylight, tungsten-bulb light, standard fluorescent light or ultraviolet irradiation to its more stable nitroso- or nitropyridine derivatives (Bach, 1983; Foster et al., 1983; Kleinbloesem et al., 1984b). The half-life of photodecomposition is 15 minutes in organic solvents and 44 minutes in plasma (Kleinbloesem et al., 1984b).

Figure 1.3

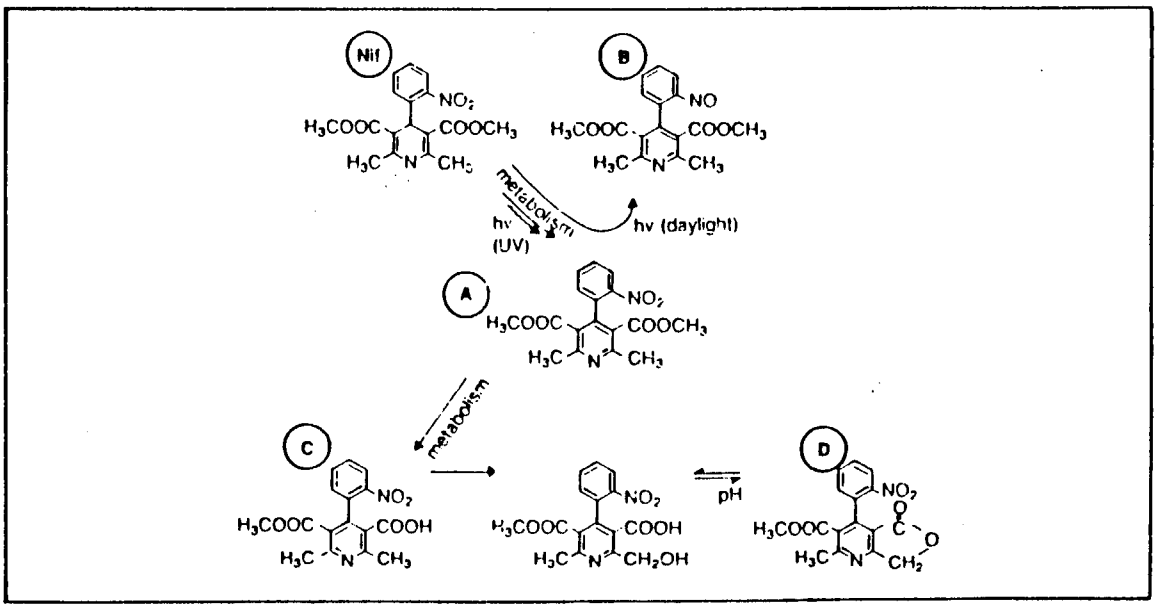


Fig. 7. Photodecomposition and biotransformation of nifedipine (Nif). Nifedipine is rapidly oxidised into its pyridine metabolite (A), which may also be formed in ultraviolet light. The 2-nitrosoderivative (B) is formed in normal daylight. Upon biotransformation, hydrolysis to an hydroxy carboxylic acid (C) and further oxidation to a methoxy carboxylic acid (D) derivative occurs (after Kleinbloesem et al., 1984b).

1.3.2.3.1 Absorption

Although nifedipine is absorbed over the whole length of the gastrointestinal tract, almost 100% of an oral dose is absorbed in the small intestine (Raemsch and Sommer, 1983). However there has been considerable variation among subjects in the manner and extent to which nifedipine is absorbed (Sorkin et al., 1985). The differences in measured plasma concentrations among subjects may be attributed to the rate of drug absorption and/or variability in the extent of first-pass hepatic extraction and metabolism (Foster et al., 1983; Kleinbloesem et al., 1984a; Snedden et al., 1984a,b; Stern et al., 1984). Capsules produce peak plasma concentrations in 0.5 to 3 hours, with an absolute bioavailability of 45 to 68% with no substantial difference between different formulations used (solution, capsule, tablet) [Foster et al., 1983; Kleinbloesem et al., 1984a; Raemsch and Sommer, 1983; Needleman et al. in Goodman and Gilman, 1985]. As studies with ^{14}C-nifedipine (Horster et al., 1972) have shown almost complete absorption after oral administration, this suggests that nifedipine is subject to substantial presystemic elimination. The liver seems to be the site of presystemic elimination since bio-availability was almost 100% in patients with liver cirrhosis (Kleinbloesem et al., 1986b).

Some investigators have indicated that nifedipine is absorbed up to 90% after a single oral dose but it is theorised that substantial first-pass metabolism is responsible for the lower bioavailability of the drug (Kleinbloesem et al., 1984a; McAllister, 1982). However, no significant changes in absorption rate or saturation of presystemic metabolism occurred at doses between 5 and 20mg in fasted volunteers (Raemsch and Sommer, 1983). Additionally, the area under the plasma concen-tration vs time curve (AUC) for nifedipine cap-sules increased proportionally to the dose administered and its kinetics were linear in the 20 to 60mg dose range (Banzet et al., 1983; Raemsch and Sommer, 1983).

The rate of absorption varies widely among individuals. Several investigators have described 'fast' and 'slow' absorbers of nifedipine depending on the time required to reach maximum plasma concentrations, which has ranged from 30 minutes to 1 hour in the 'fast' group and from 2 to 4 hours in the 'slow' group (Foster et al., 1983; Nakashima et al., 1984; Snedden et al., 1984b). Similarly, Kleinbloesem et al. (1984d) identified 'rapid metabolisers' as the principal phenotype describing the polymorphism that exists regarding the disposition kinetics of nifedipine. Nakashima et al. (1984) have suggested that in 'fast' and 'slow' absorbers nifedipine is absorbed in the stomach and small intestine respectively.

1.3.2.3.2 Distribution

The steady-state volume of distribution of nifedipine in man after oral administration has been investigated in one study only and was found to be 1.32 l/kg (Foster et al., 1983). In a study by Kleinbloesem et al. (1984a), the steady-state volume of distribution after intravenous administration was noted to be 0.8l/kg, whereas the volume of the central or plasma compartment was only 0.25 l/kg. Since nifedipine is very highly bound to plasma proteins (92 to 98%) (Schlossman et al., 1975; Kleinbloesem et al., 1984a,c; Needleman et al. in Goodman and Gilman, 1985), this would appear to indicate that nifedipine undergoes extensive tissue distribution in man (Sorkin et al., 1985). Protein binding of nifedipine is independent of drug concentration in the range of 100 to 1200Ìg/l (Otto and Lesko, 1986). In patients with liver cirrhosis, the nifedipine free fraction was almost twice as much as in healthy volunteers. Patients with renal disease also exhibited a decrease in protein binding, from 96 þ 0.5% in controls to 93.5 þ 0.4% in patients with severe renal impairment (Kleinbloesem et al., 1984a)

1.3.2.3.3 Metabolism

Animal studies have shown that nifedipine metabolism appears to involve hepatic enzyme systems other than the cytochrome P-450 monooxygenase system (Hamann et al., 1985).

Two metabolites of nifedipine have been isolated and identified in human plasma and urine (Kleinbloesem et al., 1984b; Kondo et al., 1980; Raemsch and Sommer, 1983). Nifedipine is rapidly enzymatically oxidised to a pyridine metabolite, which then undergoes further metabolism via hydrolysis of the ester moiety to a carboxylic acid which accounts for 60 to 70% of the dose. A minor metabolic pathway accounting for 3 to 5% of the dose involves the further oxidation of this carboxylic acid and the methyl group. It is assumed that both the metabolites are devoid of pharmacological activity (Sorkin et al., 1985). The plasma half-lives of the carboxylic acid (about 10 hours) and the hydroxymethyl carboxylic acid (4 to 5 hours) metabolites are considerably longer than that of the parent drug (about 2 hours). During multiple oral dosing these metabolites accumulate (Raemsch and Sommer, 1983), although their contribution to the overall clinical effect is negligible, since these metabolites do not contain the intact dihydropyridine structure required for pharmacological activity.

Radiolabelled nifedipine has been found to undergo hepatic oxidation to 3 pharmacologically inactive metabolites which are excreted in the urine (Kroneberg and Krebs, 1980). Two of these metabolites, the hydroxy carboxylic acid derivative and the methoxy carboxylic acid derivative, contain 95% of the total detectable urinary radioactivity. Thus, this amount of nifedipine undergoes biotransformation. Only traces of unchanged parent drug are excreted in the urine (Kondo et al., 1980; Kroneberg, 1975; Raemsch and Sommer, 1983). Waller and co-workers (1984) found that the nitropyridine analogue of nifedipine, which is also formed from nifedipine by a photochemical reaction under ultraviolet light, shows a marked presence in the plasma after nifedipine is given orally. Peak plasma concentrations and AUCs in the same study suggested that this nitropyridine analogue was a major first-pass metabolite of nifedipine.

Following enteric absorption of nifedipine, some drug (30 to 40%, if 100% absorption is assumed) is eliminated metabolically during the first pass through the liver and does not enter the systemic circulation (Raemsch and Sommer, 1983).

(a) Half-life

The elimination half-life of nifedipine is apparently dependent upon the dosage form in which it is administered (Table VI). The prolonged half-life after oral administration of tablets may reflect more the absorption half-life than the elimination half-life of the drug (Taburet et al., 1983).

The elimination half-life of nifedipine after oral adminstration in tablet form has been found to vary between 6 and 11 hours, which is about 2 to 3 times longer than previously reported after the administration of capsules (Banzet et al., 1983; Foster et al., 1983; Kleinbloesem et al., 1984a; Ochs et al., 1984; Taburet et al., 1983).

The half-life of nifedipine is 1.3 to 1.9 hours after intravenous administration (Foster et al., 1983; Kleinbloesem et al., 1984c; Raemsch and Sommer, 1983; Waller et al., 1984).

(b) Elimination

After enteral and intravenous administration of radioactively labelled nifedipine, 70 to 80% of activity (in the form of highly water-soluble metabolites) is eliminated in the urine. 90% of this amount is eliminated within 24 hours (Horster 1975; Raemsch and Sommer, 1983). The remainder is excreted in the faeces also in metabolised form (Raemsch and Sommer, 1983). Unchanged nifedipine is excreted in the urine in trace amounts approximating 0.1% of the total dose (Kondo et al., 1980; Kleinbloesem et al., 1984a).

The total systemic clearance (intravenous) of nifedipine from plasma ranges from 27 to about 66 l/h, while its intrinsic clearance (oral) ranges from 33 to 37 l/h (Table VI). Kleinbloesem et al., (1984a,b) found the clearance of nifedipine after oral and intravenous administration in volunteers to be 27 to 33 l/h and suggested that the rate of nifedipine elimination depended on drug metabolising enzyme activity as well as on hepatic blood flow.

1.3.2.4 Effect of liver cirrhosis on pharmacokinetics

The pharmacokinetics of nifedipine are grossly altered in patients with liver cirrhosis. After intravenous administration, the terminal half-life increased to 7 hours (controls 2 hours). The volume of distribution (V-sys/f) also increased, with a value of 1.29 l/kg compared to 0.97 l/kg in healthy volunteers. Total systemic clearance decreased in patients with liver cirrhosis to 13.98 l/h as compared with 35.28 l/h in healthy controls. Plasma protein binding was also lower in the cirrhosis patients. With all these data considered, the concentration-effect relationship in cirrhotic patients was not different from that in healthy volunteers, thus indicating that sensitivity to the drug effect was not altered by liver cirrhosis (Kleinbloesem, 1986b).

1.3.2.5 Effect of age on pharmacokinetics

Robertson and co-workers (1988) investigated age-related changes in the pharmacokinetics of nifedipine following intravenous (2.5mg) and oral (10mg sustained release) administration. The area under the plasma concentration vs time curve after both forms of administration was significantly greater in the older age group (mean age 77.8 years) than in the younger age group (mean age 27.1 years). The half-life was also significantly longer in the old than in the young.

1.3.2.6 Side effects

Analysis of composite studies of nifedipine usage worldwide has shown an overall incidence of side effects of about 20% (Lewis, 1983). These side effects, which are generally extensions of the vasodilating effects of nifedipine, can be alleviated by either decreasing the nifedipine dose or by combining the drug with a ß-blocker. Side effects from nifedipine increase with increasing dosage (Covinsky and Hamburger, 1983).

Table 1.2

Incidence (%) of the most common categories of adverse experiences in patients receiving nifedipine (after Ebner and Donath, 1980 and Terry, 1982).

Adverse Experience	Ebner and Donath (1980) n = 4863	Terry,(1982)	
		Total population. n = 3081	Long term therapy (≥ 6 months) n = 795
Headache	7.2	7.1	7.2
Facial flush, burning,heat sensitivity, numbness,reddening,tingling	5.3	7.4	9.4
Dizziness,giddiness,lightheadedness	3.1	12.1	16.5
GI symptoms	5.2	7.5	9.3
Oedema,swelling fluid retention	0.6	7.7	11.6

(From Sorkin et al., 1985)

Ebner and Donath (1980) analysed nifedipine side effects and found that side effects usually occurred within the first 14 days of treatment, with the vasodilating effects being dose related.

According to Needleman and colleagues (in Goodman and Gilman, 1985), the predominant difficulty with nifedipine is excessive vasodilatation which results most commonly in peripheral oedema and dizziness and less commonly in headaches, hypotension, digital dysesthesia, flushing, nausea, vomiting and sedation. These side effects, which occur in 20% of patients, are usually benign and may abate with time or with adjustment of the dose. Aggravation of myocardial ischaemia has been reported, potentially due to excessive hypotension and decreased coronary perfusion, selective coronary vasodilatation in nonischaemic regions of the myocardium or an increase in oxygen demand due to excessive tachycardia.

In general, the major toxicities associated with the use of calcium channel blockers involve excessive vasodilatation, negative inotropy, depression of the sinus nodal rate and A-V nodal conduction disturbances.

1.3.2.7 Drug interactions

H_2-Receptor Blockers: While both ranitidine and cimetidine have been shown to significantly increase the bioavailability of nifedipine, cimetidine has additionally been shown to increase the hypotensive effect of nifedipine in healthy volunteers. Cimetidine strongly inhibited the metabolism of nifedipine, as deduced from an increase in AUC and C_{max} of 80%. The increase after ranitidine was not significant (Kirch et al., 1983,1984, 1985; Renwick et al., 1987; Schwartz et al., 1988). This effect is probably due to the non-specific inhibition of cytochrome P-450 by cimetidine (Renwick et al., 1987). However, neither drug has been found to significantly affect the antianginal or other pharmacodynamic effects of nifedipine (Dylewics et al., 1984; Kirch et al., 1983,1984, 1985).

1.3.3 Metabolic polymorphisms

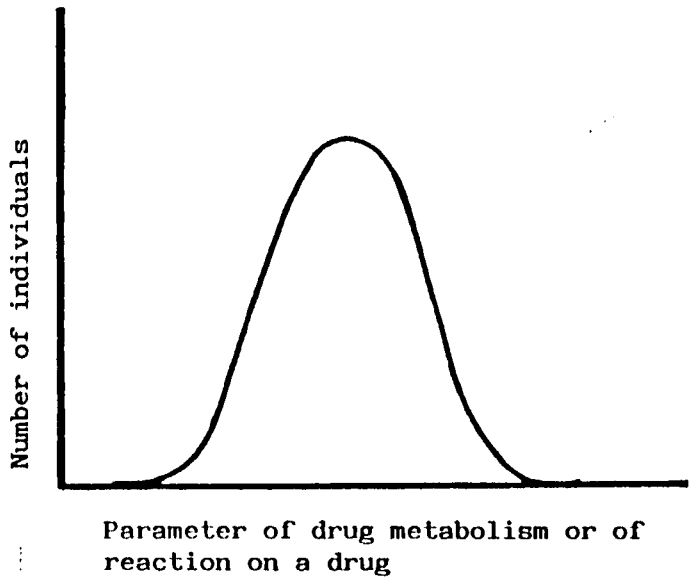
1.3.3.1 Introduction

Inter-individual variation in response to drugs may result from environmental and/or genetic factors which influence the absorption, distribution, excretion and especially the metabolism of the drug. Because of these factors, decreases in therapeutic responses and an increased risk of toxic manifestations may result (Clark, 1985).

Microsomal enzymes of the liver, which play a major role in the metabolism of most drugs, are under polygenic control. A continual variation in a population is seen in the majority of pharmacological parameters. The distribution curves for these parameters reveal an unimodal Gauss distribution (Fig 1.4)[Goth, 1978].

Figure 1.4

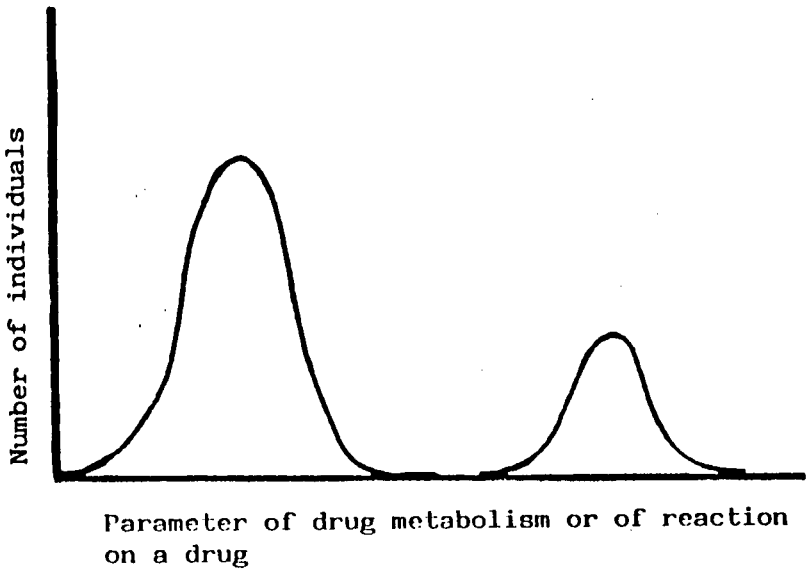
Unimodal distribution of polygenic heriditary variations.



Single gene anomalies or polymorphisms result when a single gene leads to the recognition of a separate phenotype in a given population. The distribution curves of monogenic characteristics are usually bimodal or trimodal and they thus show a discontinual variation (Fig 1.5) [Goth, 1978].

Figure 1.5

Bimodal distribution of monogenic hereditary anomalies.



1.3.3.2 Polymorphic oxidation of drugs

Oxidation is probably the most common metabolic pathway in the human body. Most oxidative reactions are catalyzed by the cytochrome P-450 group of enzymes which possesses shared substrate specificity. An increase in oxidation tempo of one drug will thus not necessarily lead to an increase of a second drug. However, it seems as if certain groups of drugs are involved in the same cytochrome P-450 system for oxidation reactions (Breimer, 1983).

Polymorphic oxidation involving cytochrome P-450 enzymes was first reported with an antihypertensive agent, debrisoquine (Mahgoub et al., 1977). A bimodal distribution is seen and individuals are classified as "effective" and "poor" metabolisers (Inaba et al., 1980,1983). Poor metabolisers shows an increased antihypertensive response to debrisoquine (Idle et al., 1978).

It was observed that some patients develop side effects when treated with the antiarrhythmic and oxytocic agent sparteine. It was consequently shown that these patients could not metabolise sparteine. This defective oxidation of sparteine, is under control of a single gene and poor metabolisers are homozygotic for the autosomal recessive gene (Eichelbaum et al., 1979).

Poor metabolisers of debrisoquine and sparteine comprise between 5 and 10% of Caucasian populations. It is seen that poor debrisoquine metabolisers also metabolise sparteine poorly and it is thus proposed that the metabolism of both drugs are controlled by the same or closely related gene (Bertilsson et al., 1980; Eichelbaum, 1982; Inaba et al., 1980,1983).

Changes in pharmacokinetics of other drugs are seen in poor metabolisers of debrisoquine and sparteine. However this polymorphism does not influence all drugs that are oxidised by the cytochrome P-450 isoenzymes. It is proposed that a separate form of cytochrome P-450 is involved (Eichelbaum et al., 1983).

1.3.3.2.1 Clinical implications of oxidative polymorphisms with reference to other drugs

ß-Blockers: The metabolism of certain ß-blocking agents seems to be related to the sparteine/debrisoquine polymorphism. Individuals with very high plasma concentrations of alprenolol, metoprolol, timolol, oxprenolol, propranolol and pindolol were phenotyped as slow sparteine metabolisers (Alvan et al., 1982; Lennard et al., 1982).

In a study with metoprolol, it was seen that ß-blockade is present for a longer period of time in poor metabolisers and they should therefore receive metoprolol only once per day. Poor metabolisers are also more prone to side effects such as bronchospasm (Lennard et al., 1983).

Perhexiline: Perhexiline is oxidised in the liver to monohydroxiperhexiline. It was seen that patients who developed peripheral neuropathy with perhexiline treatment, had higher plasma concentrations and longer half lives than those who did not develop peripheral neuropathy (Singlas et al., 1978). Recently it was seen that poor debrisoquine/sparteine metabolisers were also poor metabolisers of perhexiline (Cooper et al., 1984).

Tricyclic antidepressants and Chlorpromazine: Bertilsson and co-workers (1980) found that nortriptyline and other tricyclic antidepressants (TAD's) showed the same polymorphism as sparteine or debrisoquine. Chlorpromazine shows the same oxidative polymorphism, but the clinical implication must still be studied (Otton et al., 1983).

Phenytoin: Ineffective parahydroxylation of phenytoin seems to be related to sparteine/debrisoquine polymorphism. Studies showed that poor oxidisers of sparteine/debrisoquine metabolised phenytoin slower than effective oxidisers of sparteine/debrisoquine The formation and elimination of metabolites were also significantly less (Idle et al., 1981; Sloan et al., 1981).

Nifedipine: In a study by Foster et al. (1983), it was confirmed that considerable variability in nifedipine plasma concentrations occurs among normal subjects as reported by Jakobsen et al. in 1979. They thought that this could be attributed to rate of drug absorption and/or variability in the extent of first-pass hepatic extraction and metabolism. Their findings suggest the presence of two distinct groups: one in which nifedipine appears rapidly in plasma and another in which the drug appears more slowly. They furthermore proposed that the finding would be consistent with duration of gastric retention time, but they had no data to substantiate their speculation. Nakashima and co-workers (1984) confirmed these findings and added an intermediate group in which a transient high peak in plasma concentration was seen prior to the maximum plasma concentration. They proposed absorption in the stomach, in the small intestine and a combination of these two.

Kleinbloesem and co-workers (1984a) have shown that the cumulative 8-hour urinary excretion of the major metabolite and the AUC of nifedipine in plasma exhibited a bimodal distribution in a study with 53 healthy subjects. The authors proposed that 2 phenotypes, rapid and slow metabolisers, can be defined in the population of which the rapid metaboliser phenotype comprises 83% and the slow metaboliser phenotype, 17%. These data seem to indicate that the oxidative metabolism of nifedipine may exhibit a genetic polymorphism. As the incidence of the slow nifedipine metaboliser phenotype is twice as high as that of the poor metaboliser of the debrisoquine/sparteine polymorphism (Eichelbaum, 1982), it is rather unlikely that nifedipine metabolism is regulated by this polymorphism.

However, Schellens and colleagues (1988) could not confirm this finding in their study with 130 healthy young subjects. They could only conclude that the disposition of nifedipine after oral administration is highly variable and thus of possible clinical importance.

C H A P T E R 2

METHODS

2.1 STUDY PERFORMANCE

2.1.1 Approval

Before commencement of the study, approval was obtained from the Ethical Committee of the University of the Orange Free State (UOFS). The study was done in accordance with the Declaration of Helsinki concerning biomedical research involving human subjects (See Appendix 1: Protocol) and local requirements.

2.1.2 Study population

Twenty healthy, non-smoking male subjects aged 20-27 years (mean 21.8 years, S.D.:1.7), body weights 64-90kg (mean 78.4kg, S.D.:6.0) and height 171-187cm (mean 181.1cm, S.D.:3.6), of which ten were known to be effective oxidisers of sparteine, nine non-metabolisers and one poor oxidiser, participated in the study.

Sparteine phenotyping was done by calculating a Q-value which is a ratio calculated by dividing the concentration of unchanged sparteine by the sum of the concentrations of the two metabolites, 2- and 5-dehydrosparteine, as determined in the urine of the volunteers after taking 100mg sparteine sulphate having fasted overnight. The volunteers emptied their bladders before receiving the sparteine sulphate and a single 24 hour urine sample was collected.

Written, informed consent was obtained from each volunteer before onset of the study.

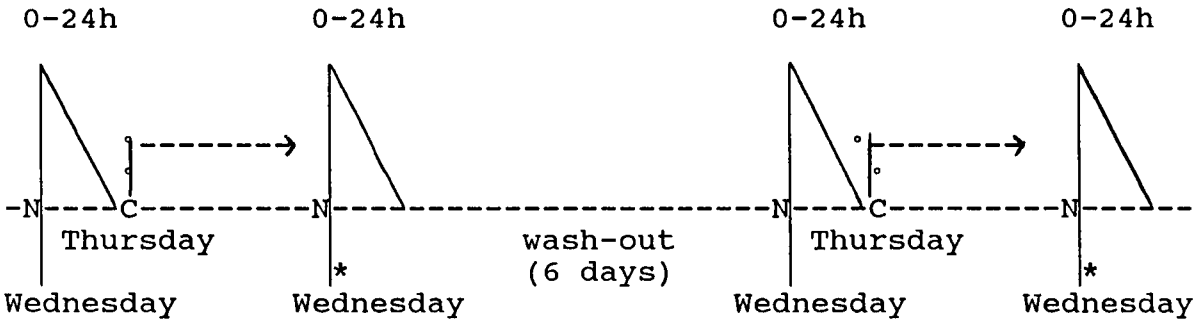
2.1.3 Study design

This single-blind, randomised, cross-over study was performed in the Farmovs Clinical Pharmacology Unit (CPU), Department of Pharmacology, UOFS, Bloemfontein.

Following an overnight fast, each subject was given a single Adalat^{R} capsule containing 10mg of nifedipine. They remained semirecumbent and continued to fast for a period of four hours. Venous blood samples (10ml) were withdrawn prior to the dose and at 10, 20, 30, 40, 50, 60, 80, 100, 120 minutes and 2½, 3, 3½, 4, 5, 7, 9 and 12 hours after the dose. The samples were centrifuged immediately, the plasma separated into two aliquots and stored at -20°C pending drug analysis. The study was divided into four different profile days of which two were bioavailability and pharmacokinetic studies of nifedipine taken with 200ml of tap water at room temperature. During the other two days,

bioavailability and pharmacokinetic studies of nifedipine were repeated, but the subjects were at steady-state for cimetidine having received 400mg Tagamet^{R} twice daily for 6½ days before the profile day. Tagamet^{R} was also given on the morning of the profile day. During the latter two days, the subjects took their nifedipine with either 200ml of tap water at room temperature or 200ml of diluted hydrochloric acid (0.1%; 0.028M HCl). These two days were randomised (See flow-diagram).

Fig. 2.1 : Flow-diagram of study design



N: Nifedipine 10mg
C: Cimetidine 400mg q12h x 6½ days
*: Nifedipine taken with either 200 ml water or 200 ml HCl (0.1% w/v, 0.028M) [Randomised]

2.2 ANALYTICS

2.2.1 Product content assay

Before onset of the study the nifedipine content of the Adalat^{R} capsules (10mg) was assayed by a spectrophotometric method.

One 10mg capsule was emptied and washed with a solution containing 96% ethanol (SVR) in 60ml of SVR into a 100ml volumetric flask and ultrasonicated for 2 minutes. The flask and its contents were cooled and filled to the 100ml mark with SVR. A 5ml aliquot of the solution was diluted to 50ml with SVR. The absorbance was measured at 237nm in a Cary 219 UV/Vis Spectrophotometer and the content of nife-dipine calculated using an E^{1}_{1} of 966. The procedure was performed on 10 individual capsules. The E^{1}_{1} was determined by measuring the absorbance of 0.545mg of nifedipine in 50ml SVR. The absorbance of this solution was equal to 1.053.

No assay was done for the cimetidine content of Tagamet^{R}.

2.2.2 Plasma levels

Gas chromatography (GC) was used for the quantitation of nifedipine in plasma. The assay procedure was developed in the Department of Pharmacology, University of the Orange Free State, Bloemfontein.

2.2.2.1 Apparatus and reagents

A Hewlett Packard Gas Chromatograph, model 5880, was used for determination of nifedipine in plasma. A 30 cm glass column with 2mm internal diameter packed with 3% SP 2100 stationary phase on Supelcoport (Mesh 100/120), was used and injection was done directly onto the column by an autosampler (Hewlett Packard model 7673A). Detection was done by an electron capture detector (^{63}Ni). A Hewlett Packard series 5880 GC Terminal was used for peak integration and operating conditions were as follows:

Injector temperature:	250°C
Column temperature:	230°C
Detector Temperature:	300°C
Carrier gas (N_2) flow:	50 ml/min

The following reagents were used:
Hydrochloric acid was diluted by mixing 27,4g of Hydrochloric acid (BDH Chemicals Batch No. 375, Product No. 28695) with 72,6g of distilled water (Milli-Q Water System) to give a 10% w/v solution of HCl. 2ml of this solution was further diluted with distilled water to 200ml to give a 0.1% w/v solution of HCl;
High purity solvent brand of toluene from American Burdick and Jackson (Batch No. AR 275, Product No. 347);
Methanol from Rathburn (Batch No. 7859; Cat. No. RH 1019);
Nitrendipine (Bayer-Miles) for the internal standard.

Amber glass ampules (Petersen Ltd.), a Heidolph Vortex mixer and a Minifuge T (Heraeus Sepatech) centrifuge were used.

2.2.2.2 Standards

The internal standard (I.S.) solution was 100ml of toluene spiked with 50 ul of a solution containing 0.5mg nitrendipine/10ml methanol. Plasma standards were prepared by spiking drug-free pooled plasma with a stock methanolic solution containing nifedipine (101ug/ml) to cover the range 0.00-200ng nifedipine/ml. The limit of quantitation (LQ) of the analyte was defined as the lowest plasma concentration measured, which had a precision (i.e. coefficient of variation, CV) less than 15% and accuracy between 90% and 110%. LQ for this study was 0.1ng/ml.

The standards and patient plasma samples were processed according to the extraction procedure described below and peak integration done on the chromatograms obtained (See 2.2.2.3). The peak height ratio of nifedipine, relative to nitrendipine, was calculated. Standard curves of peak height ratios versus concentrations were used to calculate drug concentrations in the unknown samples by interpolation.

Because of the photodecomposition of nifedipine, all preparations, extractions and determinations concerning nifedipine were done under a sodium light.

2.2.2.3 Extraction procedure

Plasma (0.5 ml) was mixed with toluene containing internal standard (1 ml). The mixture was vortexed for 20sec after which it was centrifuged for 5 min at 4°C at 1250g. The aqueous phase was then frozen in an alcoholbath and the supernatant toluene phase decanted into an autosampler vial. 4ul was injected onto the column.

2.2.3 Precision

The precision of the assay procedure was continuously monitored during the period of assay of the plasma samples by including quality control specimens containing known concentrations of nifedipine. These *in vitro* quality control samples were stored under identical conditions (-20°C) to the actual trial samples.

2.2.4 Stability of the analyte in plasma

Additional blood samples were drawn from the volunteers on the first profile day and divided into five aliquots. These ex vivo quality control samples covering the therapeutic range were analysed throughout the course of the assay period and indicate the stability of the analyte under storage conditions. Ex vivo quality control samples were stored under identical conditions (-20°C) to actual trial samples.

2.3 BIOMETRICS

2.3.1 INTRODUCTION

The aim of the study was to investigate the influence of cimetidine on the bioavailability and pharmacokinetics of nifedipine and the importance of metabolic polymorphism on this interaction.

The individual data are presented together with the following descriptive statistics: mean, standard deviation (SD), minimum (MIN), maximum (MAX) and the number of observations (N). A summary table, reflecting the mean values and standard deviations, is also included (See Chapter 3).

2.3.2 PARAMETERS ANALYSED

In order to determine the rate and extent of absorption of nifedipine when taken with cimetidine, the following parameters were calculated:

the maximum plasma concentration (C_{max})

the area under the plasma concentration vs time data pairs (AUD)

the area under the plasma concentration vs time data pairs with extrapolation to infinity (AUDC)

area under the extrapolated part (%Extr)

apparent terminal half-life ($t_{\frac{1}{2}};z$)

relative total clearance (Cl-tot/f) [also expressed per body mass]

total mean time (MT-vsys)

relative volume of distribution (V-sys/f) [also expressed per body mass]

the time to maximum plasma concentration (T_{max})

(These abbreviations are currently in use in the Department of Pharmacology, University of the Orange Free State, Bloemfontein, because of a computer program for statistics used by the Department).

2.3.3 METHOD OF PARAMETER CALCULATION

2.3.3.1 The apparent terminal half-life ($t_{\frac{1}{2}};z$)

The apparent terminal half-life of nifedipine was calculated from the adjustment of a single exponential function (Ce^{-zt}) to the terminal phase of the log-linear plasma concentration vs time profile. C is a constant and z is the apparent terminal rate constant. The adjustments were done using the method of least squares. The terminal half-life was then calculated by:

$$t_{\frac{1}{2}};z = 0.693/z$$

2.3.3.2 The maximum plasma concentration (C_{max})

The values of C_{max} were read directly from the observed concentrations.

2.3.3.3 The area under the plasma concentration vs time data pairs (AUD)

The AUD was calculated by the linear trapezoidal rule between the first and last concentration vs time data pairs.

2.3.3.4 The area under the plasma concentration vs time data pairs with extrapolation to infinity (AUDC)

AUD was extrapolated to infinity using the terminal rate constant (z).

Thus:

$$AUDC = AUD + C_{last}(t)/z$$

where AUDC is the area under the curve from 0h to infinity, z is the terminal rate constant and $C_{last}(t)$ is the observed concentration corresponding to the last blood-sampling time (t_{last}) for which a concentration was reported.

2.3.3.5 The time to maximum concentration (T_{max})

The values of T_{max} were read directly from the observed concentrations as the blood sampling time corresponding to C_{max}.

2.3.3.6 Relative total clearance (Cl-tot/f)

Relative total clearance time was calculated by Cl-tot/f = Dose/AUDC.

2.3.3.7 Total mean time (MT-vsys)

The total mean time was calculated from

$$MT\text{-}vsys = PAUDC_1/PAUDC_0$$

where $PAUDC_0$ and $PAUDC_1$ are the zero and first order prospective areas under the curve (extrapolated to infinity) respectively (Brockmeier, 1986).

2.3.3.8 Relative volume of distribution (V-sys/f)

Relative volume of distribution was calculated from V-sys/f = Cl-tot/f.MT-vsys

2.3.4 METHOD OF ANALYSIS

Due to the nature of T_{max}, the statistics in respect of this parameter are descriptive only. A frequency table for the values of T_{max} was constructed for each case and is presented graphically in the form of a histogram in Chapter 3.

Analysis of C_{max} (as a measure of the rate of absorption), AUD, AUDC, $t_{\frac{1}{2}};z$, Cl-tot/f, MT-vsys and V-sys/f (as measures of the extent of absorption) was done in the following manner:

2.3.4.1 Point estimate

Point estimates for the ratio of each of the phases, relative to nifedipine (Phase I) as single medication, were calculated as the ratios of the respective means.

2.3.4.2 Analysis of variance

The parameters were subjected to an analysis of variance with treatment and subject as the main effects for intertreatment comparisons or a treatment effect only when the two groups (effective oxidisers and non-metabolisers of sparteine) were compared within a specific treatment. If the period effect turned out to be significant, it would be indicative of the presence of a carry-over effect. The mean sum of squares for errors was used to construct confidence intervals.

2.3.4.3 Confidence interval estimates

90% Conventional t-confidence intervals for the true difference between the product means for the ratio of each of the phases, relative to nifedipine (Phase I) when taken as sole medication, were calculated. These intervals were also calculated for the ratio of the combination phase which included diluted hydrochloric acid relative to the nifedipine/cimetidine combination phase.

C H A P T E R 3

RESULTS

3.1 DEMOGRAPHIC DATA

The demographic data of the volunteers who participated in this study, are summarised in Table 3.1. The Q-value is a ratio calculated by dividing unchanged sparteine by the sum of the two metabolites, 2- and 5-dehydrosparteine, as determined in the urine of the volunteers after taking 100mg sparteine sulphate having fasted overnight. The volunteers emptied their bladders before receiving the sparteine sulphate and a single 24 hour urine sample was collected.

Values are interpreted as follows: (Rupp et al., 1985)

* Effective oxidisers:	Q < 2.5
Intermediate oxidisers:	Q = 2.5 - 20
Poor oxidisers:	Q = 20 - 80
Non-metabolisers:	Q > 80

(See Table 3.1)

Table 3.1 DEMOGRAPHIC DATA

Subj. No.	Name	Age	Mass (kg)	Height (cm)	Oxidising Phenotype *(Q)
1	DFB	22	81	183	132
2	WPH	20	64	182	85.1
3	JL	23	85	186	1.12
4	JDuT	21	80	180	190
5	TW	23	86	183	0.88
6	GJPN	22	90	183	1.76
7	MvdW	22	77	179	0.86
8	RAN	20	82	186	163
9	JAH	21	74	176	126
10	GPG	23	78	179	1.07
11	HvB	27	72	181	0.67
12	ENH	20	76	181	0.42
13	GT	22	85	187	103
14	AM	22	79	171	53.8
15	IFT	20	80	183	0.65
16	AV	23	77	182	1.48
17	DJS	22	82	179	100
18	PHP	20	72	182	1.77
19	JBH	21	72	180	116
20	HMN	21	75	178	160
Mean		21.8	78.4	181.1	
S.D.		1.7	6.0	3.6	

3.2 QUALITY CONTROL

3.2.1 Product content assay

The results of the product content assay procedure, repeated with 10 individual capsules, are summarised in Table 3.2.

Table 3.2 NIFEDIPINE CONTENT OF CAPSULES USED IN THIS STUDY, EXPRESSED AS A PERCENTAGE OF THE DECLARED CONTENT.

ADALAT^{R} (10mg) 87017*		
TABLET	ABSORBANCE	% CONTENT
1	0.973	100.7
2	0.958	99.2
3	0.958	99.2
4	0.957	99.1
5	0.960	99.4
6	0.952	98.6
7	0.950	98.3
8	0.956	99.0
9	0.934	96.7
10	0.931	96.4
MEAN		98.7
CV(%)		1.30

* Batch number

These data comply with the British Pharmacopoeial standards, which state that the actual content must be within 95-105% of the declared content.

3.2.2 Method validation

The *in vitro* and *ex vivo* quality controls of another nifedipine study performed in the Department of Pharmacology, University of the Orange Free State, Bloemfontein (UOFS 10/88), were used as validation data (See Tables 3.3 and 3.4).

Table 3.3 IN VITRO QUALITY CONTROLS (UOFS 10/88)

	Spiked concentration of analyte (ng/ml)	Mean concentration determined (ng/ml)	N	CV (%)
Q1	202.2	193.9	8	3.26
Q2	101.8	98.2	8	3.68
Q3	51.7	51.0	8	2.41
Q4	25.8	26.2	8	4.18
Q5	7.00	7.44	8	8.54

Table 3.4 EX VIVO QUALITY CONTROLS (UOFS 10/88)

	Concentrations determined (ng/ml)				
DATE	1	2	3	4	5
10/3/88	83.4	35.2	20.3	9.12	4.76
11/3/88	92.6	35.3	22.7	9.15	4.74
21/3/88	86.6	35.2	21.0	8.82	4.64
23/3/88	88.9	35.4	21.2	8.57	4.49
24/3/88	88.5	35.1	20.7	8.94	4.58
N	5	5	5	5	5
MEAN	88.0	35.2	21.2	8.92	4.64
CV (%)	3.83	0.32	4.32	2.66	2.42

3.2.3 In vitro quality control (FRM 5/88)

The accuracy and the precision of the assay procedure were continuously monitored throughout the assay period. The results of the in vitro quality control assay for nifedipine are summarised in Table 3.5. The accuracy and the precision of the analytical method were within acceptable limits for the analyte throughout the assay period.

Table 3.5 IN VITRO QUALITY CONTROL OF NIFEDIPINE (FRM 5/88)

	CONCENTRATION (ng/ml)					
	Q1	Q2	Q3	Q4	Q5	Q6
	207	110	52.0	26.5	10.9	2.79
	210	111	52.7	26.7	11.0	2.83
	210	103	48.7	27.0	12.1	2.84
	210	104	49.3	27.1	12.0	2.86
	224	110	56.7	27.2	11.4	3.02
	218	109	56.2	27.0	11.3	3.03
	218	111	54.2	25.6	11.0	2.91
	214	109	54.3	25.7	10.8	2.91
	205	121	59.5	28.8	11.8	2.81
	199	120	59.7	29.2	12.1	2.91
	216	114	52.5	26.4	11.8	3.09
	202	110	51.8	26.6	11.8	3.08
	210	112	51.8	28.2	11.1	2.84
	203	110	51.4	27.9	11.1	2.85
	209	111	54.2	26.7	11.3	2.86
	203	109	54 2	26.9	11.4	2.82
	217	109	55.9	27.5	11.4	3.09
	208	106	55.3	27.2	11.4	2.99
		113	54.0	26.9	11.7	3.06
		110	53.8	26.9	11.6	3.09
			54.0	26.5	11.0	2.68
N	18	20	21	21	21	21
Mean	210	111	53.9	27.1	11.4	2.92
SD	6.61	4.21	2.78	0.88	0.40	0.12
Precision CV (%)	3.14	3.81	5.16	3.26	3.53	4.14
Spiked value	212	111	54.7	27.7	11.9	2.87
Accuracy (Bias %)	-1.01	-0.11	-1.37	-2.17	-3.79	1.74

3.2.4 Ex vivo quality control (FRM 5/88)

The stability of the analyte under storage conditions was continuously monitored. The results of the ex vivo quality control samples for nifedipine are summarised in Table 3.6.

Nifedipine was stable under the storage conditions.

Table 3.6 EX VIVO QUALITY CONTROL OF NIFEDIPINE (FRM 5/88)

	CONCENTRATION (ng/ml)				
	Ex Vivo 1	Ex Vivo 2	Ex Vivo 3	Ex Vivo 4	Ex Vivo 5
	114	55.8	32.9	16.5	2.60
	107	49.7	33.8	17.2	3.40
	111	57.9	35.2	16.8	3.32
	107	51.8	31.8	18.1	3.36
	107	49.3	33.2	17.2	3.17
N	5	5	5	5	5
Mean	109	52.9	33.4	17.2	3.17
SD	3.24	3.80	1.27	0.61	0.33
CV (%)	2.97	7.19	3.79	3.55	10.43

See Fig. 3.1 - 3.4 for graphic presentations of these quality controls.

Fig. 3.1

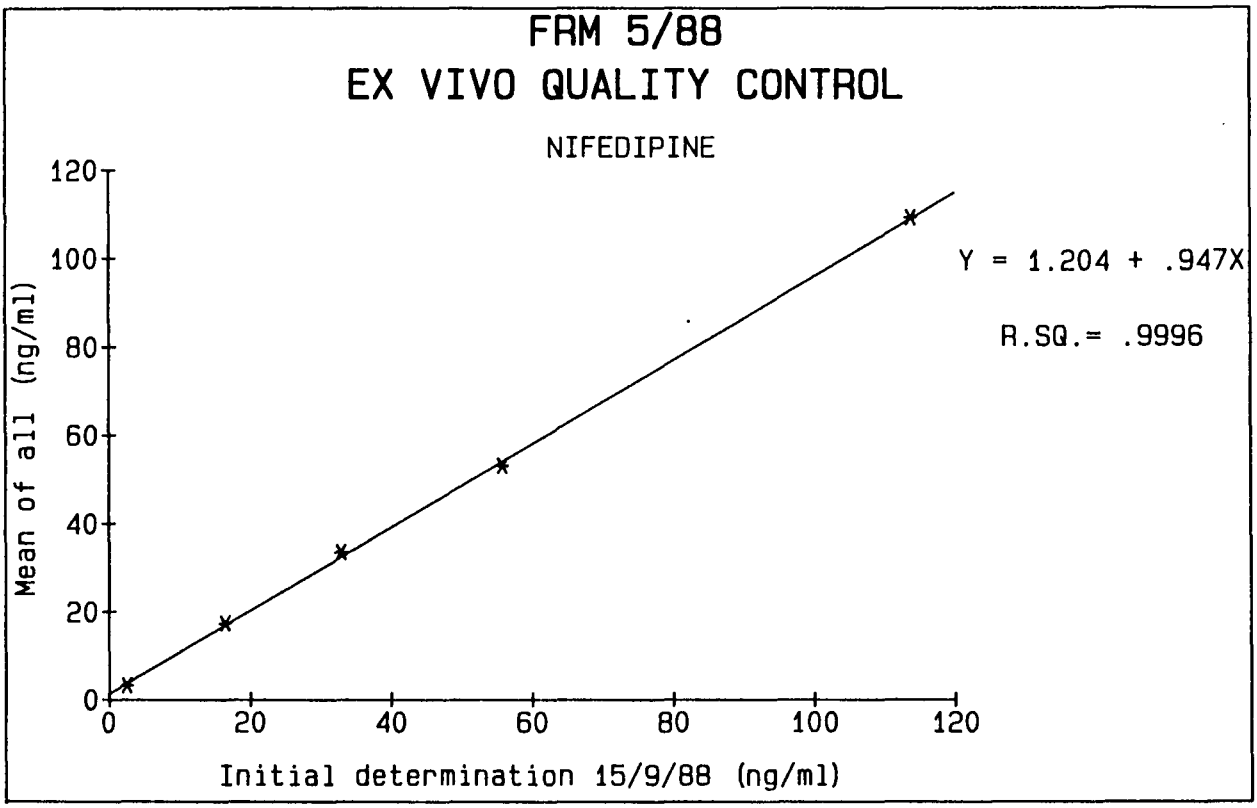

FRM 5/88
EX VIVO QUALITY CONTROL
NIFEDIPINE
Y = 1.204 + .947X
R.SQ.= .9996
Mean of all (ng/ml)
Initial determination 15/9/88 (ng/ml)
0
20
40
60
80
100
120

Fig. 3.2

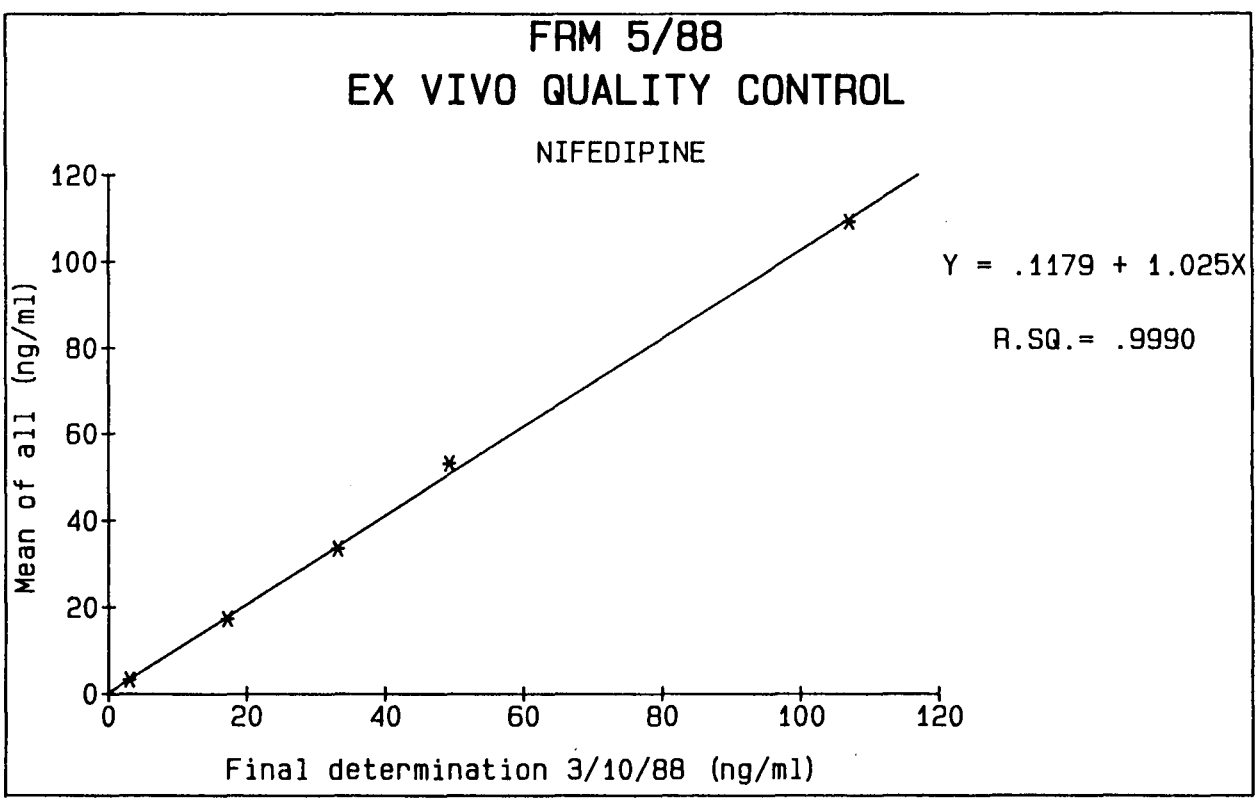

FRM 5/88
EX VIVO QUALITY CONTROL
NIFEDIPINE
Y = .1179 + 1.025X
R.SQ.= .9990
Mean of all (ng/ml)
Final determination 3/10/88 (ng/ml)
0
20
40
60
80
100
120

Fig. 3.3

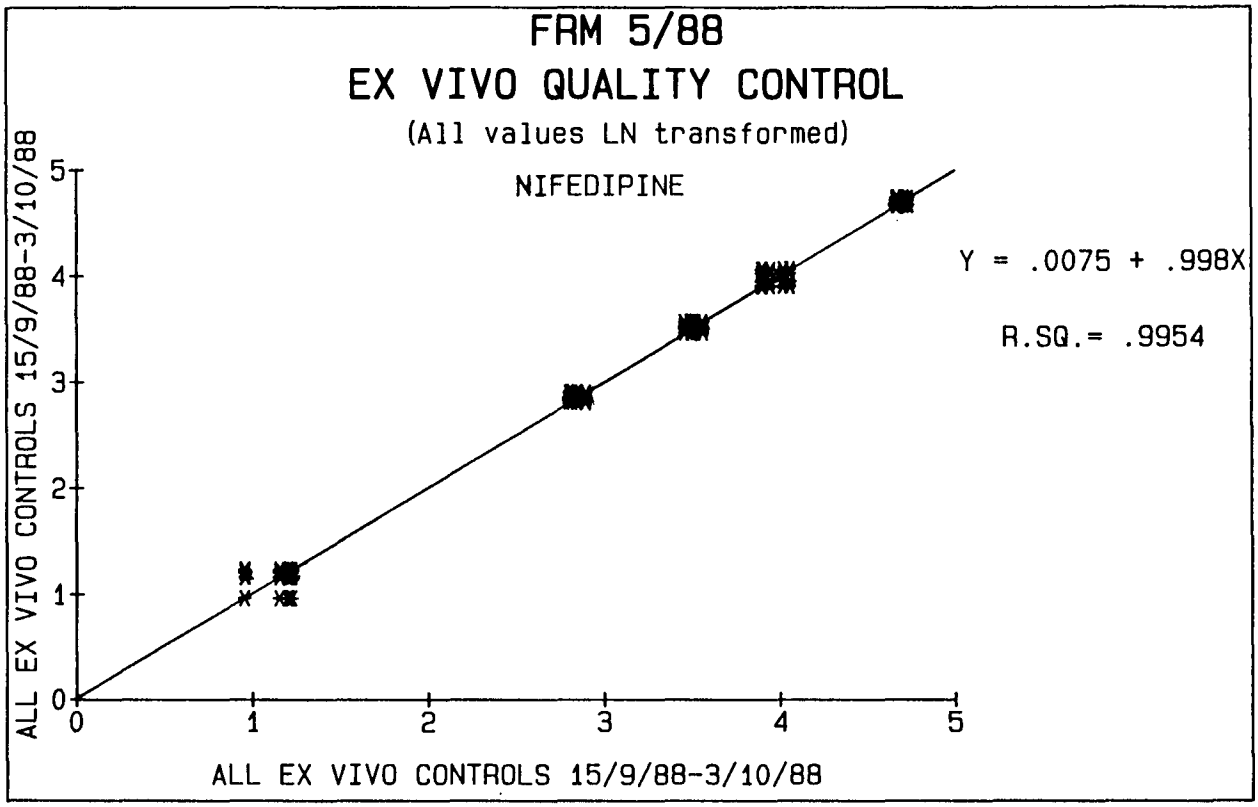
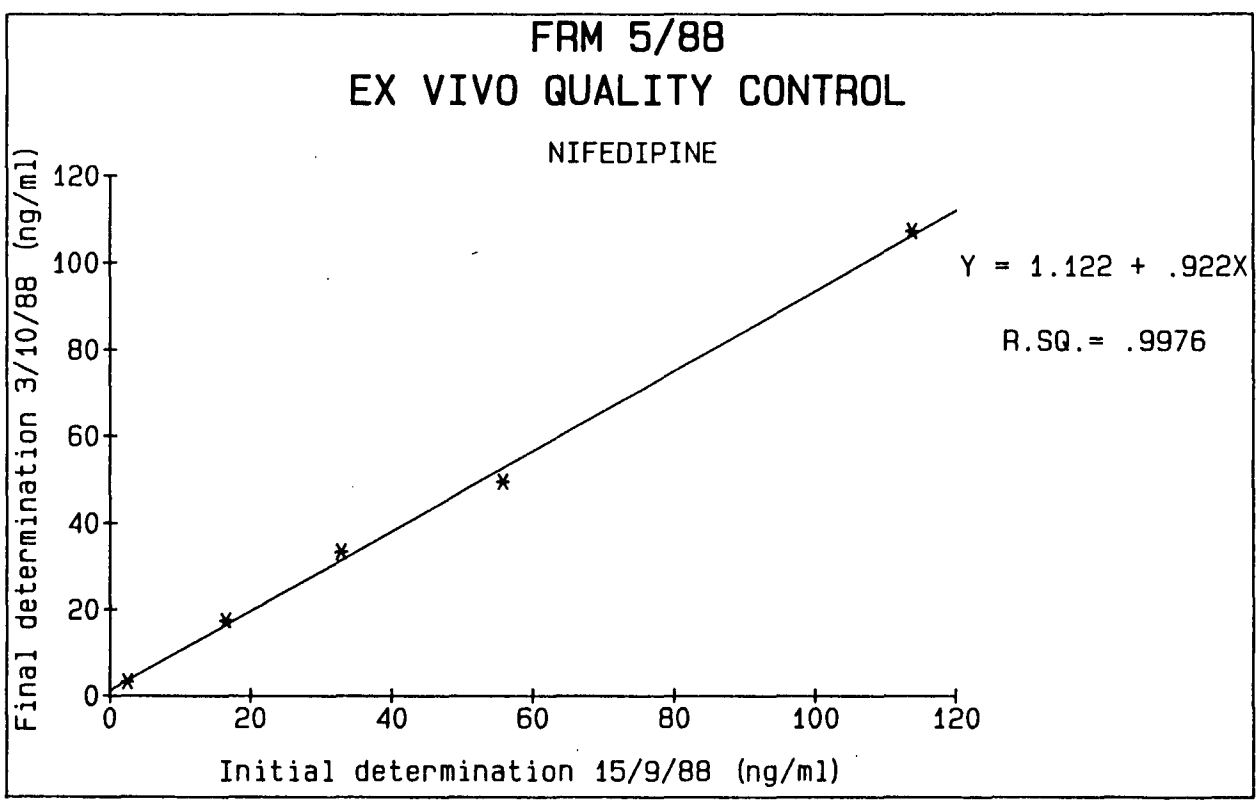

FRM 5/88
EX VIVO QUALITY CONTROL
(All values LN transformed)
NIFEDIPINE
Y = .0075 + .998X
R.SQ.= .9954
ALL EX VIVO CONTROLS 15/9/88-3/10/88
ALL EX VIVO CONTROLS 15/9/88-3/10/88
0
1
2
3
4
5

Fig. 3.4


FRM 5/88
EX VIVO QUALITY CONTROL
NIFEDIPINE
Y = 1.122 + .922X
R.SQ.= .9976
Final determination 3/10/88 (ng/ml)
Initial determination 15/9/88 (ng/ml)
0
20
40
60
80
100
120

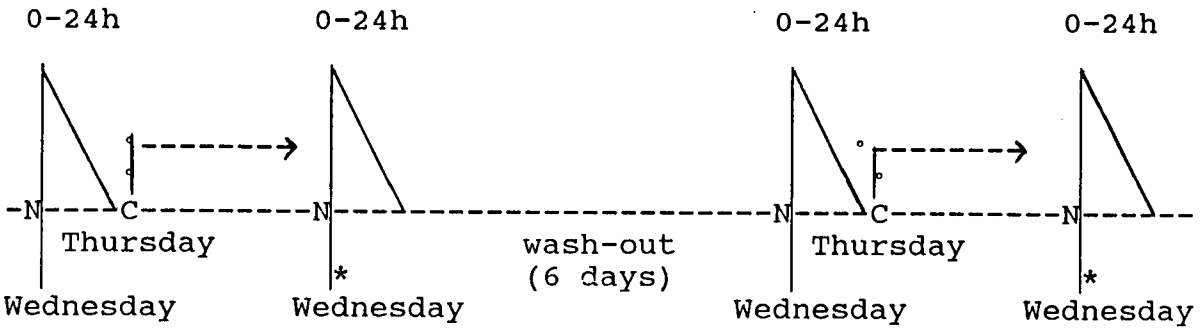
3.3 PLASMA CONCENTRATIONS AND PHARMACOKINETIC PROPERTIES OF NIFEDIPINE

The individual plasma concentrations, together with the mean and standard deviation (SD) of nifedipine, at each sampling time on profile days, are summarised in Tables 3.7 - 3.10. Mean values and the SD for the three groups (i.e. effective oxidisers + non-metabolisers, effective oxidisers and non-metabolisers of sparteine) are tabulated for all the phases (Tables 3.11 - 3.14). Values below the limit of quantitation are indicated by L.Q. (L.Q. for this study is 0.1ng/ml). The plasma concentration vs time curves of the mean values of nifedipine during the four profile days, as well as the individual plasma concentration vs time curves, are graphically presented in Fig. 3.6 - 3.31.

Although all values are given as three significant numbers, the original calculations was done on plasma concentration values which were expressed to include three decimal numbers.

The following subjects were found to be effective oxidisers of sparteine: 3, 5, 6, 7, 10, 11, 12, 15, 16 and 18, whilst the following were found to be non-metabolisers: 1, 2, 4, 8, 9, 13, 17, 19 and 20. Subject 14 was classified as a poor oxidiser of sparteine (See Table 3.1).

Fig. 3.5 : Flow-diagram of study design



N: Nifedipine 10mg
C: Cimetidine 400mg q12h x 6½ days
*: Nifedipine taken with either 200 ml water or 200 ml HCl (0.1%, 0.028M) [Randomised]

Table 3.7 NIFEDIPINE PLASMA CONCENTRATIONS (ng/ml)
PHASE 1: Nifedipine

Subj.	TIME (h)																	
No.	0	0.167	0.333	0.5	0.667	0.833	1.0	1.333	1.667	2.0	2.5	3.0	3.5	4.0	5.0	7.0	9.0	12.0
1	0.00	L.Q.	56.0	101	67.7	47.3	41.2	30.2	24.2	20.0	14.7	10.6	7.58	7.45	4.80	2.89	1.68	1.02
2	0.00	L.Q.	L.Q.	101	85.9	63.9	75.2	77.3	62.7	52.3	43.6	34.0	27.3	24.5	17.2	7.66	5.05	2.09
3	0.00	L.Q.	67.9	76.2	56.4	45.9	35.5	27.7	23.9	18.6	13.3	11.8	8.69	8.08	5.41	2.13	1.31	L.Q.
4	0.00	L.Q.	3.44	125	102	114	94.4	65.9	50.9	38.6	29.2	22.5	18.3	16.5	11.7	8.57	5.53	2.88
5	0.00	L.Q.	L.Q.	109	83.6	56.3	39.8	31.0	23.5	19.7	13.2	10.4	8.43	7.58	4.31	2.02	1.27	1.00
6	0.00	L.Q.	L.Q.	7.93	21.8	23.9	23.3	24.6	20.4	18.4	14.0	10.5	8.43	7.41	5.85	2.47	1.59	1.14
7	0.00	L.Q.	L.Q.	7.45	50.5	38.7	28.6	23.2	18.9	11.6	10.4	8.88	7.05	6.51	4.89	2.49	1.43	0.67
8	0.00	L.Q.	L.Q.	3.16	7.47	10.8	19.7	18.5	13.2	14.2	13.5	10.8	8.52	9.48	5.59	4.44	2.49	1.00
9	0.00	3.25	129	116	84.0	59.3	48.3	34.6	28.1	21.4	16.3	12.8	9.16	8.85	5.62	2.97	1.53	1.29
10	0.00	L.Q.	92.0	160	148	119	95.8	71.1	58.8	44.4	34.1	26.5	19.0	17.0	11.1	7.71	4.28	2.07
11	0.00	L.Q.	L.Q.	53.5	123	108	92.5	64.6	43.4	39.9	33.0	28.9	22.3	19.0	15.5	9.43	5.88	3.01
12	0.00	L.Q.	0.85	5.12	6.49	6.43	6.29	6.28	6.81	6.93	7.86	26.3	23.4	22.8	16.2	6.55	3.23	1.60
13	0.00	1.53	146	89.9	61.1	53.2	46.7	36.3	30.4	27.3	22.9	21.0	19.0	17.3	13.6	11.2	8.19	4.15
14	0.00	28.4	116	57.5	34.0	26.4	22.9	18.5	15.3	12.0	9.74	7.96	7.00	6.30	5.00	2.29	1.50	0.89
15	0.00	L.Q.	36.4	124	106	81.8	62.6	48.1	37.7	34.4	27.4	21.6	18.9	15.0	12.1	7.17	5.37	2.36
16	0.00	L.Q.	2.77	45.0	70.3	72.8	61.9	42.9	34.2	28.4	26.5	25.5	21.6	18.9	13.3	7.31	3.43	2.44
17	0.00	2.22	171	106	70.3	54.5	44.2	33.9	27.6	25.7	20.8	16.3	14.8	13.4	11.3	7.09	4.17	2.45
18	0.00	L.Q.	L.Q.	6.75	62.5	82.2	81.5	58.7	47.2	35.3	21.6	17.2	13.6	11.5	8.33	3.14	2.25	1.07
19	0.00	L.Q.	L.Q.	1.49	8.00	11.9	15.5	11.5	10.5	8.71	7.71	9.32	10.0	10.4	10.2	4.97	2.40	1.26
20	0.00	L.Q.	1.45	10.2	28.8	42.6	34.3	27.7	27.6	25.3	22.5	19.6	15.2	13.1	9.12	5.07	2.74	1.42
MEAN	0.00	8.85	68.5	65.3	63.9	55.9	48.5	37.6	30.3	25.1	20.1	17.6	14.4	13.1	9.54	5.39	3.27	1.78
SD	0.00	13.1	61.6	51.6	39.0	33.0	27.5	20.4	15.6	12.5	9.82	7.82	6.42	5.58	4.23	2.78	1.93	0.92
MIN	0.00	1.53	0.85	1.49	6.49	6.43	6.29	6.28	6.09	6.93	7.71	7.96	7.00	6.30	4.31	2.02	1.27	0.67
MAX	0.00	28.4	171	160	148	119	95.8	77.3	62.7	52.3	43.6	34.0	27.3	24.5	17.2	11.2	8.19	4.15
N	20	4	12	20	20	20	20	20	20	20	20	20	20	20	20	20	20	19

Table 3.8 NIFEDIPINE PLASMA CONCENTRATIONS (ng/ml)
PHASE III: Nifedipine

Subj.	TIME (h)																	
No.	0	0.167	0.333	0.5	0.667	0.833	1.0	1.333	1.667	2.0	2.5	3.0	3.5	4.0	5.0	7.0	9.0	12.0
1	0.00	L.Q.	L.Q.	25.3	32.5	33.0	30.3	25.4	18.4	15.2	13.3	19.1	18.3	17.4	12.3	5.81	3.70	2.06
2	0.00	L.Q.	L.Q.	19.9	29.7	25.0	30.4	28.2	33.4	37.5	35.5	33.1	32.4	31.4	23.4	15.4	9.36	4.92
3	0.00	L.Q.	L.Q.	5.42	21.4	26.0	26.6	24.2	20.6	16.8	14.3	13.1	11.7	12.0	13.8	6.32	3.76	1.44
4	0.00	L.Q.	L.Q.	183	130	88.4	67.8	49.8	35.2	27.0	19.9	14.7	12.6	10.4	7.23	3.41	2.22	1.09
5	0.00	13.4	151	131	91.3	69.1	58.2	43.4	35.8	26.3	19.8	15.3	12.0	11.4	6.55	3.73	2.11	1.42
6	0.00	L.Q.	L.Q.	24.9	55.7	40.9	28.6	20.5	16.8	13.4	11.0	9.25	7.29	7.28	7.29	4.41	2.84	1.90
7	0.00	L.Q.	L.Q.	0.94	8.31	17.4	17.0	13.2	10.8	9.47	9.03	10.5	11.5	11.8	12.9	8.65	4.31	1.70
8	0.00	L.Q.	L.Q.	19.5	65.3	75.3	91.6	61.8	45.0	34.1	25.1	18.2	13.5	13.9	9.58	4.87	2.80	1.44
9	0.00	L.Q.	L.Q.	80.7	138	88.0	58.7	47.8	30.7	24.0	18.3	14.3	10.7	9.47	6.19	2.56	1.69	0.67
10	0.00	L.Q.	0.69	7.64	37.0	64.4	71.0	97.3	102	82.0	64.4	46.7	39.0	33.2	23.5	13.0	8.33	3.64
11	0.00	L.Q.	L.Q.	9.35	126	113	96.2	68.3	54.3	43.0	33.4	28.2	23.7	20.4	16.3	8.80	5.64	2.89
12	0.00	L.Q.	L.Q.	1.30	12.6	20.0	22.1	19.8	17.6	16.0	15.4	16.6	16.0	16.6	17.9	7.77	3.95	1.70
13	0.00	L.Q.	53.1	164	126	85.2	65.8	51.5	44.3	39.5	35.8	30.6	27.8	23.8	19.5	14.4	11.6	6.67
14	0.00	L.Q.	62.6	153	90.5	60.0	46.5	33.5	28.3	23.5	17.5	14.3	12.1	10.2	8.17	4.42	2.13	1.49
15	0.00	L.Q.	76.8	102	82.5	65.3	53.1	48.2	38.8	33.5	29.0	23.7	20.0	17.4	13.2	7.90	5.01	2.51
16	0.00	L.Q.	L.Q.	41.0	99.5	102	110	74.9	47.8	39.7	29.6	21.6	15.1	12.5	9.47	5.30	3.08	2.01
17	0.00	L.Q.	L.Q.	94.6	122	83.4	60.5	43.5	33.7	27.4	22.1	19.0	16.8	14.9	12.1	7.18	5.04	2.64
18	0.00	L.Q.	2.57	119	130	92.1	73.6	49.5	39.4	27.6	19.8	16.7	12.8	11.3	7.70	4.02	2.62	1.20
19	0.00	L.Q.	L.Q.	107	96.8	60.4	47.8	32.5	24.3	20.6	16.6	13.2	10.3	8.21	5.63	2.42	1.07	L.Q.
20	0.00	L.Q.	70.0	119	84.4	66.6	54.5	39.2	29.7	26.5	18.7	14.1	12.4	10.5	6.32	3.31	2.11	1.39
MEAN	0.00	13.4	59.6	70.5	79.1	63.8	55.5	43.6	35.4	29.2	23.4	19.6	16.8	15.2	12.0	6.68	4.17	2.25
SD	0.00	0.00	50.9	61.4	43.6	28.5	25.5	20.8	19.4	15.6	12.4	9.05	8.12	7.16	5.64	3.80	2.75	1.46
MIN	0.00	0.00	0.69	0.94	8.31	17.4	17.0	13.2	10.8	9.47	9.03	9.25	7.29	7.28	5.63	2.42	1.07	0.67
MAX	0.00	13.4	151	183	138	113	110	97.3	102	82.0	64.4	46.7	39.0	33.2	23.5	15.4	11.6	6.67
N	20	1	7	20	20	20	20	20	20	20	20	20	20	20	20	20	20	19

Table 3.9 NIFEDIPINE PLASMA CONCENTRATIONS (ng/ml)
Nifedipine + Cimetidine

Subj.	TIME (h)																	
No.	0	0.167	0.333	0.5	0.667	0.833	1.0	1.333	1.667	2.0	2.5	3.0	3.5	4.0	5.0	7.0	9.0	12.0
1	0.00	L.Q.	L.Q.	8.86	10.6	13.8	16.4	21.4	37.8	45.7	43.6	34.7	27.9	23.3	16.4	9.59	6.00	3.66
2	0.00	L.Q.	73.8	243	156	117	99.4	80.0	64.1	56.3	45.3	38.6	29.5	29.0	20.9	10.6	7.37	3.95
3	0.00	L.Q.	40.5	148	114	86.6	72.4	53.0	43.6	35.2	28.7	21.3	15.7	16.8	10.7	5.84	2.63	1.92
4	0.00	L.Q.	4.49	122	184	129	99.9	89.4	71.2	64.5	55.8	47.6	39.4	35.8	26.3	16.7	11.1	6.26
5	0.00	L.Q.	91.0	115	90.7	66.2	59.2	45.4	36.6	27.6	24.0	21.4	17.2	14.8	9.00	5.09	3.39	1.75
6	0.00	L.Q.	L.Q.	55.0	83.5	55.7	42.2	35.0	26.5	22.1	18.3	16.0	13.2	11.8	9.80	6.19	3.33	2.10
7	0.00	L.Q.	L.Q.	3.10	17.2	32.4	47.2	38.2	32.5	31.4	24.4	22.2	19.6	20.6	23.2	11.3	6.86	3.13
8	0.00	L.Q.	L.Q.	14.1	110	75.7	48.8	35.6	32.2	27.6	24.2	19.7	18.0	14.6	14.1	9.37	4.51	2.12
9	0.00	L.Q.	L.Q.	44.4	192	142	115	94.0	74.3	64.9	49.0	38.5	33.2	27.3	21.7	11.2	6.91	3.93
10	0.00	L.Q.	2.14	20.1	99.3	204	193	128	108	87.4	67.0	58.2	46.2	41.1	31.4	19.0	10.9	5.62
11	0.00	L.Q.	36.4	189	126	88.4	73.6	55.3	47.7	39.5	31.6	28.1	22.3	19.4	15.8	9.03	6.05	3.30
12	0.00	L.Q.	15.7	111	118	101	87.9	65.6	49.7	42.0	36.9	29.9	27.2	23.0	18.1	11.1	5.08	2.41
13	0.00	L.Q.	L.Q.	132	130	94.2	70.1	49.5	48.0	40.4	36.5	33.3	28.7	24.6	19.8	16.1	12.4	5.71
14	0.00	L.Q.	215	116	80.8	62.9	46.9	37.3	34.1	32.7	26.8	20.0	17.3	14.0	11.3	6.19	4.64	2.62
15	0.00	L.Q.	L.Q.	174	130	101	75.6	57.7	52.3	43.8	33.8	29.2	24.4	20.9	18.6	10.9	7.90	4.26
16	0.00	L.Q.	29.5	143	154	130	94.9	67.5	52.9	50.6	37.2	32.2	27.2	24.4	16.9	10.8	6.99	3.71
17	0.00	L.Q.	L.Q.	10.8	24.8	24.0	21.2	20.5	31.9	34.6	38.9	36.8	32.7	26.9	21.6	13.7	8.66	4.38
18	0.00	L.Q.	L.Q.	55.2	122	141	109	79.2	67.3	56.2	40.3	36.6	29.5	24.0	19.4	10.6	5.57	3.24
19	0.00	L.Q.	42.0	144	104	77.8	64.6	48.6	37.5	30.1	26.5	21.3	16.7	15.5	13.1	5.99	3.49	1.15
20	0.00	L.Q.	156	147	105	81.6	68.9	52.4	44.2	39.2	29.5	22.8	18.5	14.8	11.6	6.03	3.91	2.31
MEAN	0.00	0.00	64.3	99.8	108	91.2	75.3	57.7	49.6	43.6	35.9	30.4	25.2	22.1	17.5	10.3	6.38	3.38
SD	0.00	0.00	67.0	69.1	48.8	45.2	38.8	26.4	19.4	15.9	12.0	10.6	8.57	7.54	5.84	3.88	2.76	1.40
MIN	0.00	0.00	2.14	3.10	10.6	13.8	16.4	20.5	26.5	22.1	18.3	16.0	13.2	11.8	8.97	5.09	2.63	1.15
MAX	0.00	0.00	215	243	192	204	193	128	108	87.4	67.0	58.2	46.2	41.1	31.4	19.0	12.4	6.26
N	20	0	11	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20

Table 3.10 NIFEDIPINE PLASMA CONCENTRATIONS (ng/ml)
Nifedipine + Cimetidine + HCl

Subj.	TIME (h)																	
No.	0	0.167	0.333	0.5	0.667	0.833	1.0	1.333	1.667	2.0	2.5	3.0	3.5	4.0	5.0	7.0	9.0	12.0
1	0.00	L.Q.	L.Q.	19.8	43.1	42.5	40.6	48.2	53.5	51.0	46.4	39.0	32.2	25.4	17.6	9.43	5.61	3.29
2	0.00	L.Q.	177	166	118	92.5	78.4	59.5	51.2	46.6	38.2	31.3	26.8	23.3	14.6	9.51	5.58	2.71
3	0.00	L.Q.	0.75	23.5	92.9	112	84.4	61.0	46.6	37.6	28.9	22.4	18.3	15.7	12.1	5.63	4.23	1.80
4	0.00	0.49	339	203	162	132	117	86.9	75.1	58.7	46.2	40.1	34.7	32.5	24.7	19.1	11.9	5.73
5	0.00	L.Q.	L.Q.	40.9	114	117	94.0	64.5	49.4	44.0	29.8	27.0	22.6	18.8	9.73	6.26	3.84	1.58
6	0.00	L.Q.	2.01	75.1	64.4	43.4	35.0	27.1	27.7	24.5	20.0	18.2	16.3	15.6	12.5	8.64	4.73	2.42
7	0.00	L.Q.	9.57	99.6	74.1	58.7	50.1	39.4	31.0	27.6	23.2	18.1	13.7	12.6	10.2	5.55	3.78	1.63
8	0.00	L.Q.	L.Q.	88.2	131	88.0	59.4	44.7	41.0	31.7	23.0	21.8	15.3	13.6	11.1	5.90	3.83	1.65
9	0.00	L.Q.	L.Q.	6.94	20.9	23.8	21.5	24.8	26.8	24.7	20.9	18.9	17.3	15.5	12.3	7.43	5.01	3.51
10	0.00	L.Q.	L.Q.	7.82	24.1	47.2	65.5	61.9	63.2	58.2	56.4	52.5	47.2	47.1	27.3	15.2	10.7	5.05
11	0.00	L.Q.	L.Q.	15.1	104	113	94.9	65.4	53.3	52.3	45.7	39.3	33.6	31.6	23.7	14.7	10.0	5.51
12	0.00	L.Q.	L.Q.	33.0	44.6	37.0	35.2	37.2	34.5	46.3	44.4	45.5	38.8	36.5	29.1	14.6	7.99	3.81
13	0.00	L.Q.	L.Q.	5.95	18.8	13.9	12.6	11.5	9.44	8.52	9.75	13.8	22.5	30.9	29.0	26.6	23.4	13.3
14	0.00	L.Q.	176	111	62.9	45.1	37.7	30.0	24.9	22.7	18.7	13.6	10.9	9.42	8.08	4.54	2.54	1.58
15	0.00	L.Q.	L.Q.	29.5	51.7	57.7	57.8	61.4	52.8	50.0	44.3	41.3	32.3	27.3	22.6	17.1	10.8	4.12
16	0.00	L.Q.	5.19	85.4	143	138	114.4	98.7	75.1	63.9	43.9	34.9	32.3	27.4	21.8	12.1	6.40	3.37
17	0.00	L.Q.	L.Q.	54.3	155	112	81.8	56.4	43.6	35.5	27.9	24.6	22.3	19.4	15.5	8.33	6.05	3.79
18	0.00	0.44	1.41	24.4	83.9	101	98.3	89.4	74.7	62.9	49.7	43.1	35.4	29.1	18.8	11.6	5.79	2.54
19	0.00	L.Q.	L.Q.	3.82	10.2	15.5	15.0	20.7	18.4	16.9	20.1	19.2	18.0	18.6	19.1	10.7	6.78	4.07
20	0.00	L.Q.	6.86	112	99.1	77.7	73.5	63.3	54.7	48.1	38.7	29.1	24.0	21.4	14.6	8.02	4.54	2.51
MEAN	0.00	0.46	79.7	60.2	80.9	73.4	63.4	52.6	45.3	40.6	33.8	29.7	25.7	23.6	17.7	11.0	7.17	3.70
SD	0.00	0.03	122	56.2	46.9	39.6	32.0	23.5	18.8	16.0	13.1	11.6	9.68	9.35	6.67	5.52	4.64	2.60
MIN	0.00	0.44	0.75	3.82	10.2	13.9	12.6	11.5	9.44	8.52	9.75	13.6	10.9	9.42	8.08	4.54	2.54	1.58
MAX	0.00	0.49	339	203	162	138	117	98.7	75.1	63.9	56.4	52.5	47.2	47.1	29.1	26.6	23.4	13.3
N	20	2	9	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20

Table 3.11 **NIFEDIPINE PLASMA CONCENTRATIONS (ng/ml)**
PHASE I: Nifedipine

Time (h)	EO + NM *			EO *			NM *		
	Mean	SD	N	Mean	SD	N	Mean	SD	N
0.00	0.00	0.00	20	0.00	0.00	10	0.00	0.00	9
0.17	8.85	13.1	4	L.Q.	-	10	2.33	0.87	3
0.33	68.5	61.6	12	40.0	40.1	5	84.4	74.1	6
0.50	65.3	51.6	20	59.6	56.2	10	72.6	51.7	9
0.67	63.9	39.0	20	72.9	43.8	10	57.3	34.6	9
0.83	55.9	33.0	20	63.5	35.9	10	50.8	30.5	9
1.00	48.5	27.5	20	52.8	30.8	10	46.6	25.0	9
1.33	37.6	20.4	20	39.8	20.8	10	37.3	21.2	9
1.67	30.3	15.6	20	31.5	15.6	10	30.6	16.6	9
2.00	25.1	12.5	20	25.8	12.5	10	25.9	13.0	9
2.50	20.1	9.81	20	20.2	9.63	10	21.2	10.5	9
3.00	17.6	7.82	20	18.7	7.88	10	17.4	7.88	9
3.50	14.4	6.42	20	15.1	6.58	10	14.4	6.46	9
4.00	13.1	5.58	20	13.4	5.91	10	13.4	5.35	9
5.00	9.54	4.23	20	9.68	4.51	10	9.89	4.12	9
7.00	5.39	2.78	20	5.07	2.81	10	6.09	2.75	9
9.00	3.27	1.93	20	3.00	1.72	10	3.75	2.19	9
12.00	1.78	0.92	19	1.71	0.80	9	1.95	1.06	9

*
EO = Effective oxidisers of sparteine
NM = Non-metabolisers of sparteine

Table 3.12 **NIFEDIPINE PLASMA CONCENTRATIONS (ng/ml)**
PHASE III: Nifedipine

Time (h)	EO + NM *			EO *			NM *		
	Mean	SD	N	Mean	SD	N	Mean	SD	N
0.00	0.00	0.00	20	0.00	0.00	10	0.00	0.00	9
0.17	13.4	0.00	1	13.4	0.00	1	0.00	0.00	0
0.33	59.6	50.9	7	57.8	71.6	4	61.5	12.0	2
0.50	70.5	61.4	20	44.3	52.4	10	90.5	60.9	9
0.67	79.1	43.6	20	66.5	45.9	10	91.9	41.8	9
0.83	63.8	28.5	20	61.1	34.5	10	67.3	23.8	9
1.00	55.5	25.5	20	55.6	32.3	10	56.4	19.1	9
1.33	43.6	20.8	20	45.9	27.6	10	42.2	12.0	9
1.67	35.4	19.5	20	38.4	26.7	10	32.8	8.52	9
2.00	29.2	15.6	20	30.8	21.3	10	28.0	7.89	9
2.50	23.4	12.4	20	24.6	16.2	10	22.8	7.99	9
3.00	19.6	9.05	20	20.2	11.0	10	19.6	7.34	9
3.50	16.8	8.12	20	16.9	9.04	10	17.2	7.86	9
4.00	15.2	7.16	20	15.4	7.29	10	15.6	7.66	9
5.00	12.0	5.64	20	12.9	5.39	10	11.4	6.30	9
7.00	6.68	3.80	20	6.99	2.84	10	6.59	4.95	9
9.00	4.17	2.75	20	4.16	1.83	10	4.40	3.69	9
12.00	2.25	1.46	19	2.04	0.76	10	2.61	2.10	8

*
EO = Effective oxidisers of sparteine
NM = Non-metabolisers of sparteine

Table 3.13 **NIFEDIPINE PLASMA CONCENTRATIONS (ng/ml)**
Nifedipine + Cimetidine

Time (h)	EO + NM *			EO *			NM *		
	Mean	SD	N	Mean	SD	N	Mean	SD	N
0.00	0.00	0.00	20	0.00	0.00	10	0.00	0.00	9
0.17	0.00	0.00	0	L.Q.	-	10	L.Q.	-	9
0.33	64.3	67.0	11	35.9	30.5	6	69.2	64.7	4
0.50	99.8	69.1	20	101	64.7	10	96.2	81.1	9
0.67	107	48.8	20	106	37.2	10	113	63.1	9
0.83	91.2	45.2	20	101	48.8	10	83.8	43.5	9
1.00	75.3	38.8	20	85.5	43.1	10	67.2	34.4	9
1.33	57.7	26.4	20	62.5	26.6	10	54.6	27.6	9
1.67	49.6	19.4	20	51.7	22.8	10	49.0	16.7	9
2.00	43.6	15.9	20	43.6	18.5	10	44.8	14.1	9
2.50	35.9	12.0	20	34.2	13.4	10	38.8	10.7	9
3.00	30.4	10.6	20	29.5	11 8	10	32.6	9.40	9
3.50	25.2	8.57	20	24.3	9.41	10	27.2	7.85	9
4.00	22.1	7.54	20	21.7	7.94	10	23.5	7.30	9
5.00	17.5	5.84	20	17.3	6.76	10	18.4	4.86	9
7.00	10.3	3.88	20	9.99	3.98	10	11.0	3.88	9
9.00	6.38	2.76	20	5.87	2.49	10	7.15	3.12	9
12.00	3.38	1.40	20	3.14	1.19	10	3.72	1.66	9

*
EO = Effective oxidisers of sparteine
NM = Non-metabolisers of sparteine

Table 3.14 **NIFEDIPINE PLASMA CONCENTRATIONS (ng/ml)**
Nifedipine + Cimetidine + HCl

Time (h)	EO + NM *			EO *			NM *		
	Mean	SD	N	Mean	SD	N	Mean	SD	N
0.00	0.00	0.00	20	0.00	0.00	10	0.00	0.00	9
0.17	0.46	0.03	2	0.44	0.00	1	0.49	0.00	1
0.33	79.7	122	9	3.79	3.65	5	174	166	3
0.50	60.2	56.2	20	43.4	31.7	10	73.3	74.3	9
0.67	80.9	46.9	20	79.7	35.6	10	84.1	61.2	9
0.83	73.4	39.6	20	82.5	37.2	10	66.4	43.8	9
1.00	63.4	32.0	20	73.0	28.1	10	55.6	35.8	9
1.33	52.6	23.5	20	60.6	22.2	10	46.2	23.8	9
1.67	45.3	18.8	20	50.8	16.8	10	41.5	20.4	9
2.00	40.6	16.0	20	46.7	13.7	10	35.8	16.8	9
2.50	33.8	13.1	20	38.6	12.2	10	30.1	12.8	9
3.00	29.7	11.6	20	34.2	12.2	10	26.4	9.14	9
3.50	25.7	9.68	20	29.0	10.9	10	23.7	6.63	9
4.00	23.6	9.34	20	26.2	10.8	10	22.3	6.44	9
5.00	17.7	6.67	20	18.8	7.19	10	17.6	5.88	9
7.00	11.1	5.52	20	11.1	4.33	10	11.7	6.74	9
9.00	7.17	4.64	20	6.82	2.84	10	8.07	6.19	9
12.00	3.70	2.60	20	3.18	1.42	10	4.51	3.49	9

*
EO = Effective oxidisers of sparteine
NM = Non-metabolisers of sparteine

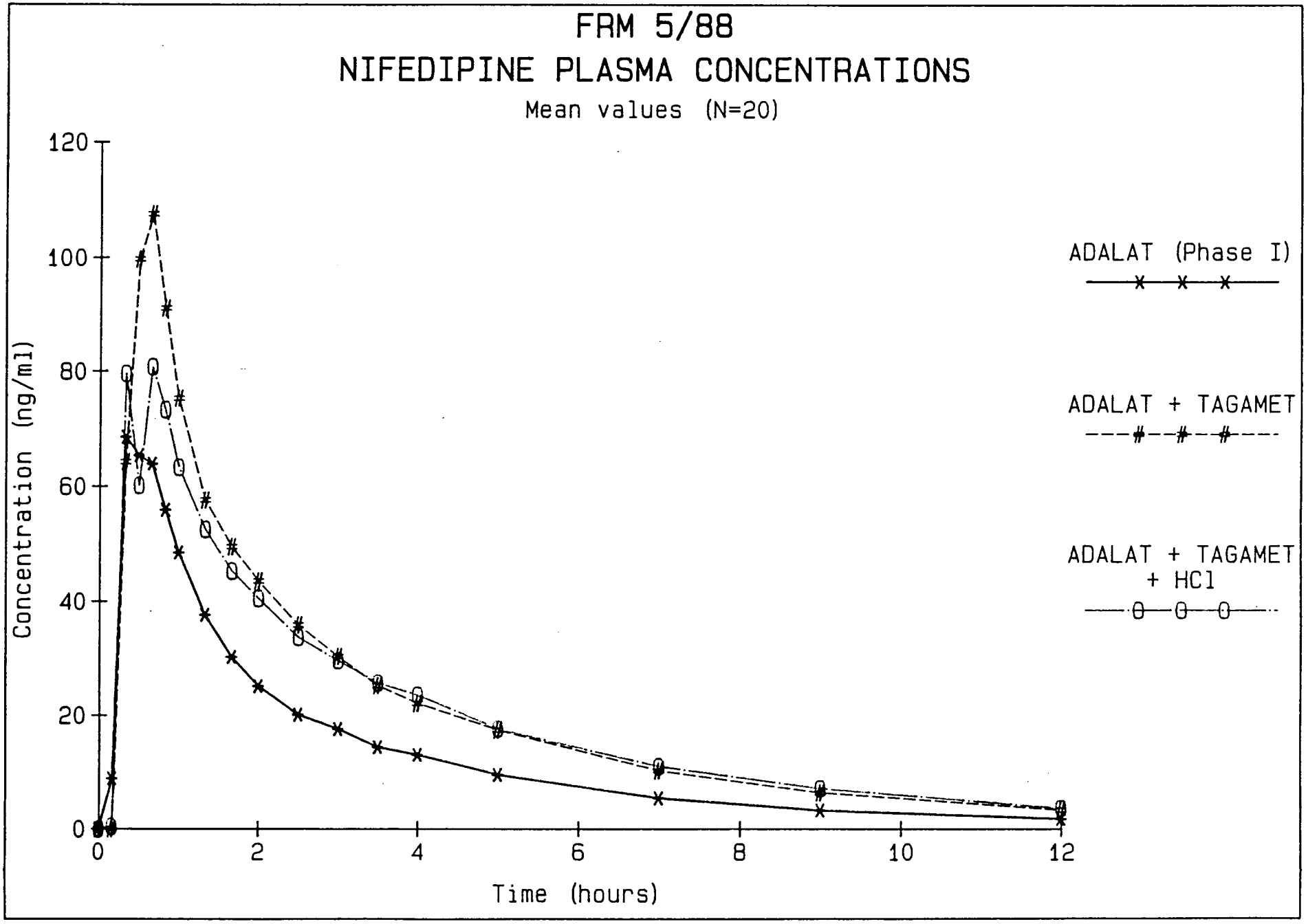

FRM 5/88
NIFEDIPINE PLASMA CONCENTRATIONS
Mean values (N=20)
Concentration (ng/ml)
120
100
80
60
40
20
0
0
2
4
6
8
10
12
Time (hours)
ADALAT (Phase I)
ADALAT + TAGAMET
ADALAT + TAGAMET + HCl

Fig. 3.6 (a)

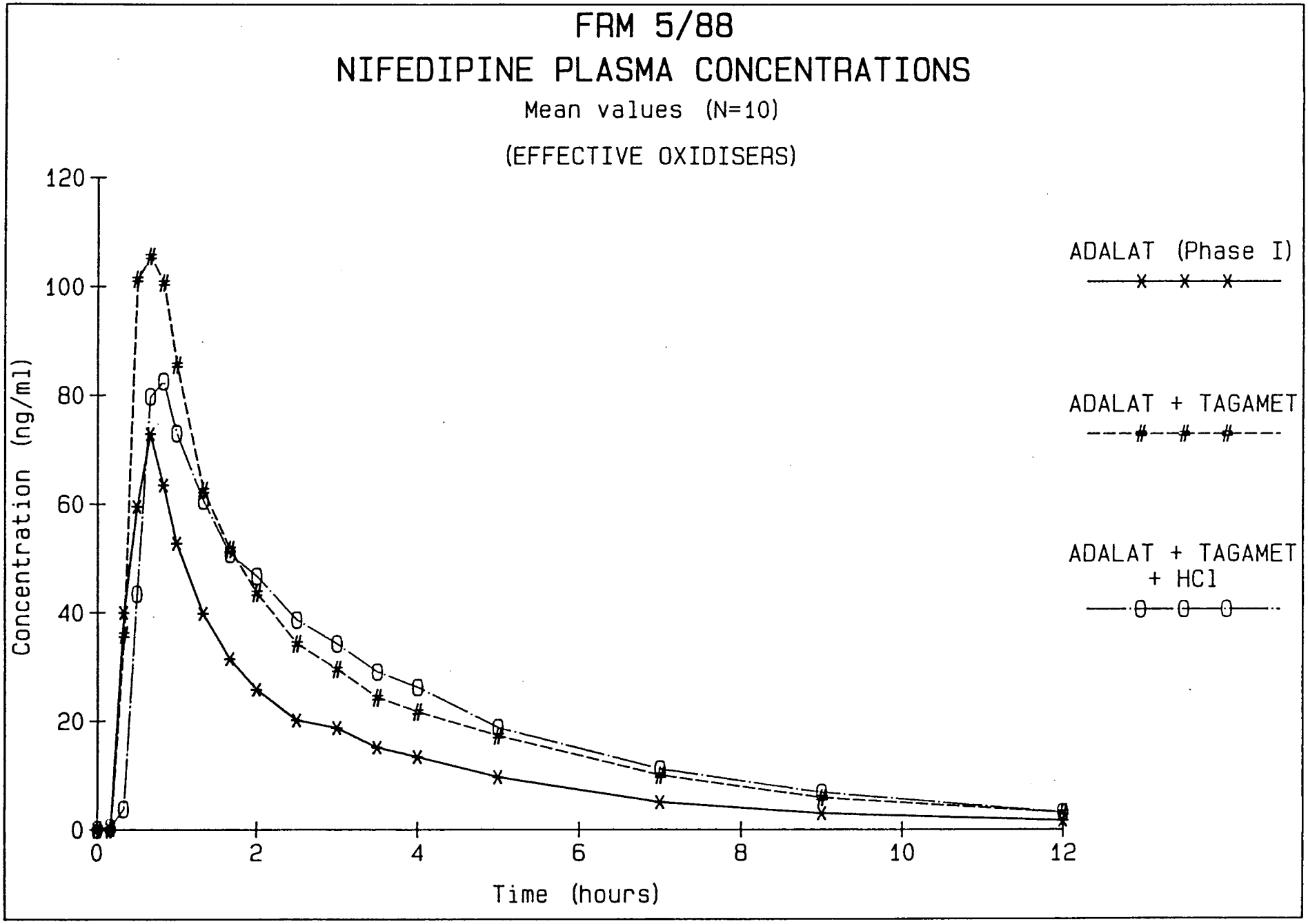

FRM 5/88
NIFEDIPINE PLASMA CONCENTRATIONS
Mean values (N=10)
(EFFECTIVE OXIDISERS)
Concentration (ng/ml)
120
100
80
60
40
20
0
0
2
4
6
8
10
12
Time (hours)
ADALAT (Phase I)
ADALAT + TAGAMET
ADALAT + TAGAMET + HCl

Fig. 3.6 (b)

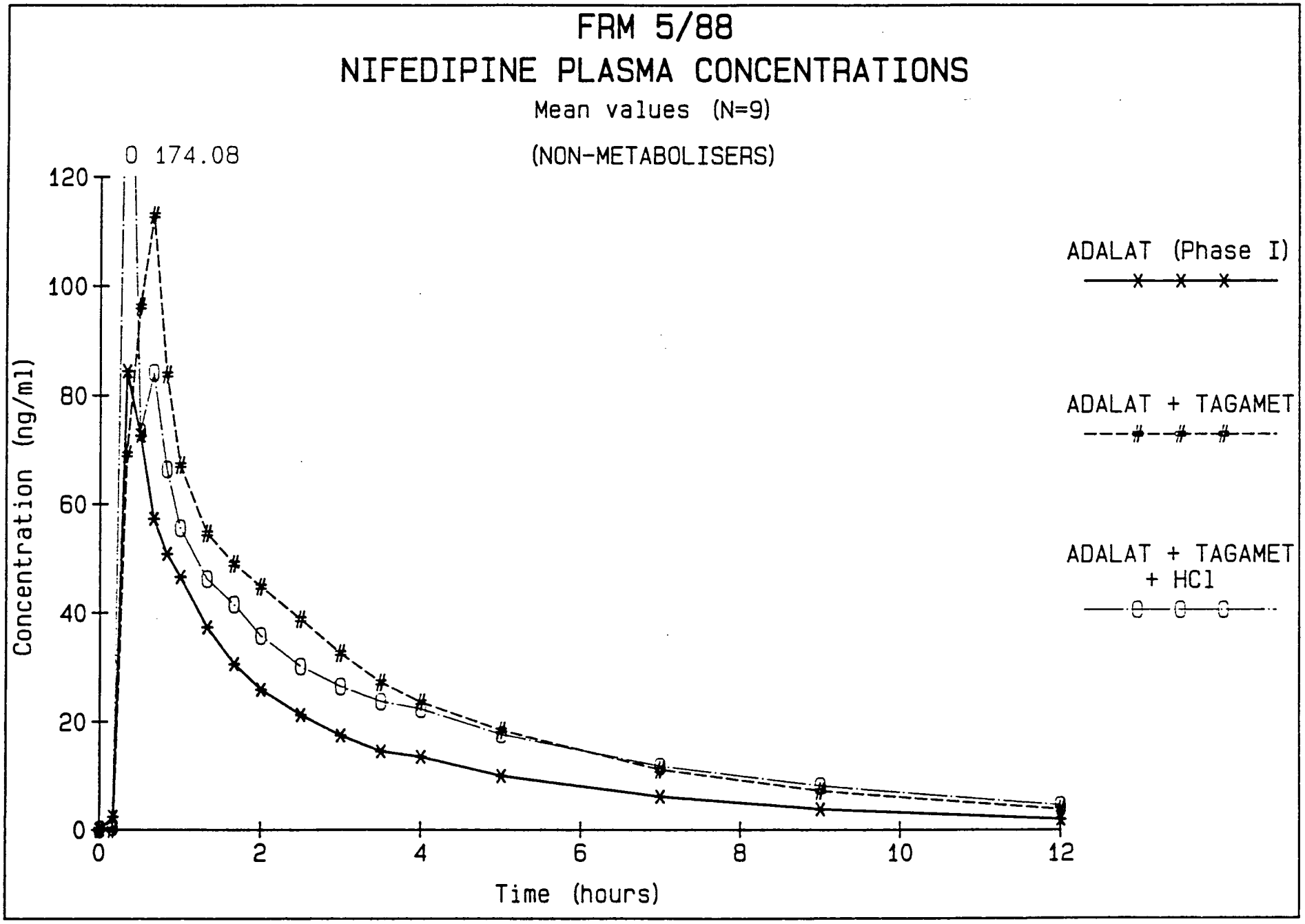

FRM 5/88
NIFEDIPINE PLASMA CONCENTRATIONS
Mean values (N=9)
(NON-METABOLISERS)
0 174.08
Concentration (ng/ml)
120
100
80
60
40
20
0
0
2
4
6
8
10
12
Time (hours)
ADALAT (Phase I)
ADALAT + TAGAMET
ADALAT + TAGAMET + HCl

Fig. 3.6 (c)

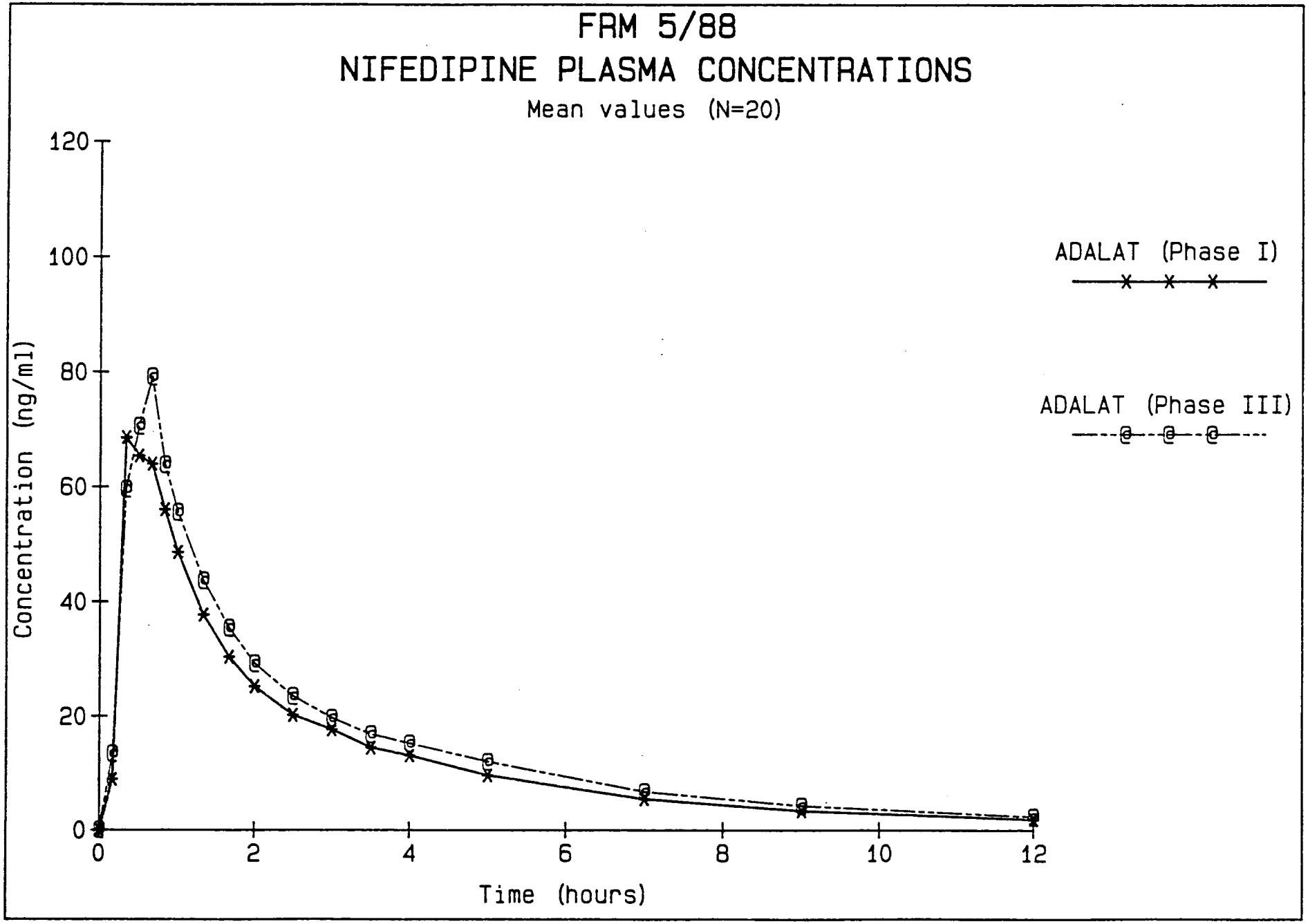

FRM 5/88
NIFEDIPINE PLASMA CONCENTRATIONS
Mean values (N=20)
Concentration (ng/ml)
120
100
80
60
40
20
0
0
2
4
6
8
10
12
Time (hours)
ADALAT (Phase I)
ADALAT (Phase III)

Fig. 3.7 (a)

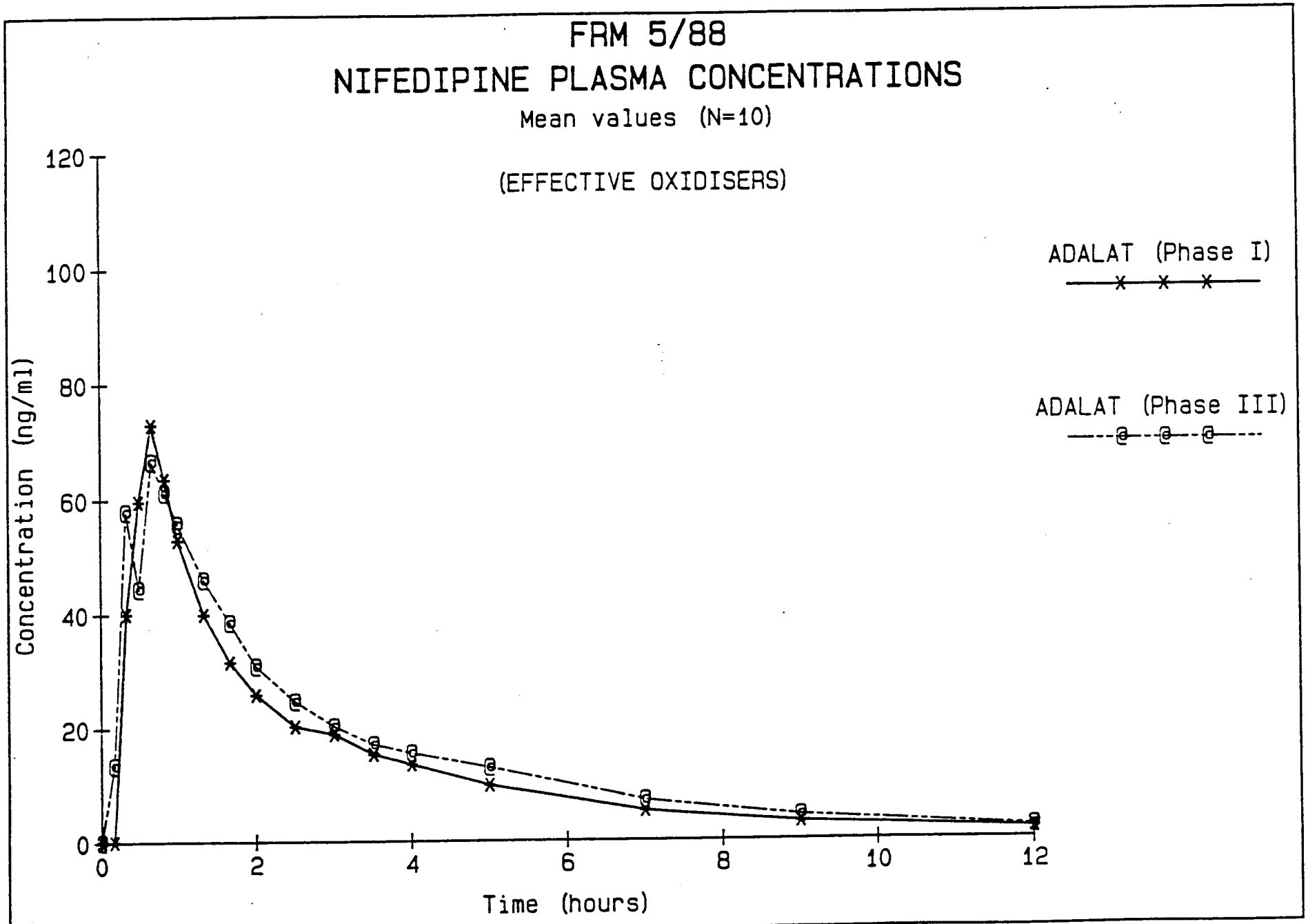

FRM 5/88
NIFEDIPINE PLASMA CONCENTRATIONS
Mean values (N=10)
(EFFECTIVE OXIDISERS)
ADALAT (Phase I)
ADALAT (Phase III)
Concentration (ng/ml)
120
100
80
60
40
20
0
0
2
4
6
8
10
12
Time (hours)

Fig. 3.7 (b)

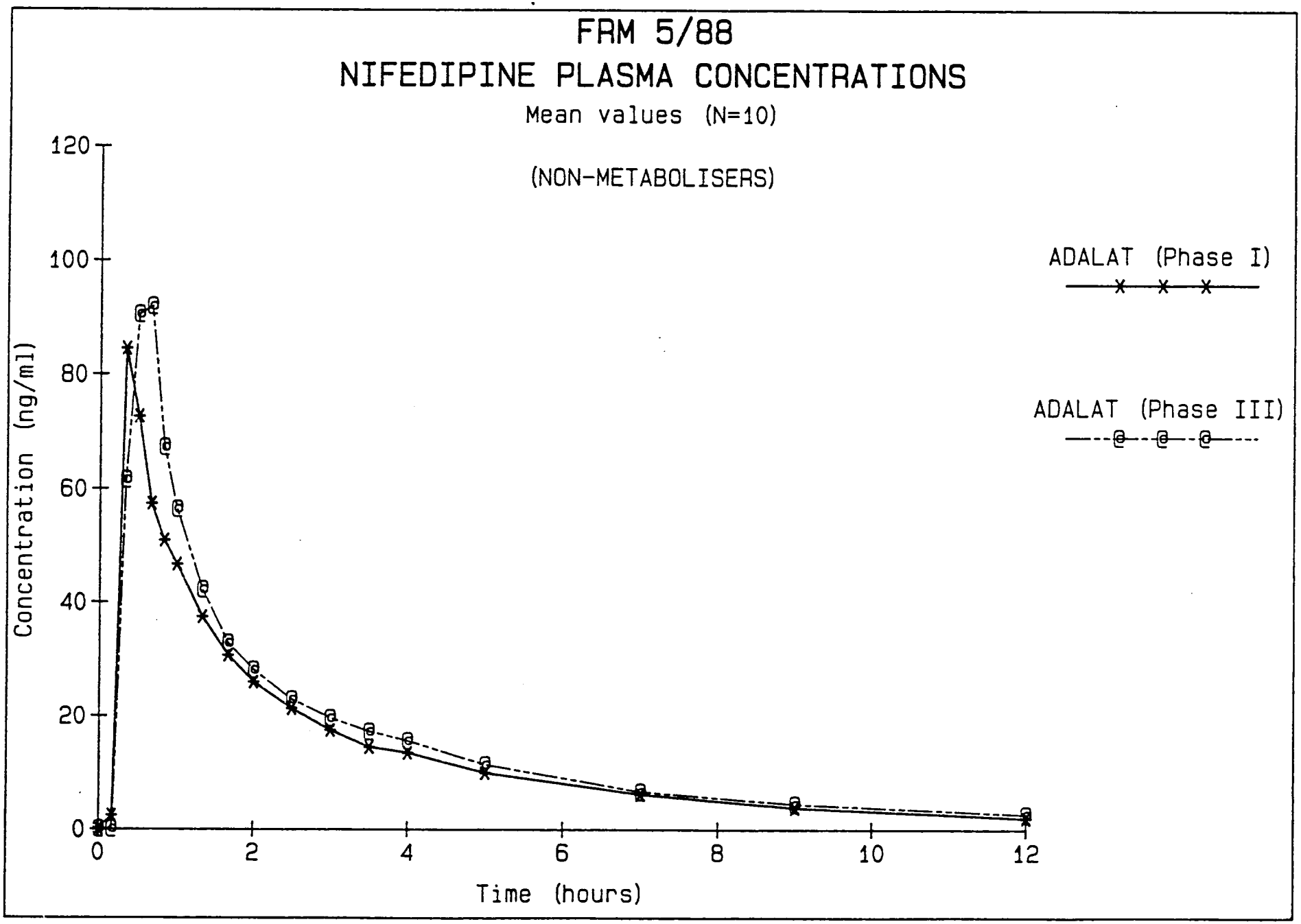
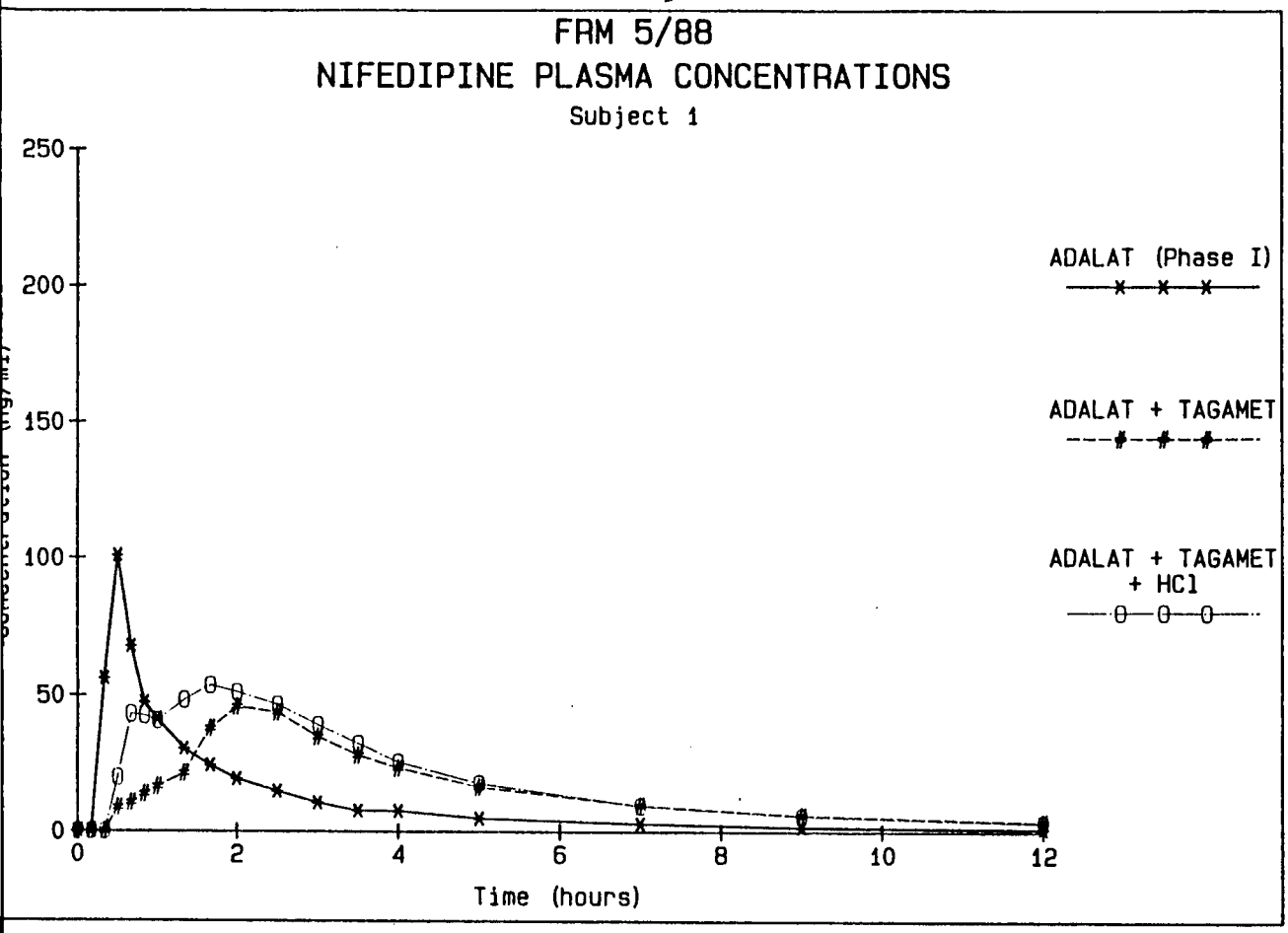

FRM 5/88
NIFEDIPINE PLASMA CONCENTRATIONS
Mean values (N=10)
(NON-METABOLISERS)
ADALAT (Phase I)
ADALAT (Phase III)
Concentration (ng/ml)
120
100
80
60
40
20
0
0
2
4
6
8
10
12
Time (hours)

Fig. 3.7 (c)

Fig. 3.8


FRM 5/88
NIFEDIPINE PLASMA CONCENTRATIONS
Subject 1
250
200
150
100
50
0
0
2
4
6
8
10
12
Time (hours)
ADALAT (Phase I)
ADALAT + TAGAMET
ADALAT + TAGAMET + HCl

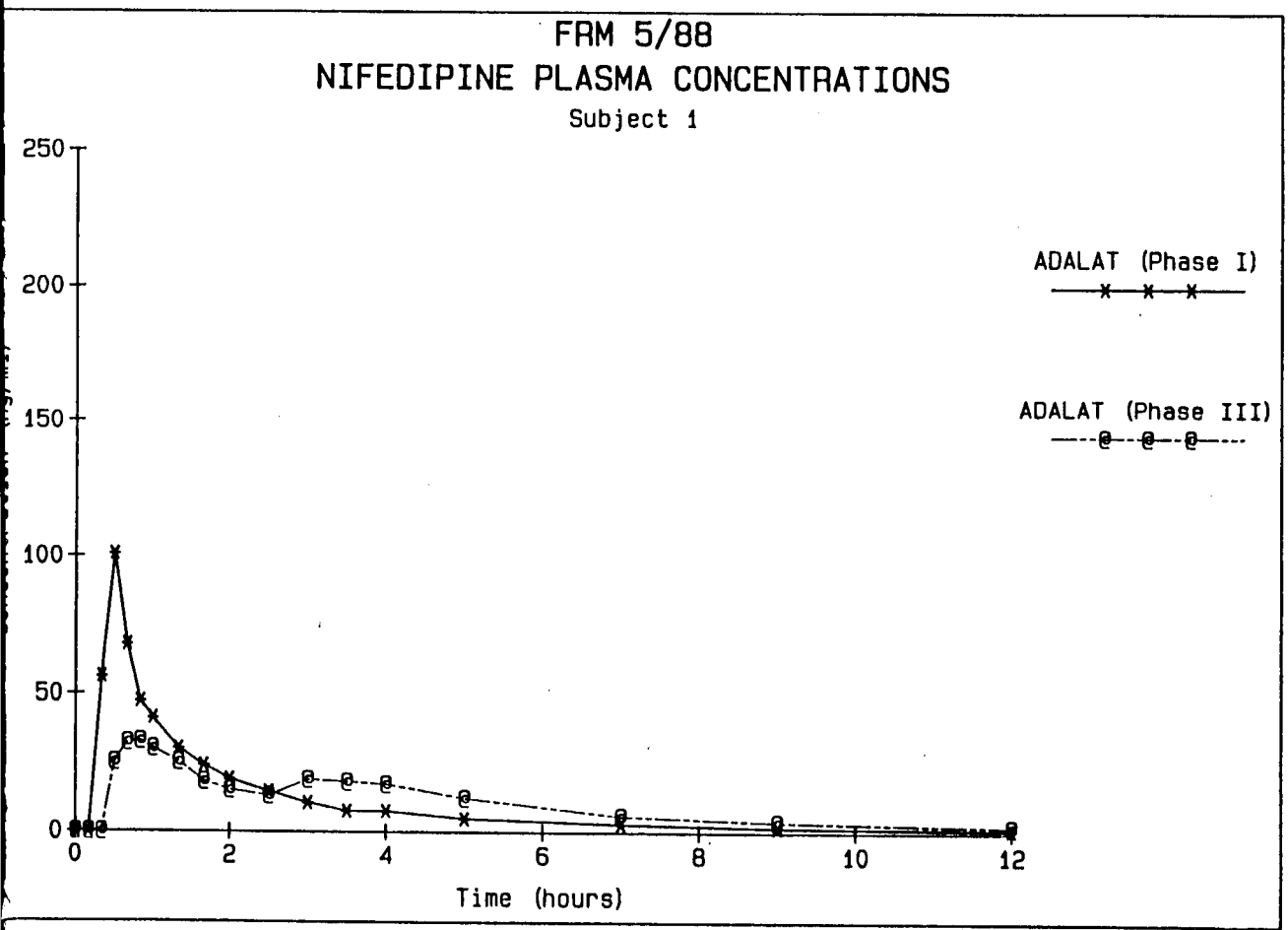
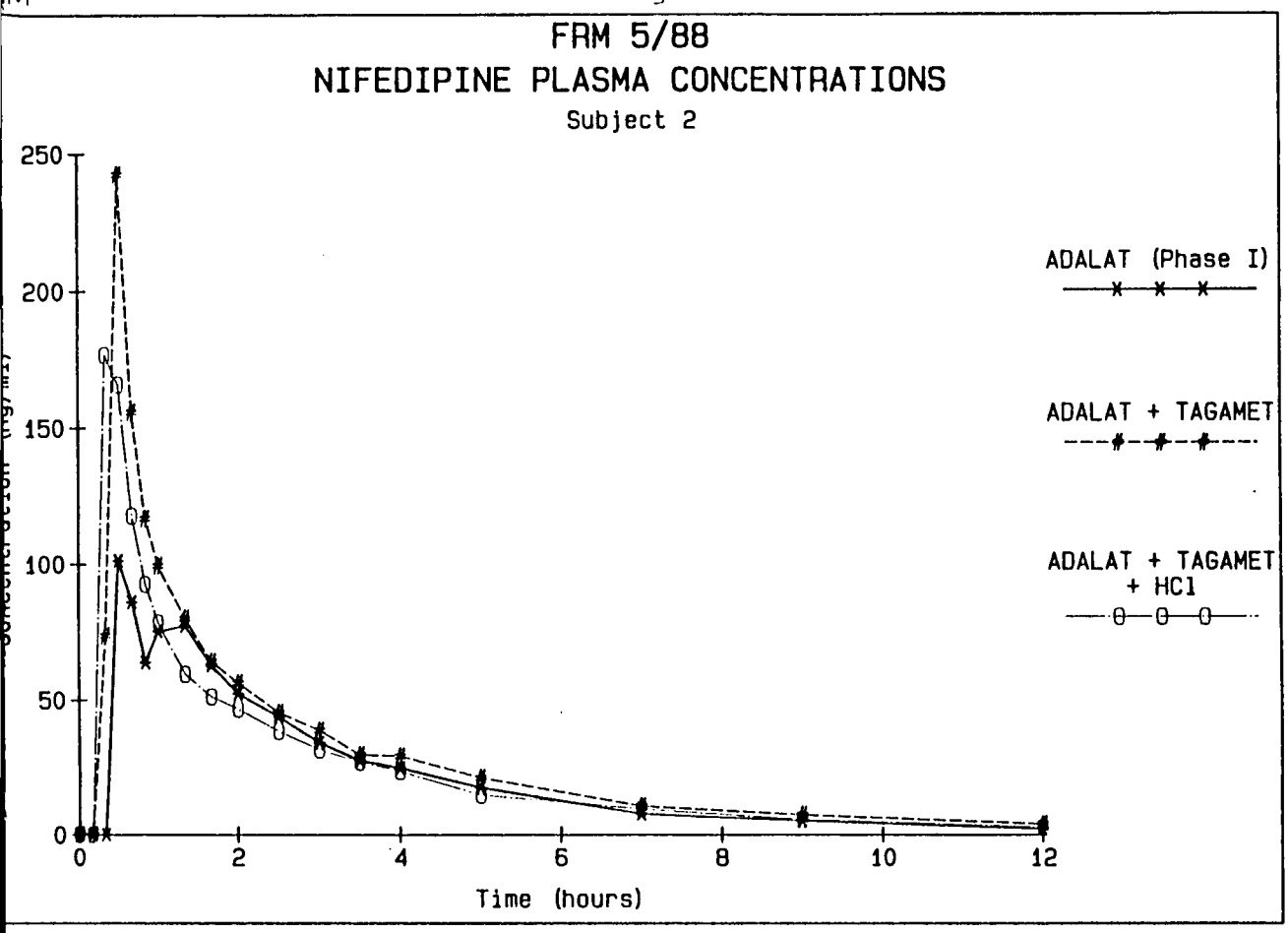

FRM 5/88
NIFEDIPINE PLASMA CONCENTRATIONS
Subject 1
250
200
150
100
50
0
0
2
4
6
8
10
12
Time (hours)
ADALAT (Phase I)
ADALAT (Phase III)

Fig. 3.9


FRM 5/88
NIFEDIPINE PLASMA CONCENTRATIONS
Subject 2
250
200
150
100
50
0
0
2
4
6
8
10
12
Time (hours)
ADALAT (Phase I)
ADALAT + TAGAMET
ADALAT + TAGAMET + HCl

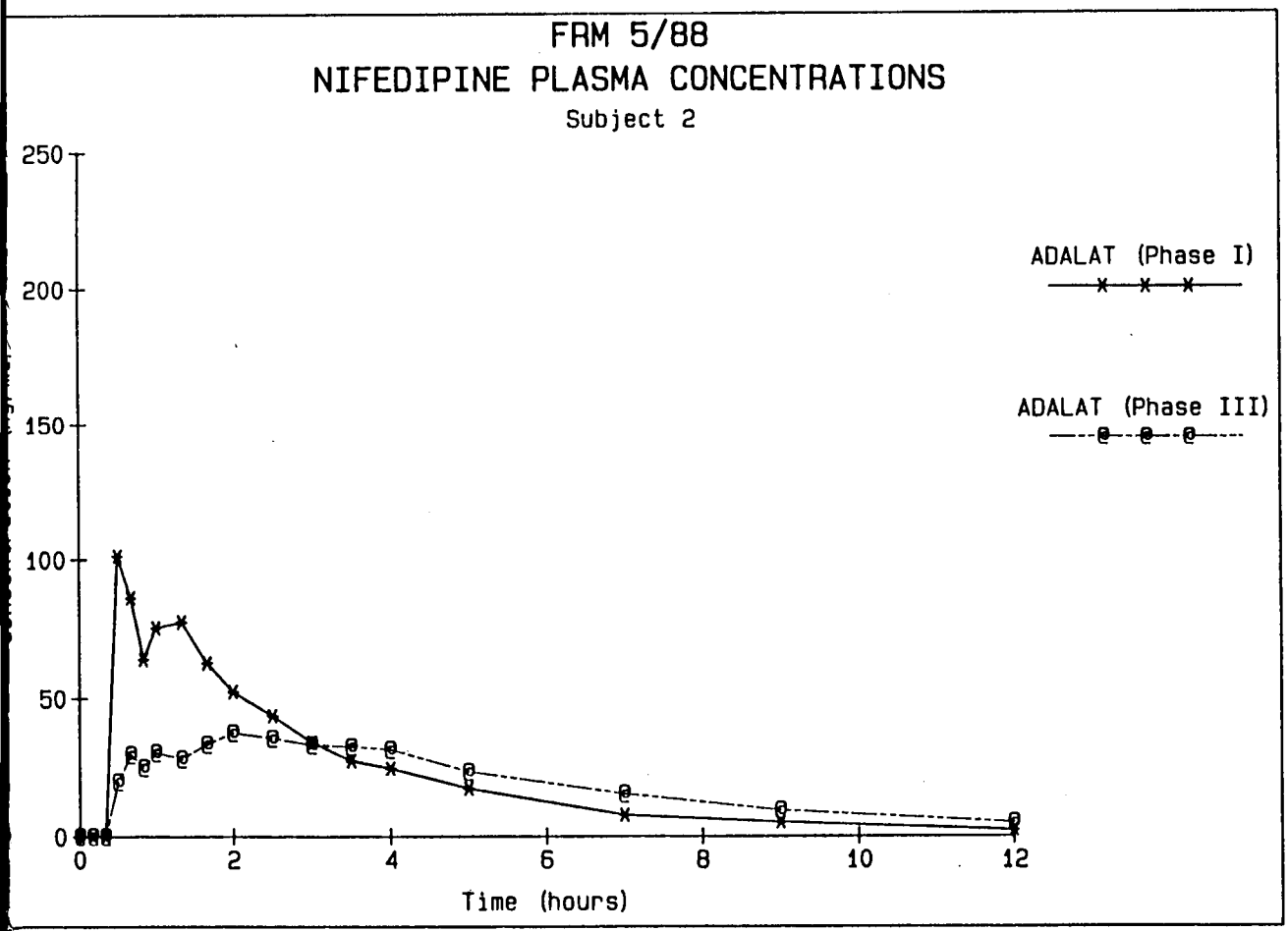
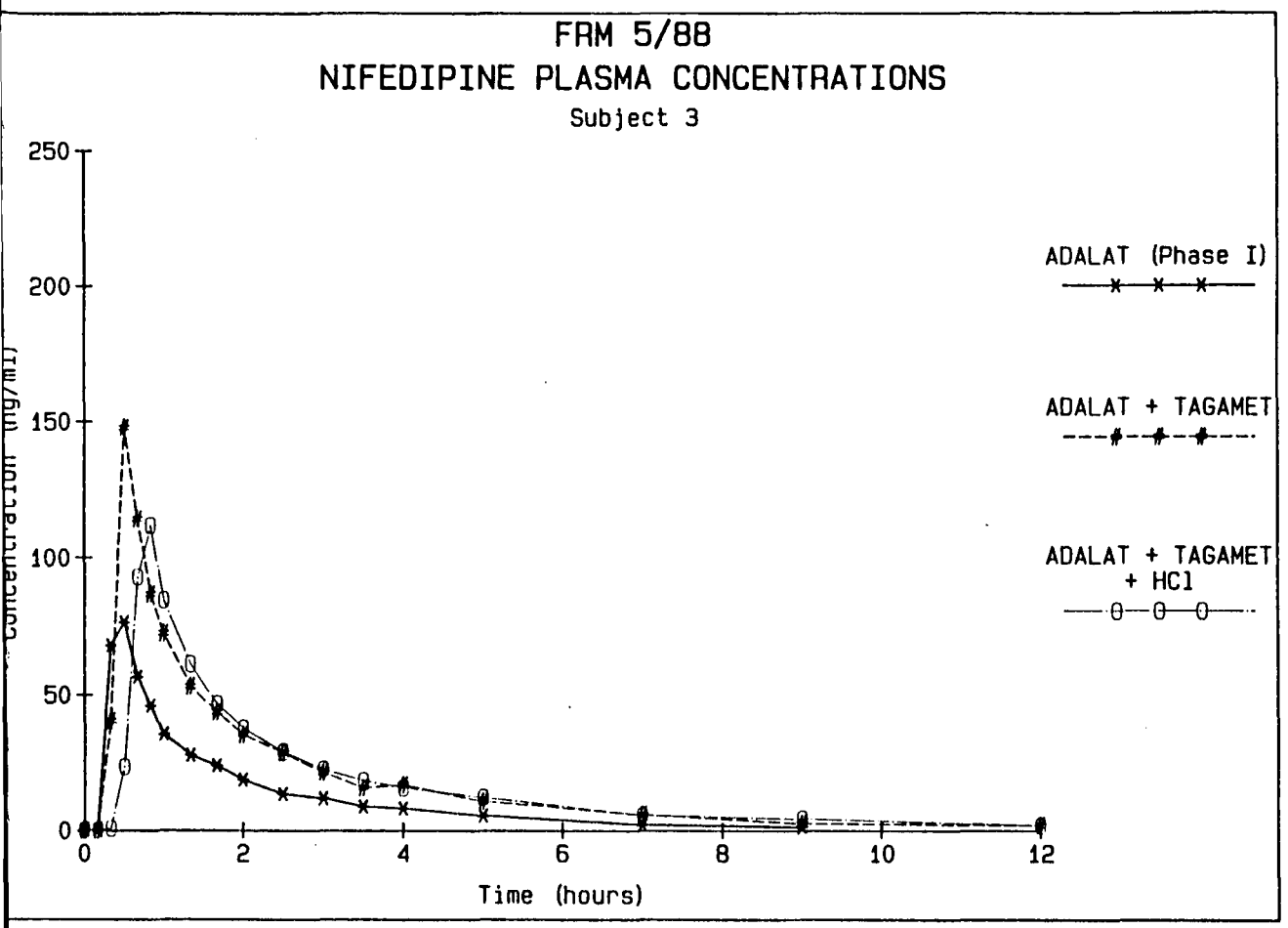
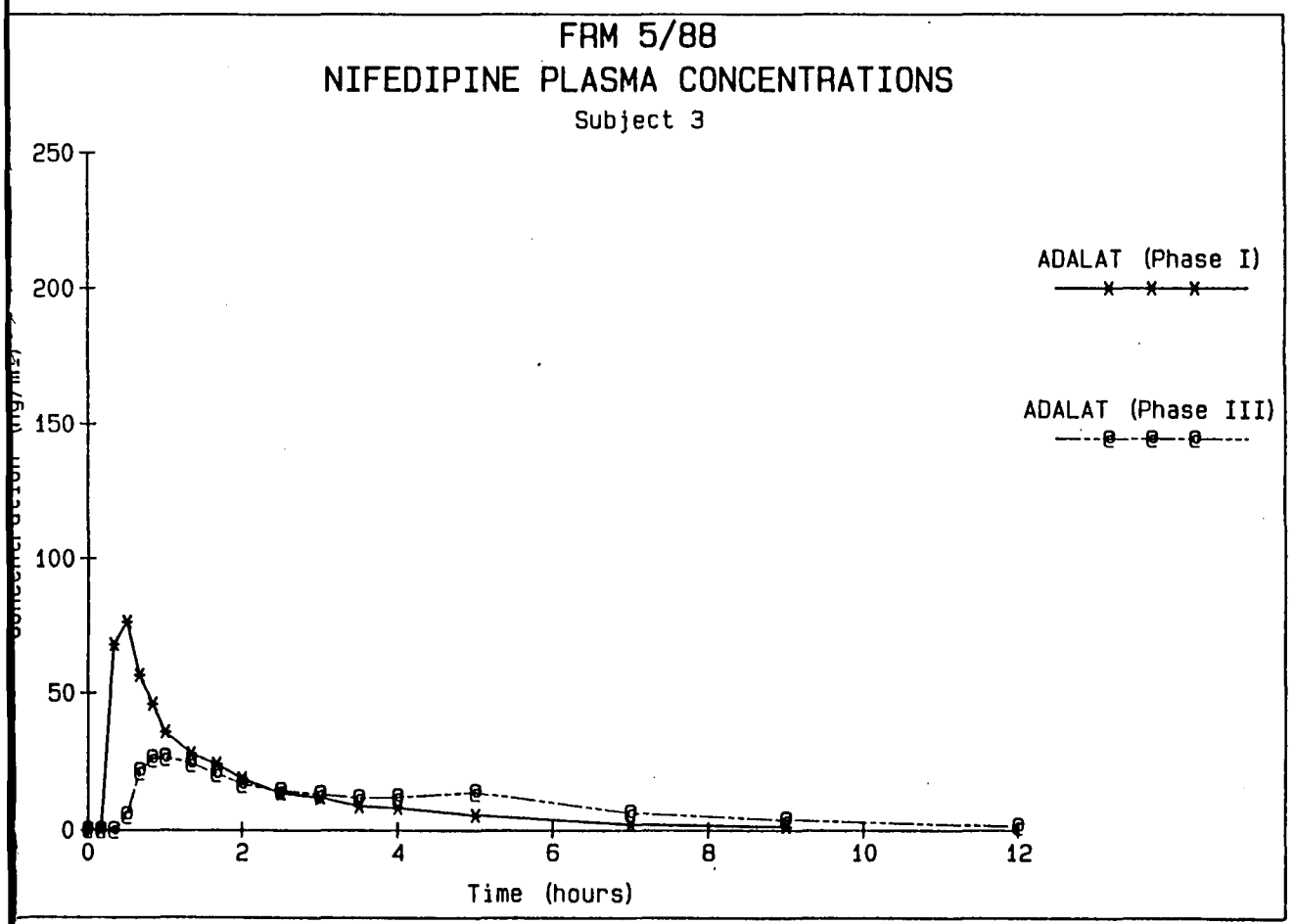

FRM 5/88
NIFEDIPINE PLASMA CONCENTRATIONS
Subject 2
250
200
150
100
50
0
0
2
4
6
8
10
12
Time (hours)
ADALAT (Phase I)
ADALAT (Phase III)

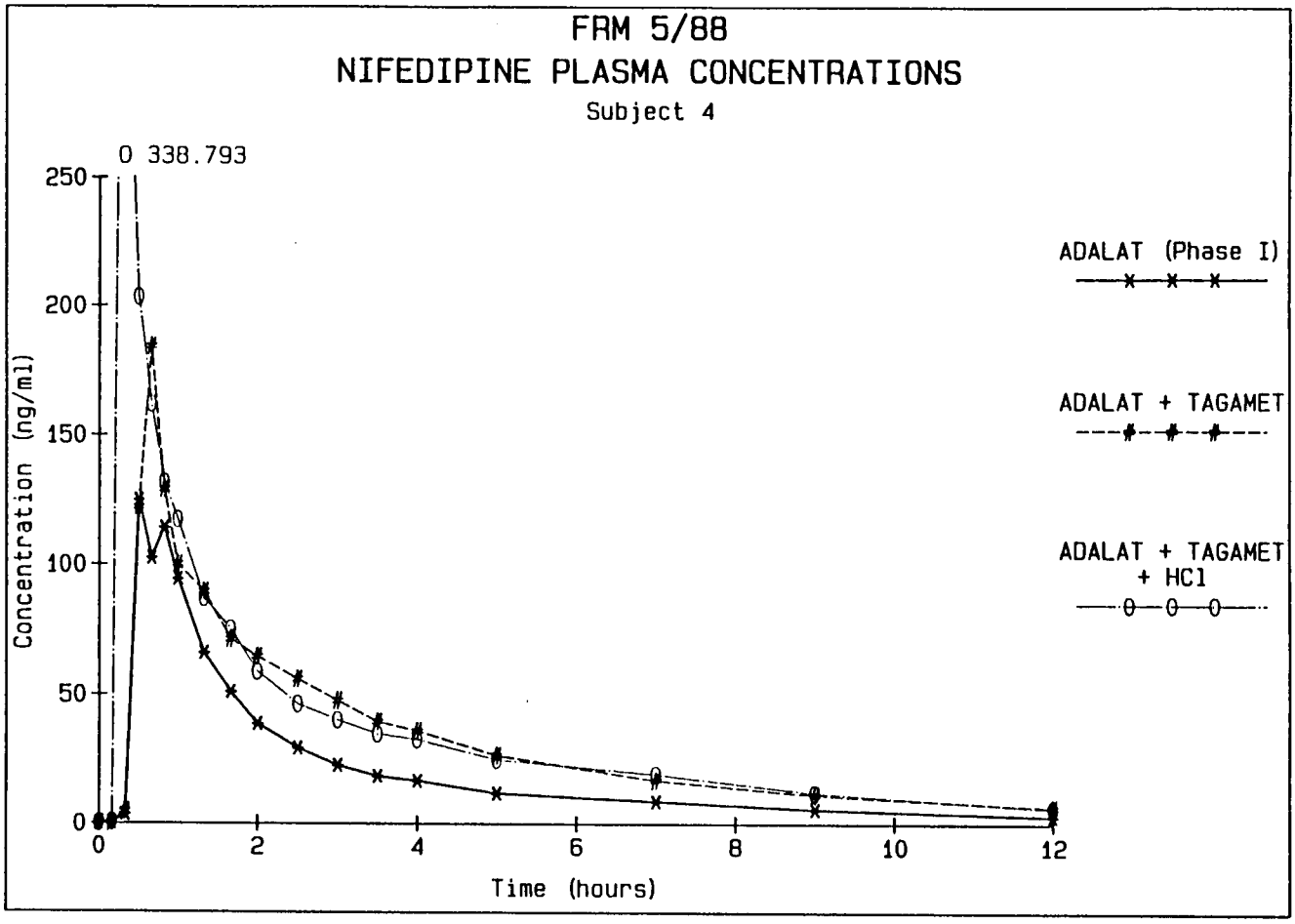
Fig. 3.10


FRM 5/88
NIFEDIPINE PLASMA CONCENTRATIONS
Subject 3
250
200
150
100
50
0
0
2
4
6
8
10
12
Time (hours)
ADALAT (Phase I)
ADALAT + TAGAMET
ADALAT + TAGAMET + HCl


FRM 5/88
NIFEDIPINE PLASMA CONCENTRATIONS
Subject 3
250
200
150
100
50
0
0
2
4
6
8
10
12
Time (hours)
ADALAT (Phase I)
ADALAT (Phase III)

NM

Fig. 3.11


FRM 5/88
NIFEDIPINE PLASMA CONCENTRATIONS
Subject 4
0 338.793
250
200
150
100
50
0
Concentration (ng/ml)
0
2
4
6
8
10
12
Time (hours)
ADALAT (Phase I)
ADALAT + TAGAMET
ADALAT + TAGAMET + HCl

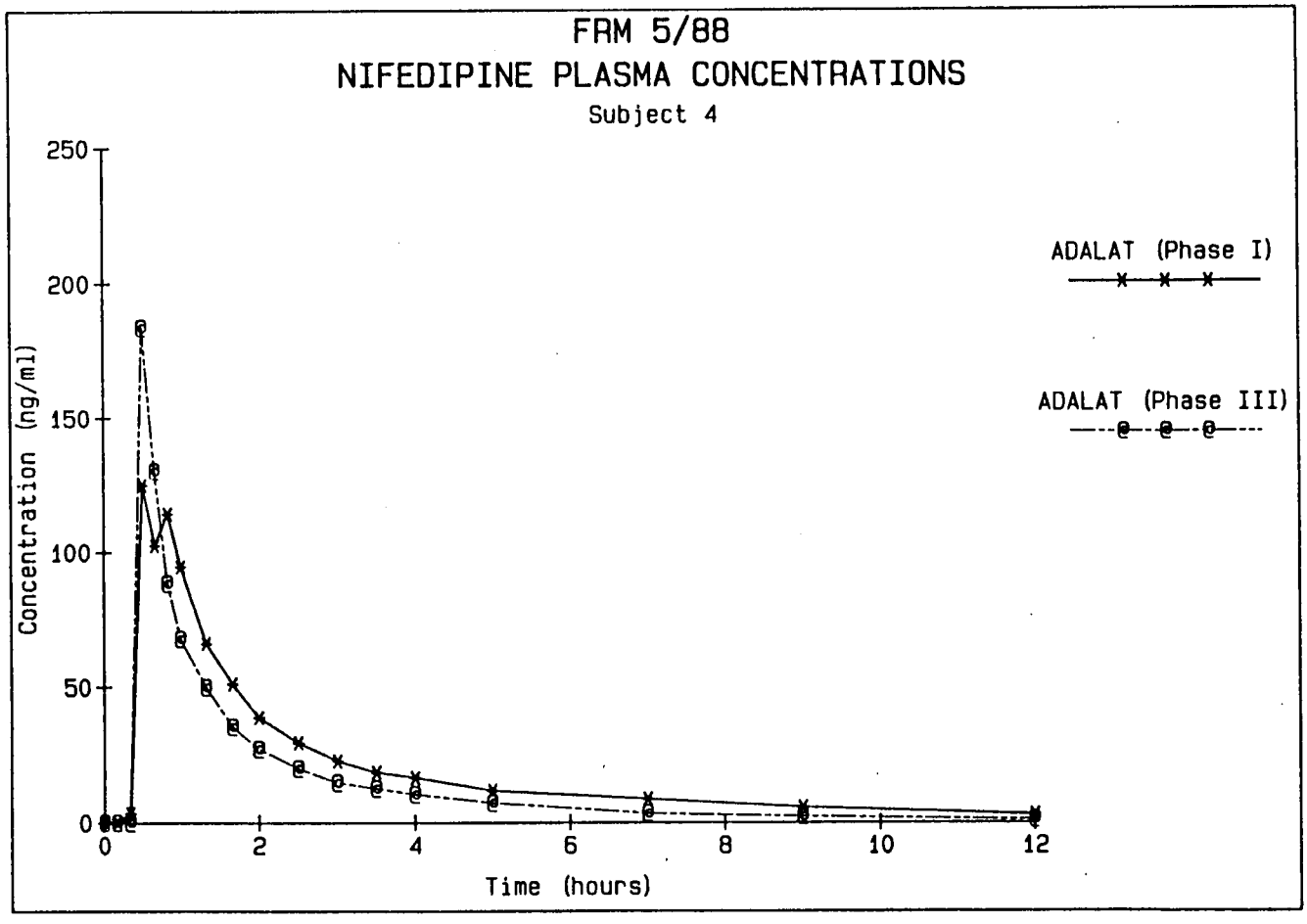
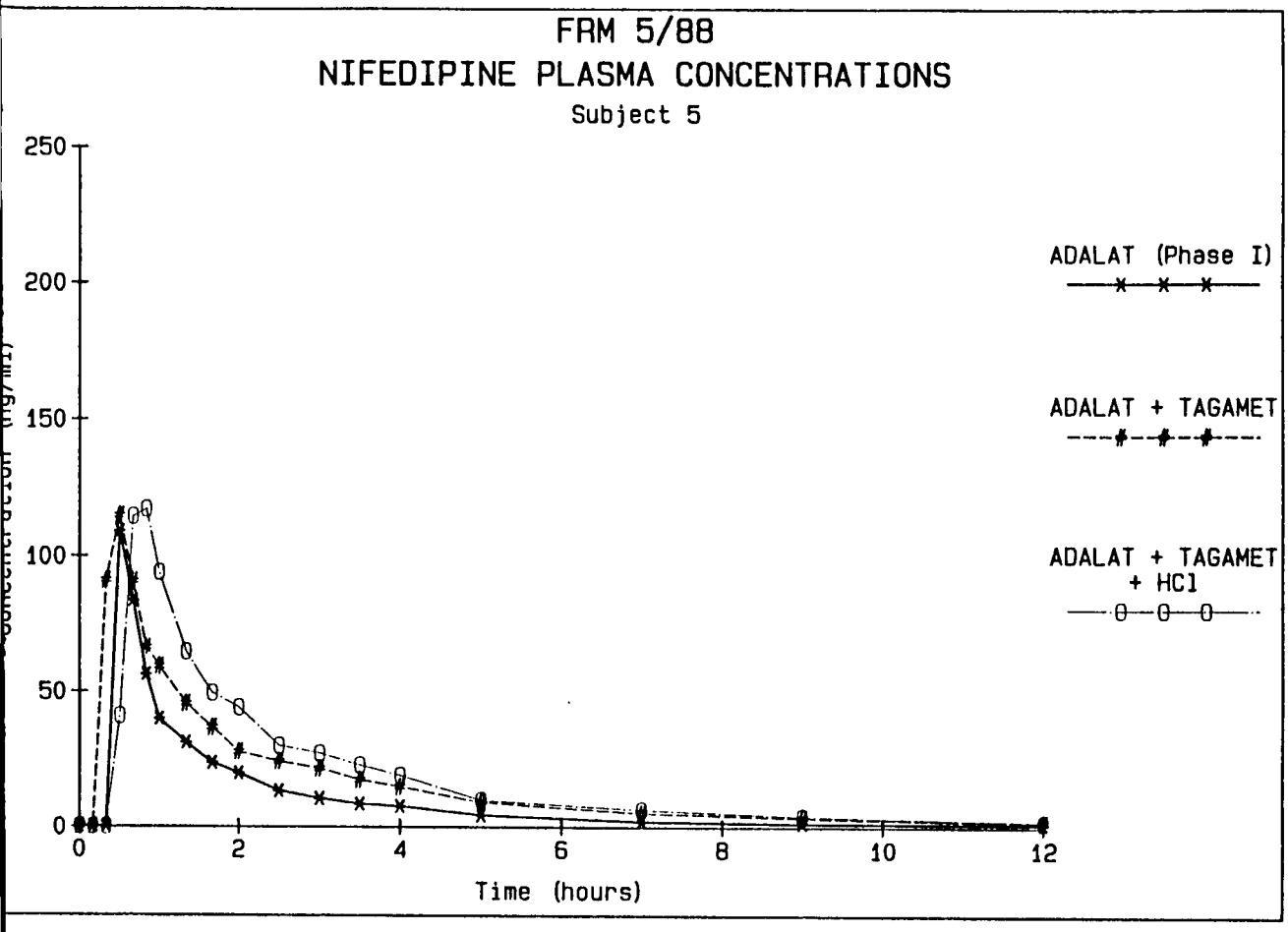
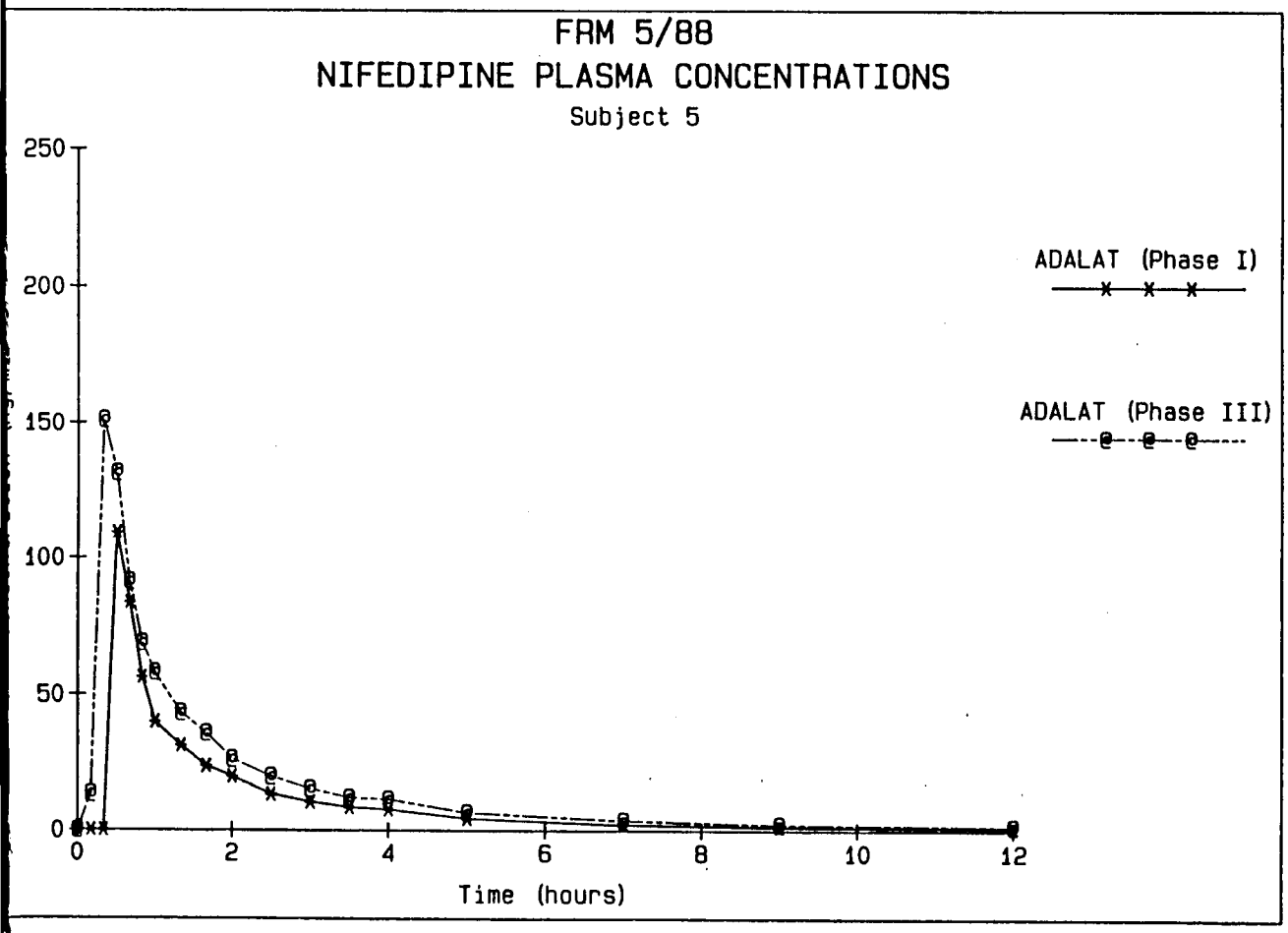

FRM 5/88
NIFEDIPINE PLASMA CONCENTRATIONS
Subject 4
250
200
150
100
50
0
Concentration (ng/ml)
0
2
4
6
8
10
12
Time (hours)
ADALAT (Phase I)
ADALAT (Phase III)

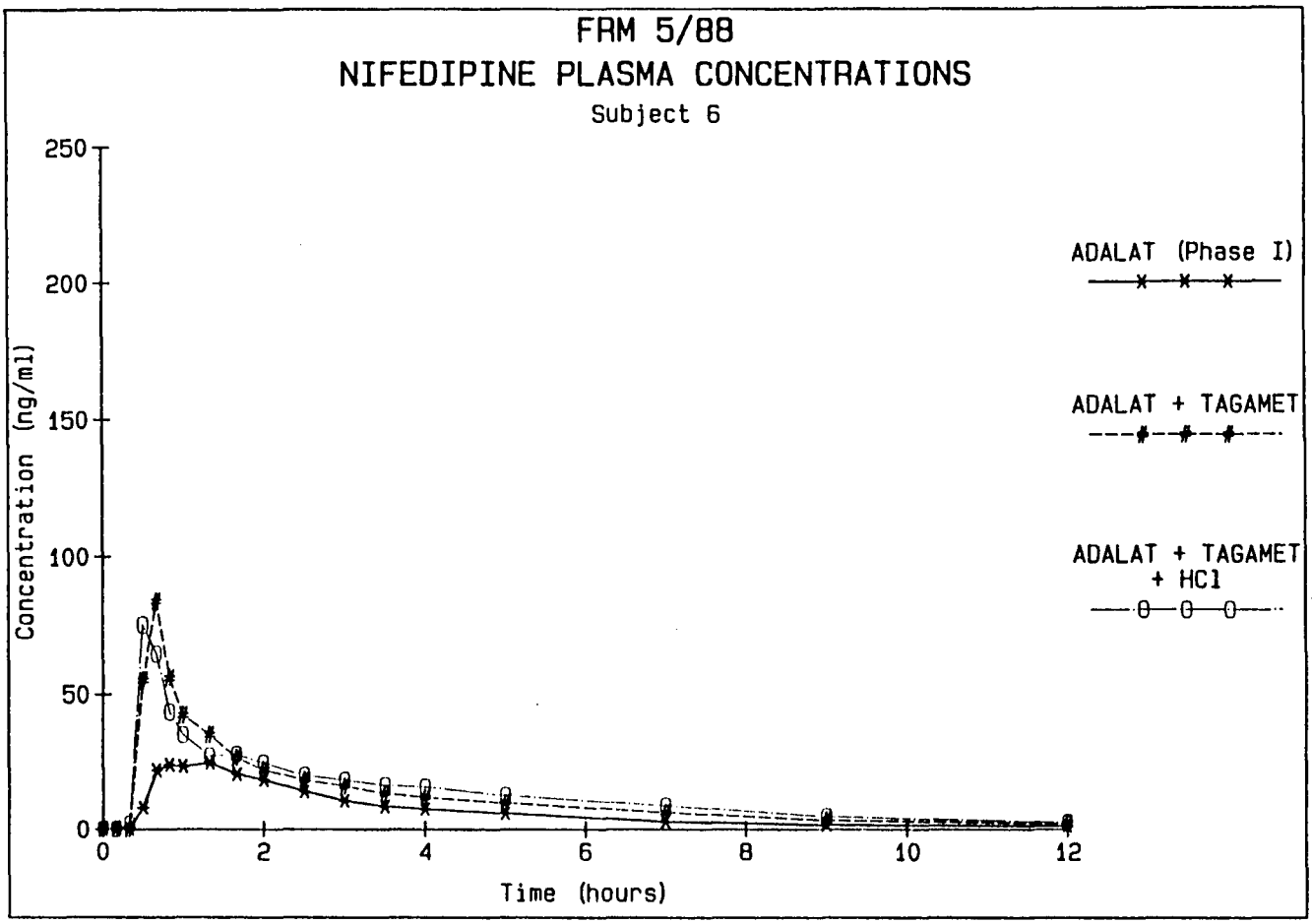
Fig. 3.12

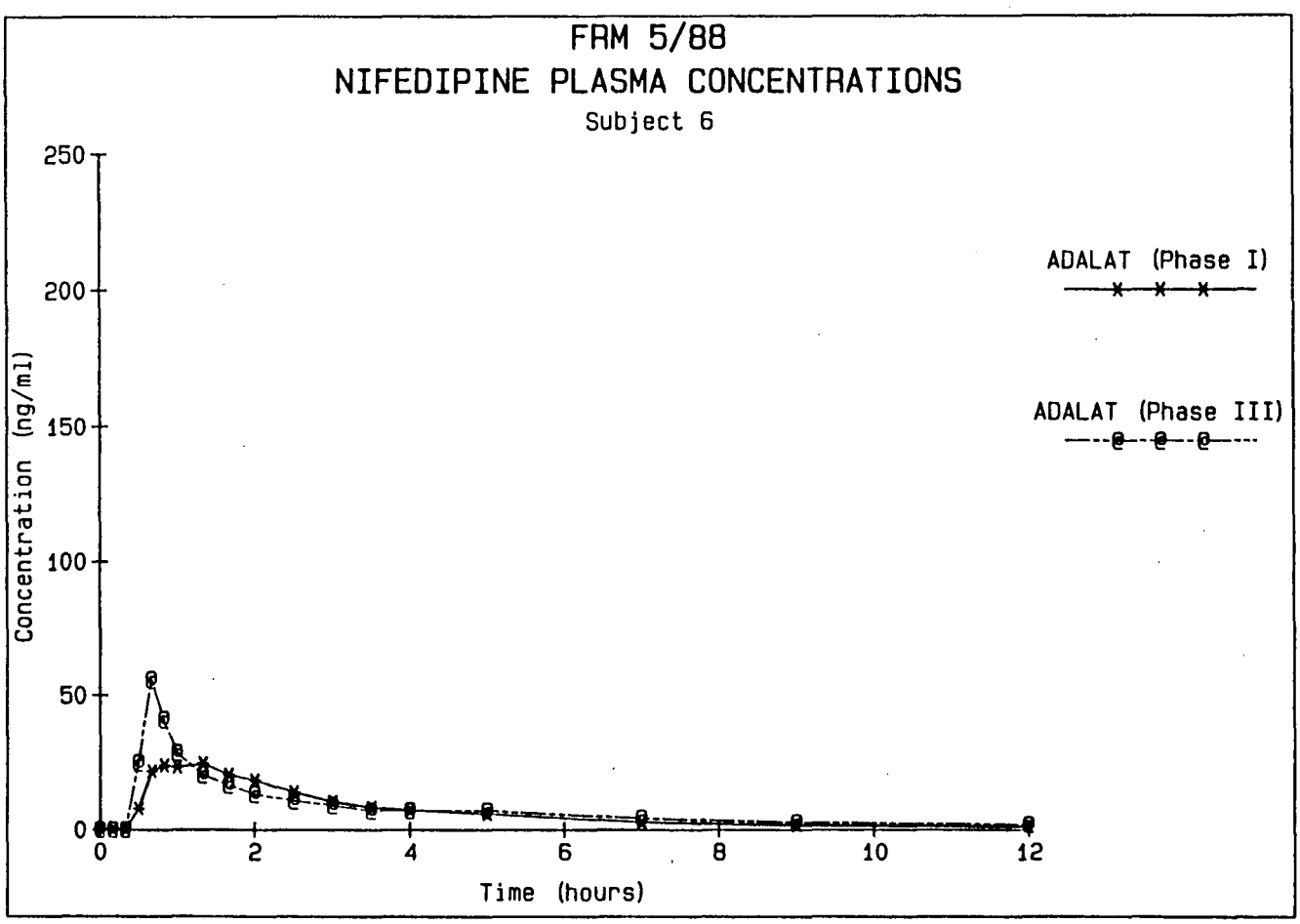

FRM 5/88
NIFEDIPINE PLASMA CONCENTRATIONS
Subject 5
250
200
150
100
50
0
0
2
4
6
8
10
12
Time (hours)
ADALAT (Phase I)
ADALAT + TAGAMET
ADALAT + TAGAMET + HCl


FRM 5/88
NIFEDIPINE PLASMA CONCENTRATIONS
Subject 5
250
200
150
100
50
0
0
2
4
6
8
10
12
Time (hours)
ADALAT (Phase I)
ADALAT (Phase III)

EO

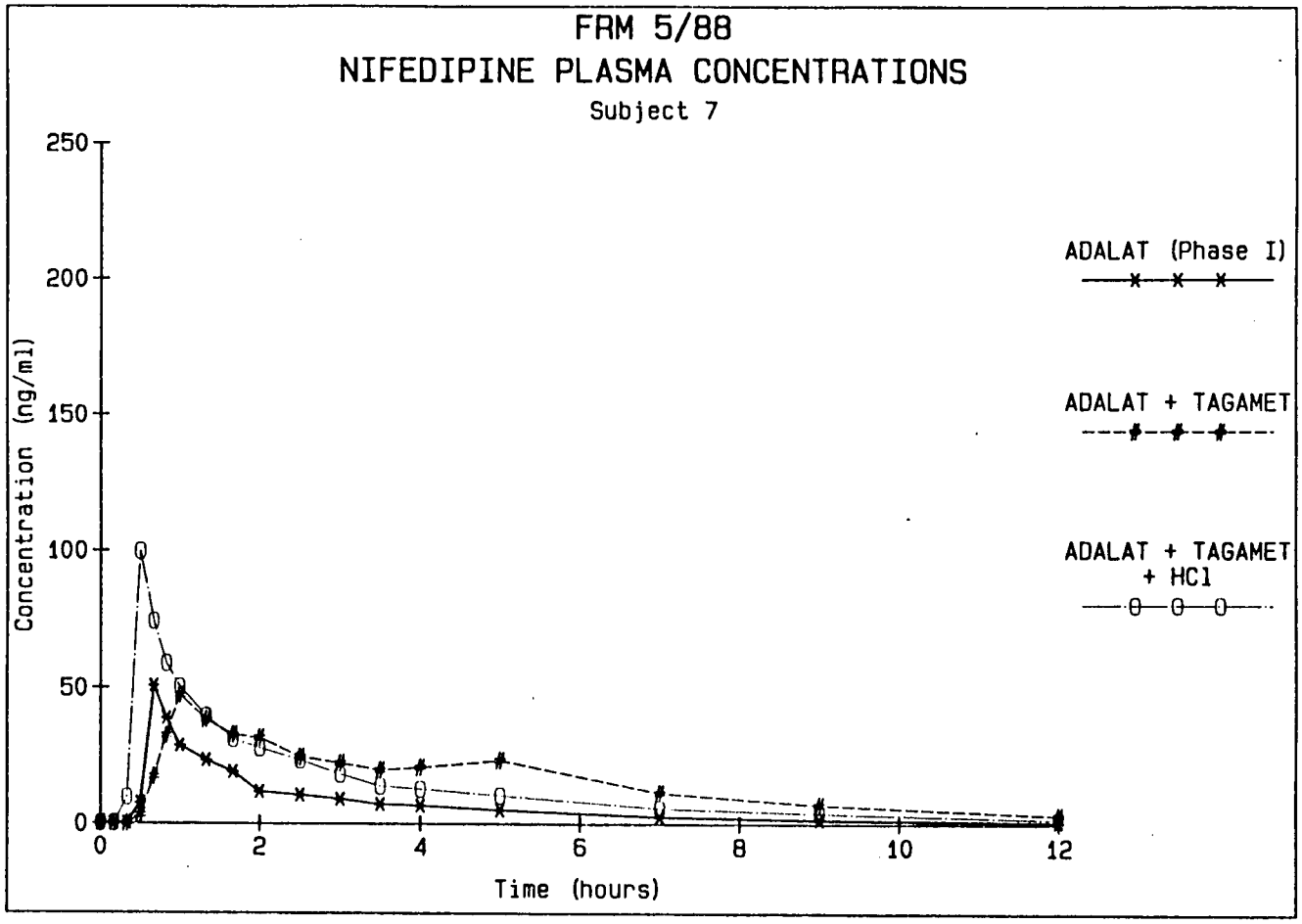
Fig. 3.13

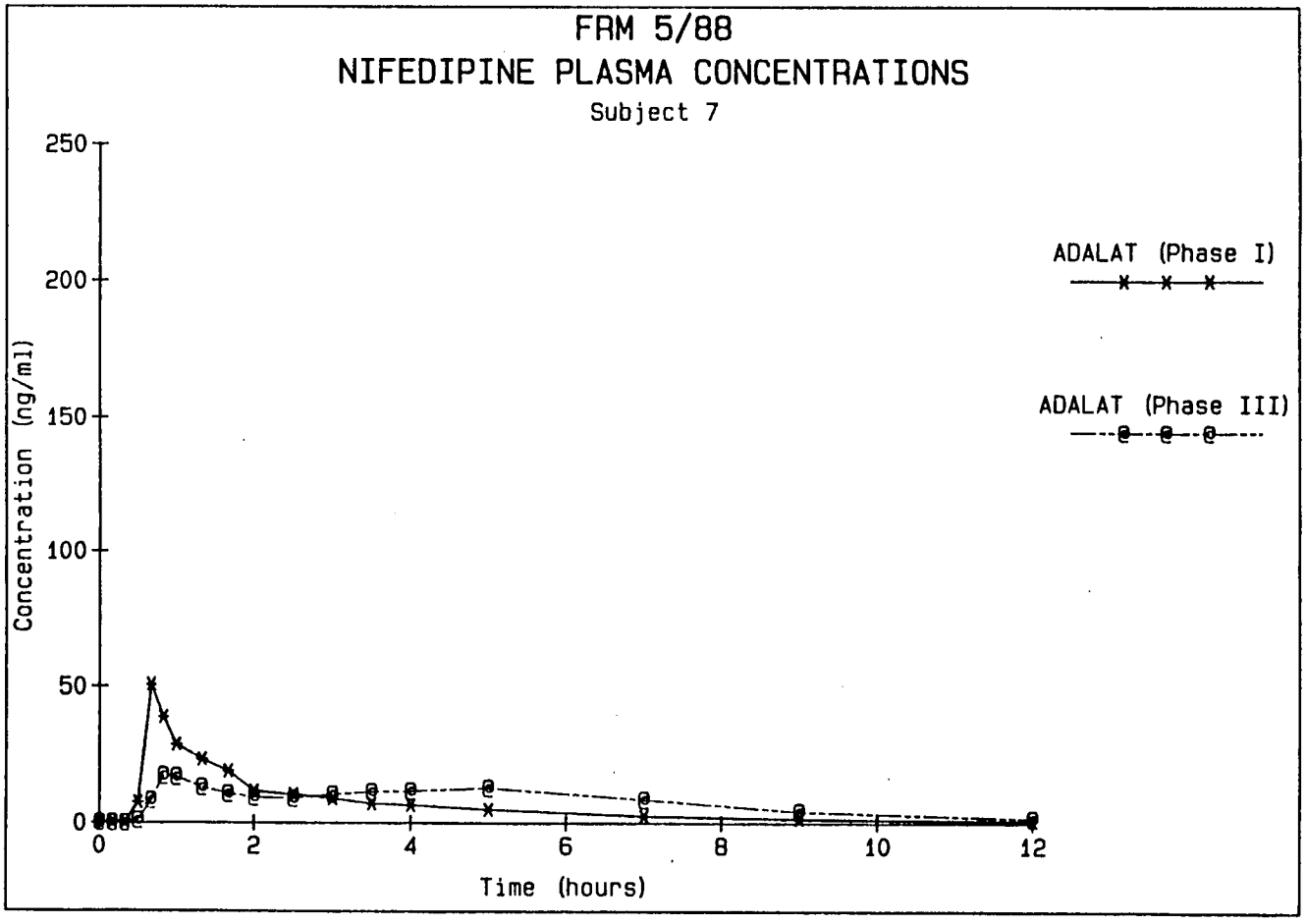

FRM 5/88
NIFEDIPINE PLASMA CONCENTRATIONS
Subject 6
Concentration (ng/ml)
250
200
150
100
50
0
0
2
4
6
8
10
12
Time (hours)
ADALAT (Phase I)
ADALAT + TAGAMET
ADALAT + TAGAMET + HCl


FRM 5/88
NIFEDIPINE PLASMA CONCENTRATIONS
Subject 6
Concentration (ng/ml)
250
200
150
100
50
0
0
2
4
6
8
10
12
Time (hours)
ADALAT (Phase I)
ADALAT (Phase III)

EO

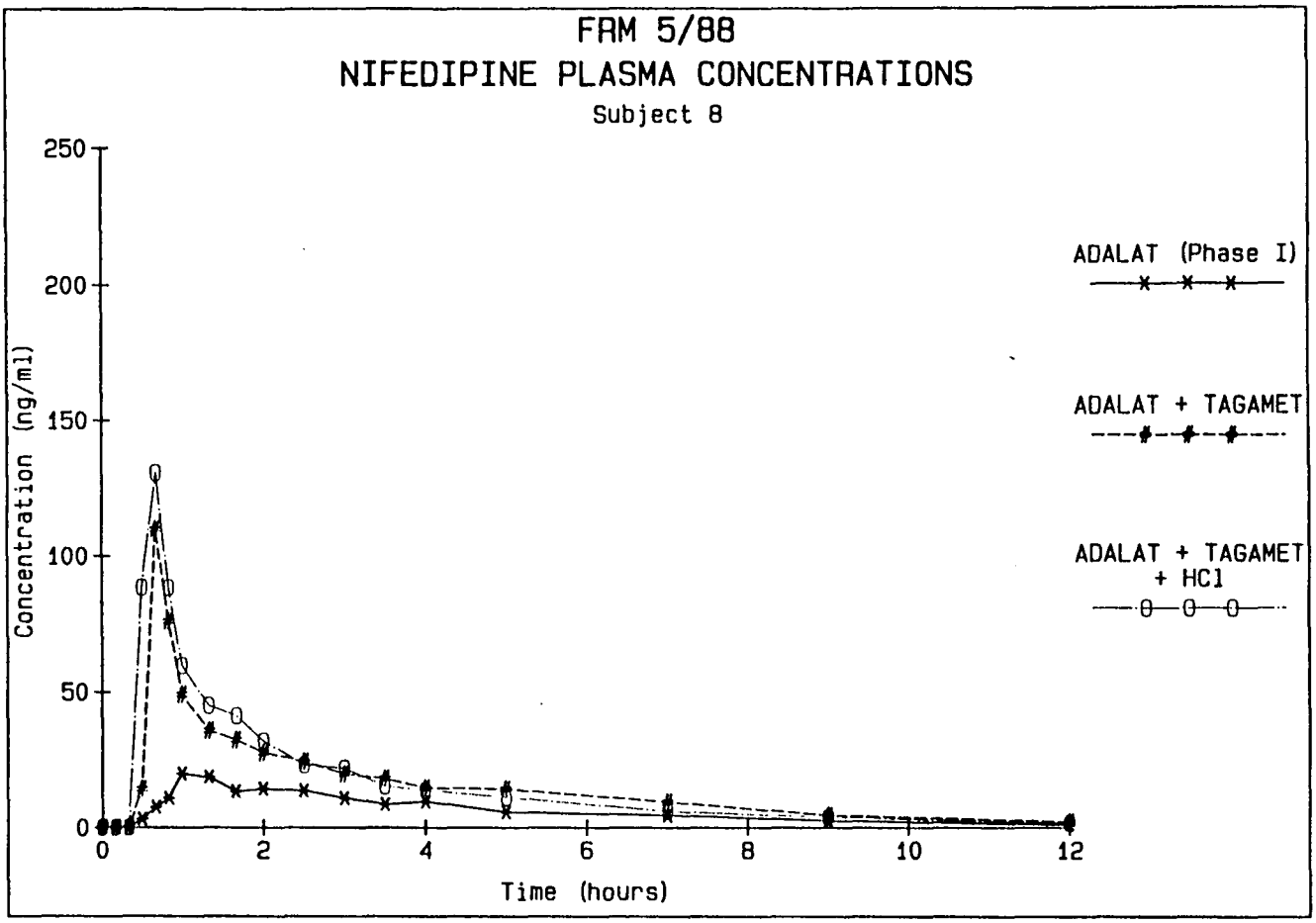
Fig. 3.14

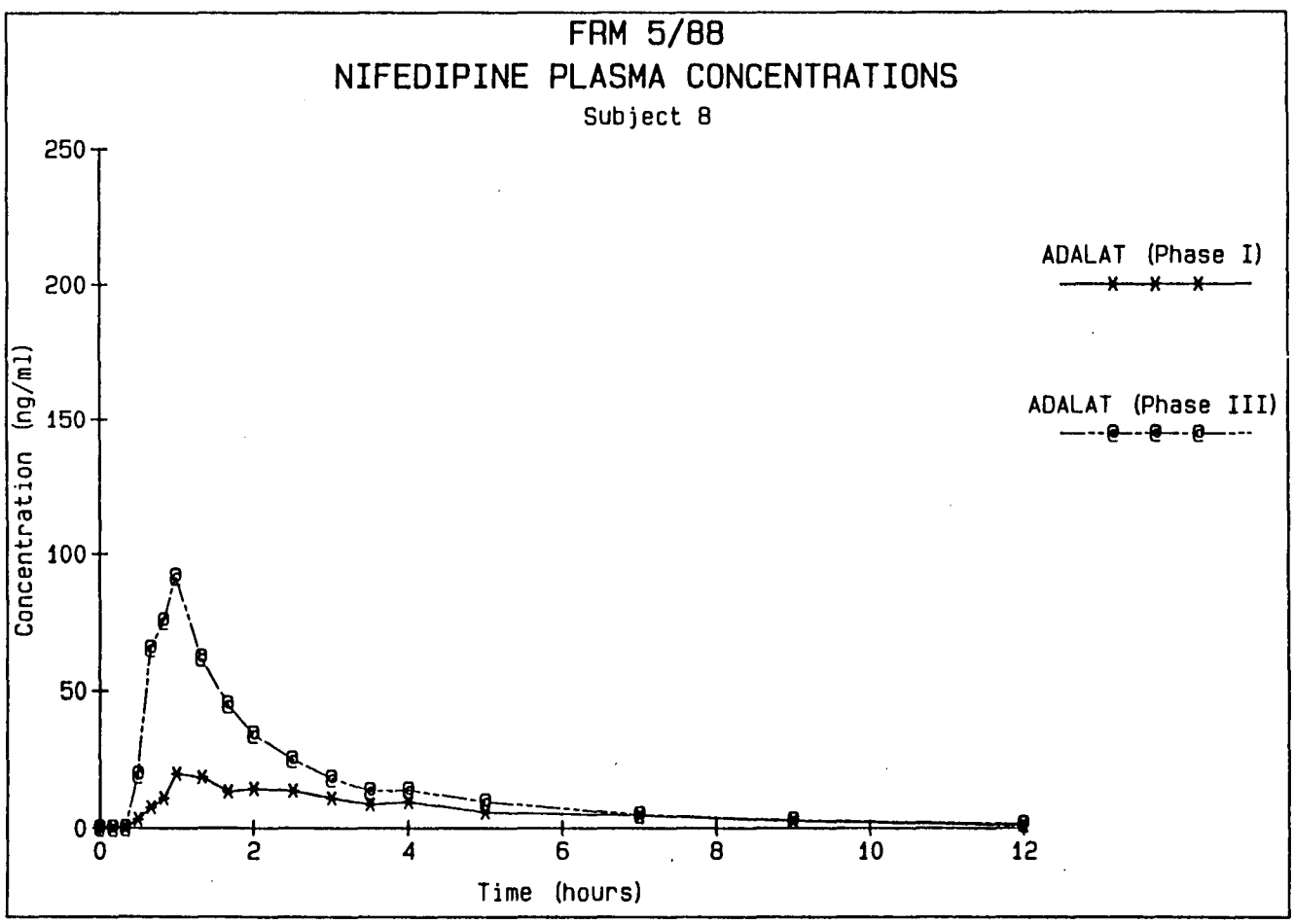

FRM 5/88
NIFEDIPINE PLASMA CONCENTRATIONS
Subject 7
Concentration (ng/ml)
250
200
150
100
50
0
0
2
4
6
8
10
12
Time (hours)
ADALAT (Phase I)
ADALAT + TAGAMET
ADALAT + TAGAMET + HCl


FRM 5/88
NIFEDIPINE PLASMA CONCENTRATIONS
Subject 7
Concentration (ng/ml)
250
200
150
100
50
0
0
2
4
6
8
10
12
Time (hours)
ADALAT (Phase I)
ADALAT (Phase III)

NM

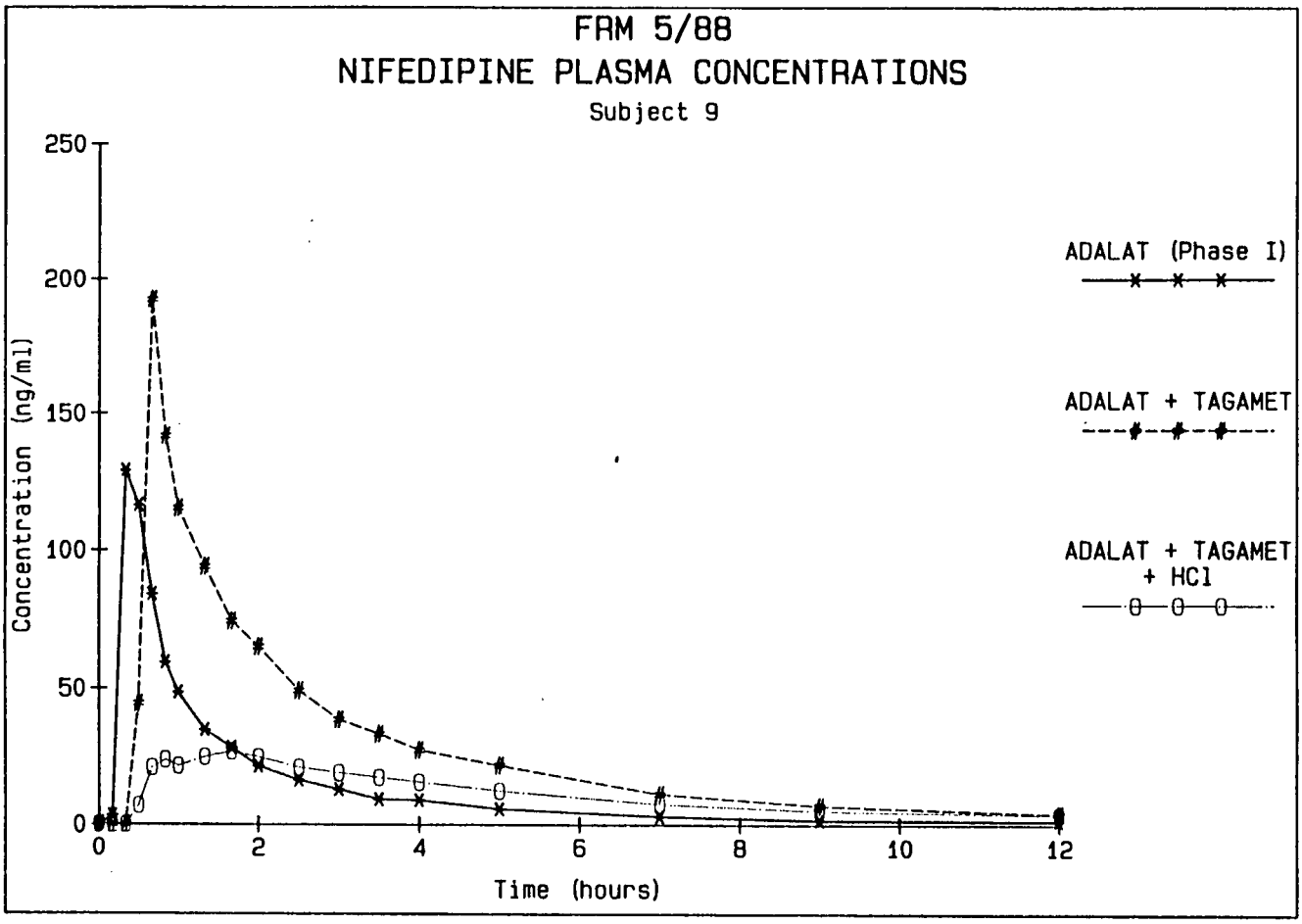
Fig. 3.15

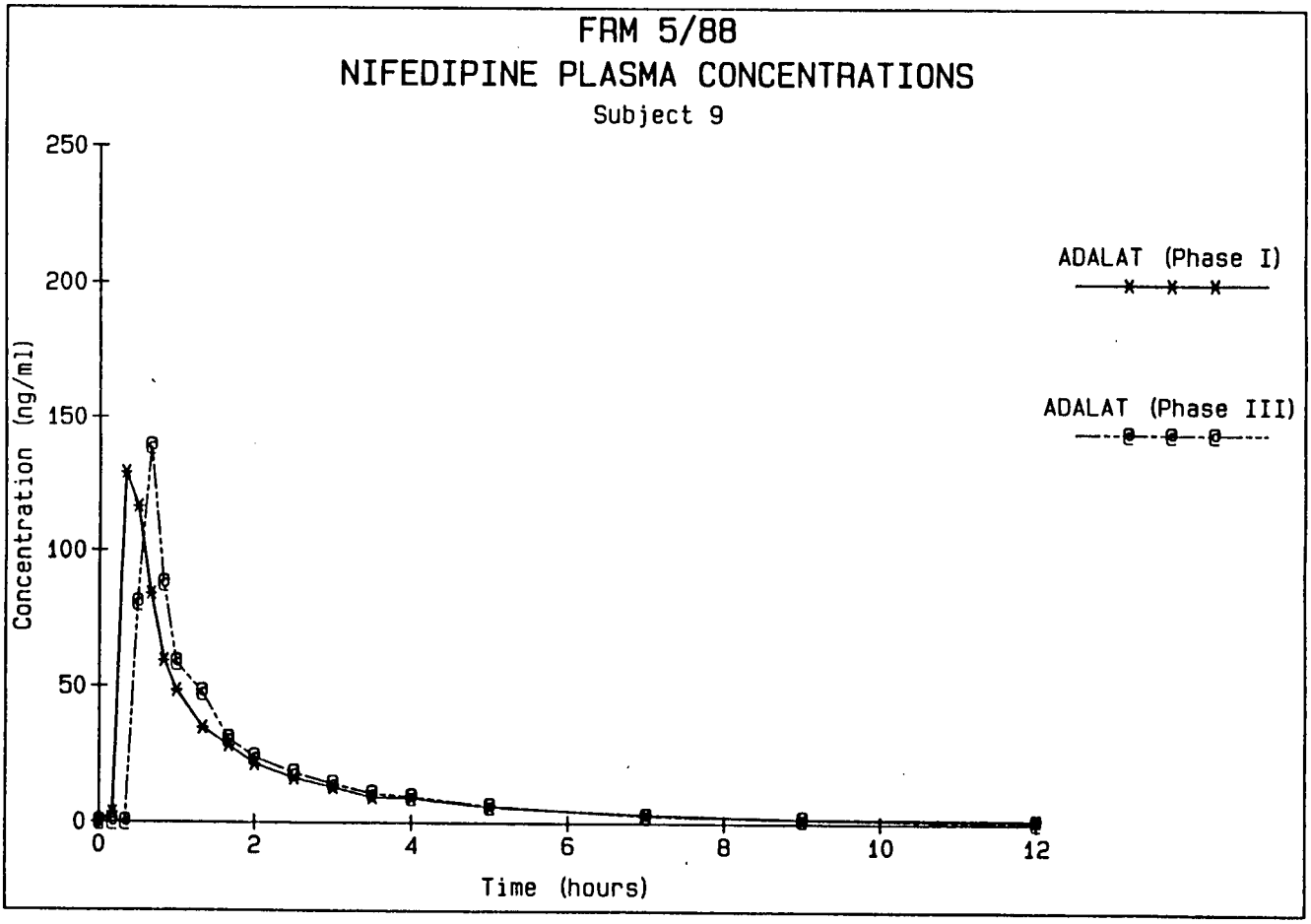

FRM 5/88
NIFEDIPINE PLASMA CONCENTRATIONS
Subject 8
Concentration (ng/ml)
250
200
150
100
50
0
0
2
4
6
8
10
12
Time (hours)
ADALAT (Phase I)
ADALAT + TAGAMET
ADALAT + TAGAMET + HCl


FRM 5/88
NIFEDIPINE PLASMA CONCENTRATIONS
Subject 8
Concentration (ng/ml)
250
200
150
100
50
0
0
2
4
6
8
10
12
Time (hours)
ADALAT (Phase I)
ADALAT (Phase III)

NM

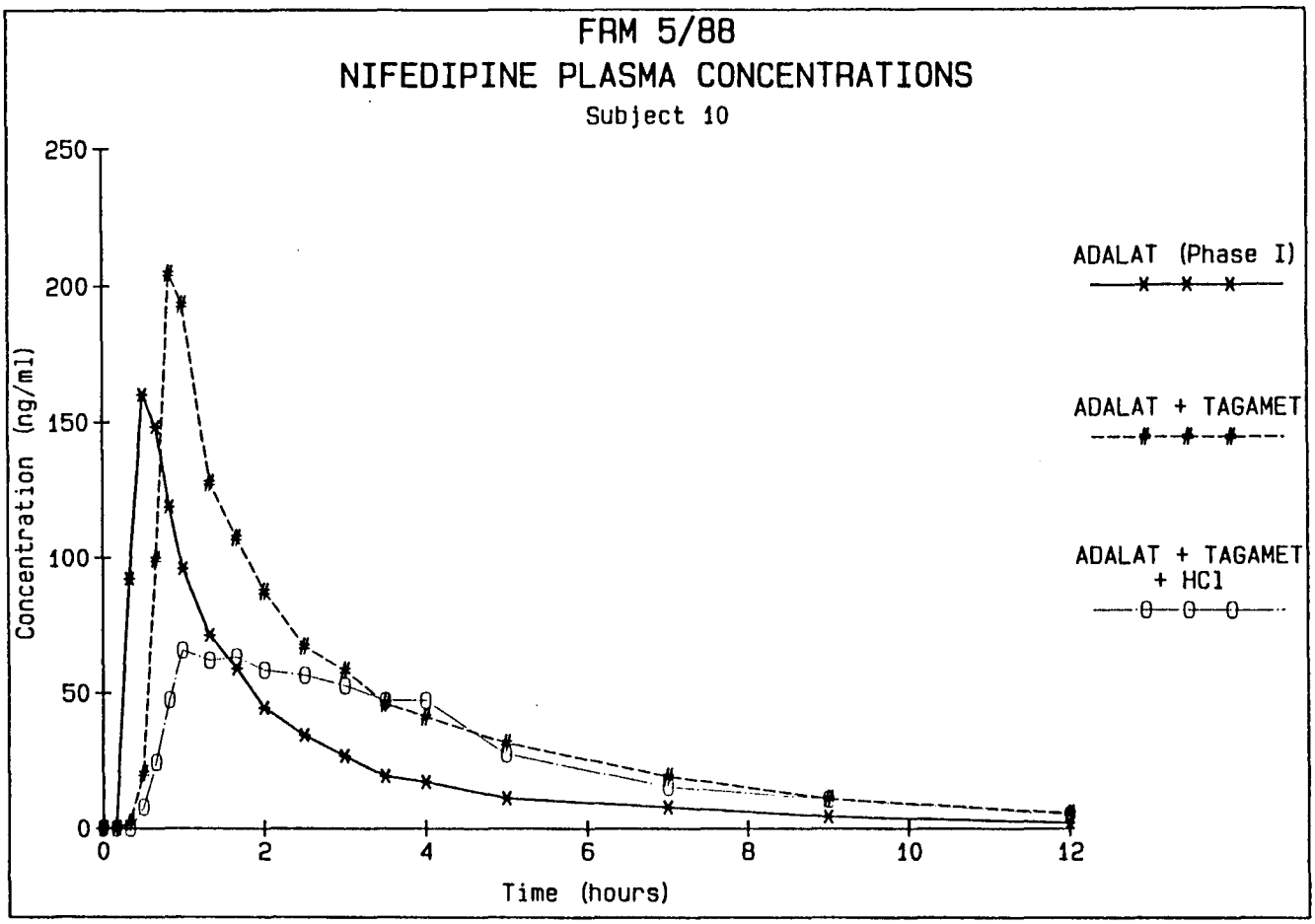
Fig. 3.16

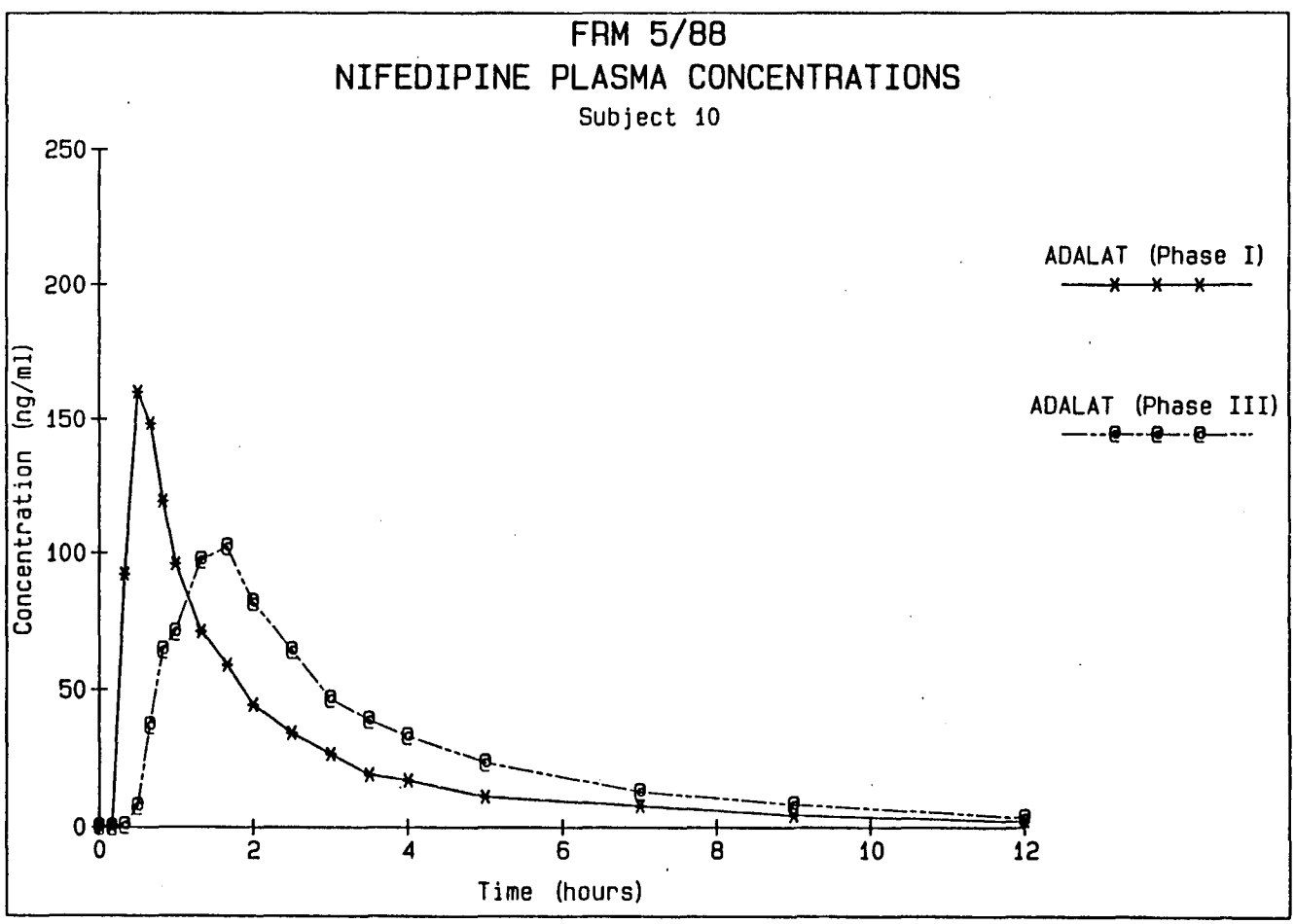

FRM 5/88
NIFEDIPINE PLASMA CONCENTRATIONS
Subject 9
Concentration (ng/ml)
250
200
150
100
50
0
0
2
4
6
8
10
12
Time (hours)
ADALAT (Phase I)
ADALAT + TAGAMET
ADALAT + TAGAMET + HCl


FRM 5/88
NIFEDIPINE PLASMA CONCENTRATIONS
Subject 9
Concentration (ng/ml)
250
200
150
100
50
0
0
2
4
6
8
10
12
Time (hours)
ADALAT (Phase I)
ADALAT (Phase III)

EO

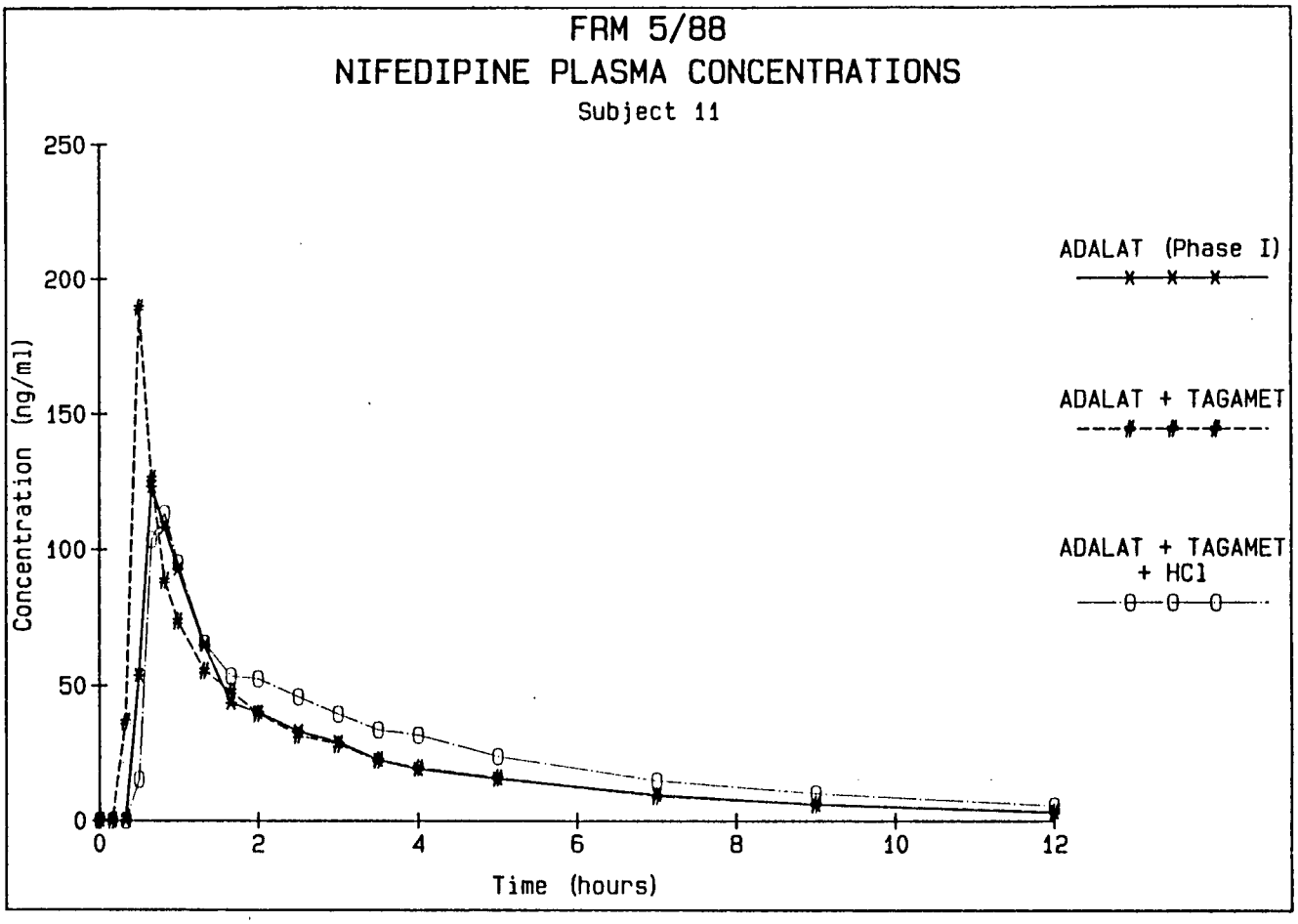
Fig. 3.17

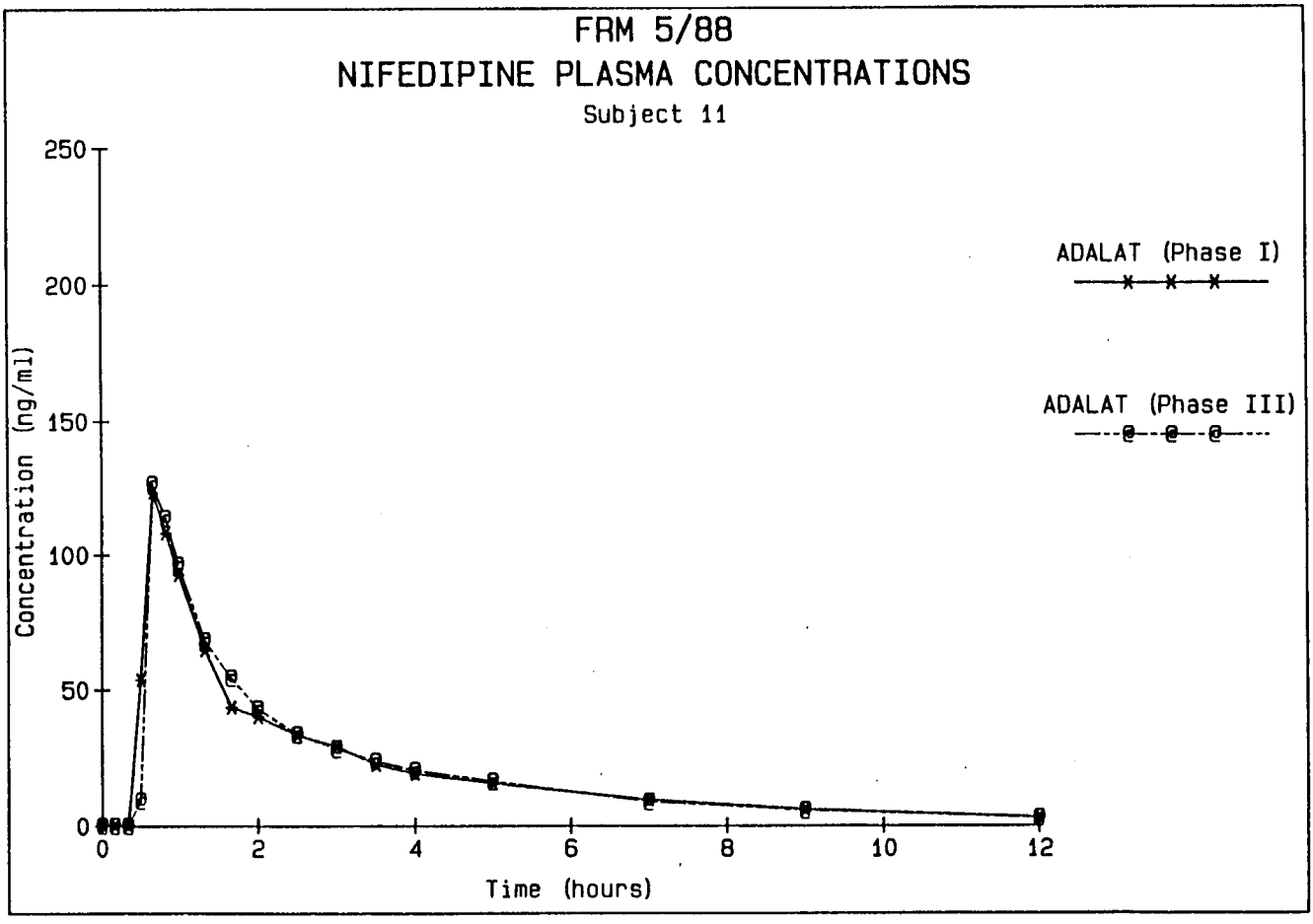

FRM 5/88
NIFEDIPINE PLASMA CONCENTRATIONS
Subject 10
Concentration (ng/ml)
250
200
150
100
50
0
0
2
4
6
8
10
12
Time (hours)
ADALAT (Phase I)
ADALAT + TAGAMET
ADALAT + TAGAMET + HCl


FRM 5/88
NIFEDIPINE PLASMA CONCENTRATIONS
Subject 10
Concentration (ng/ml)
250
200
150
100
50
0
0
2
4
6
8
10
12
Time (hours)
ADALAT (Phase I)
ADALAT (Phase III)

EO

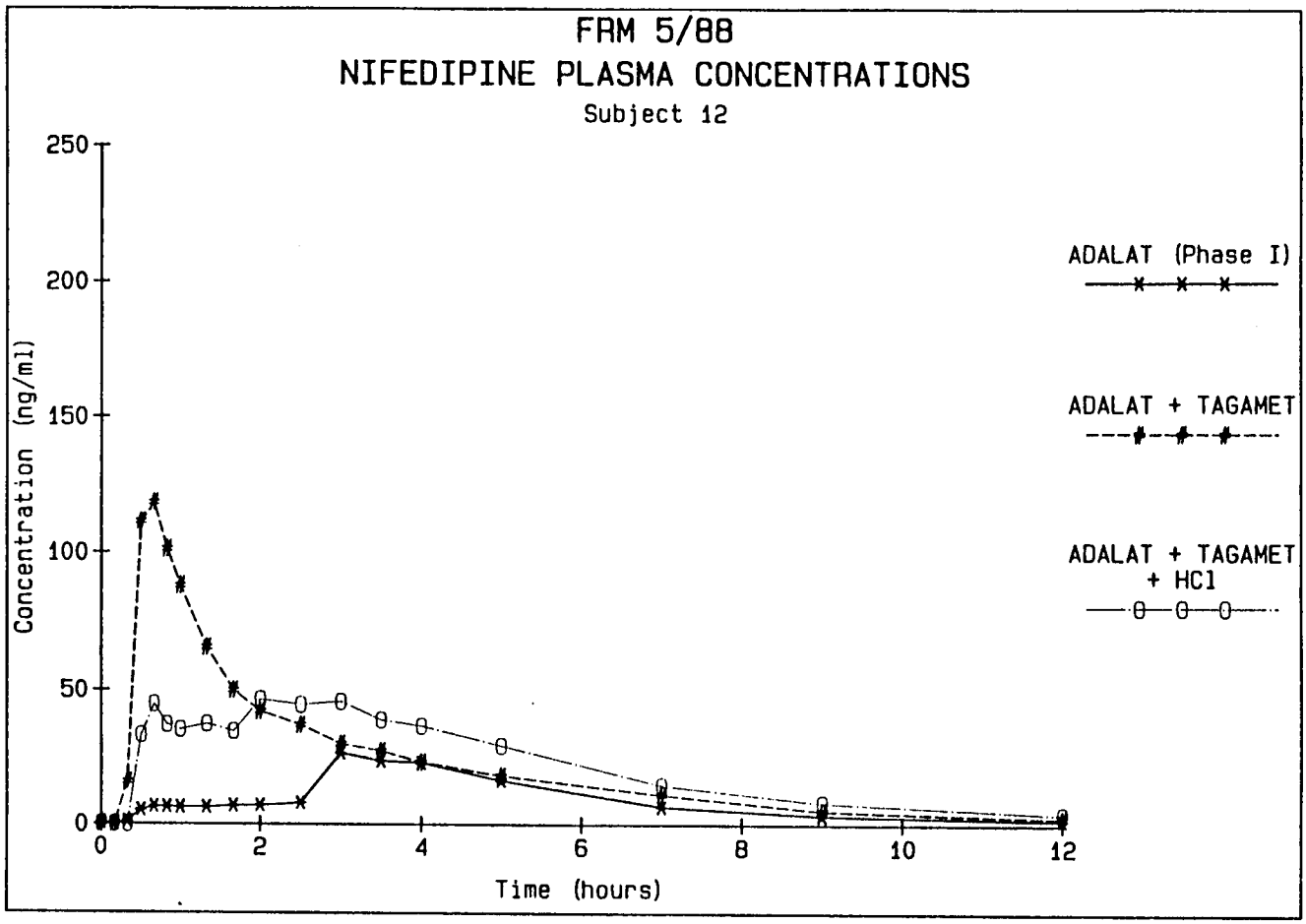
Fig. 3.18

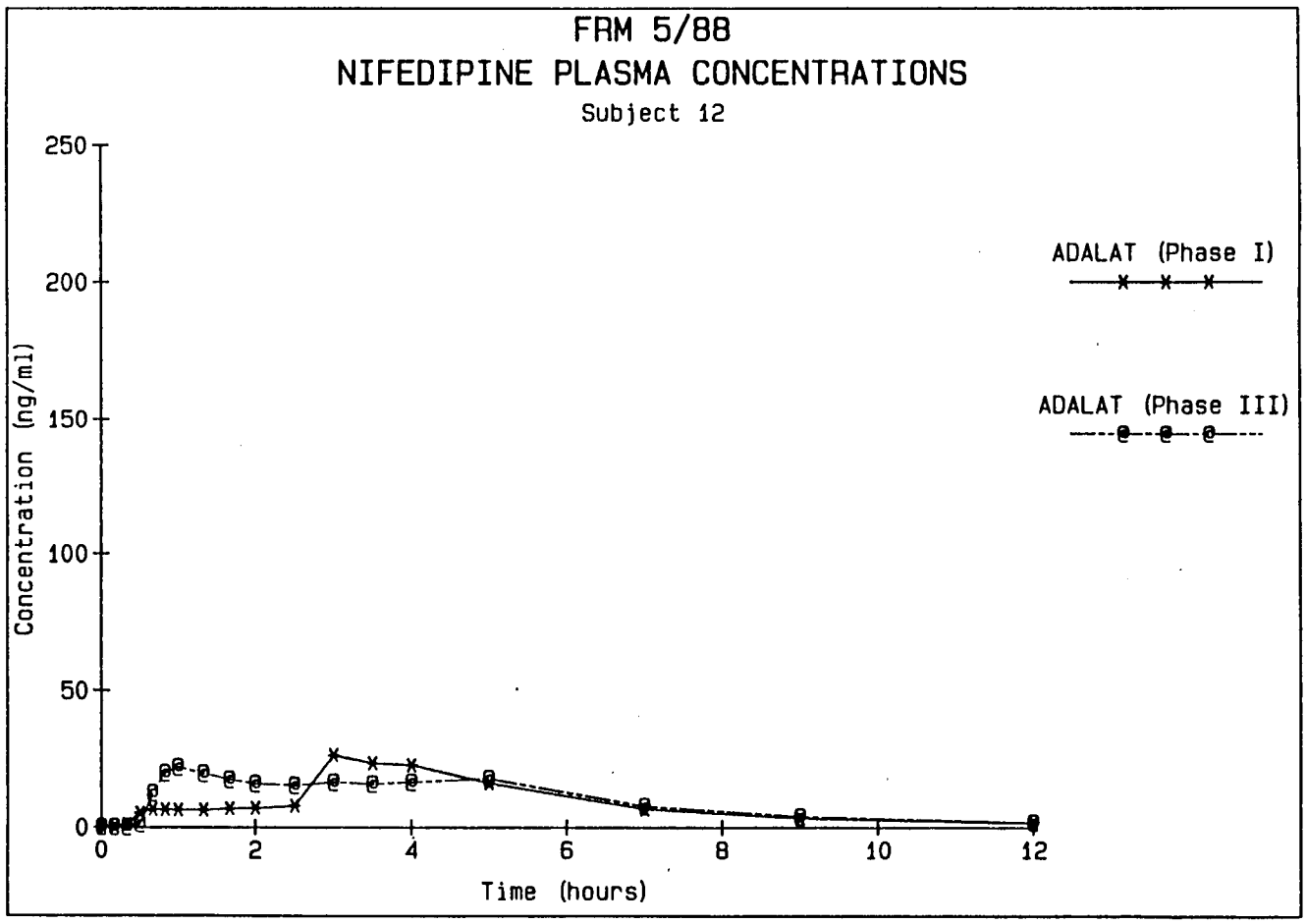

FRM 5/88
NIFEDIPINE PLASMA CONCENTRATIONS
Subject 11
Concentration (ng/ml)
250
200
150
100
50
0
0
2
4
6
8
10
12
Time (hours)
ADALAT (Phase I)
ADALAT + TAGAMET
ADALAT + TAGAMET + HCl


FRM 5/88
NIFEDIPINE PLASMA CONCENTRATIONS
Subject 11
Concentration (ng/ml)
250
200
150
100
50
0
0
2
4
6
8
10
12
Time (hours)
ADALAT (Phase I)
ADALAT (Phase III)

EO

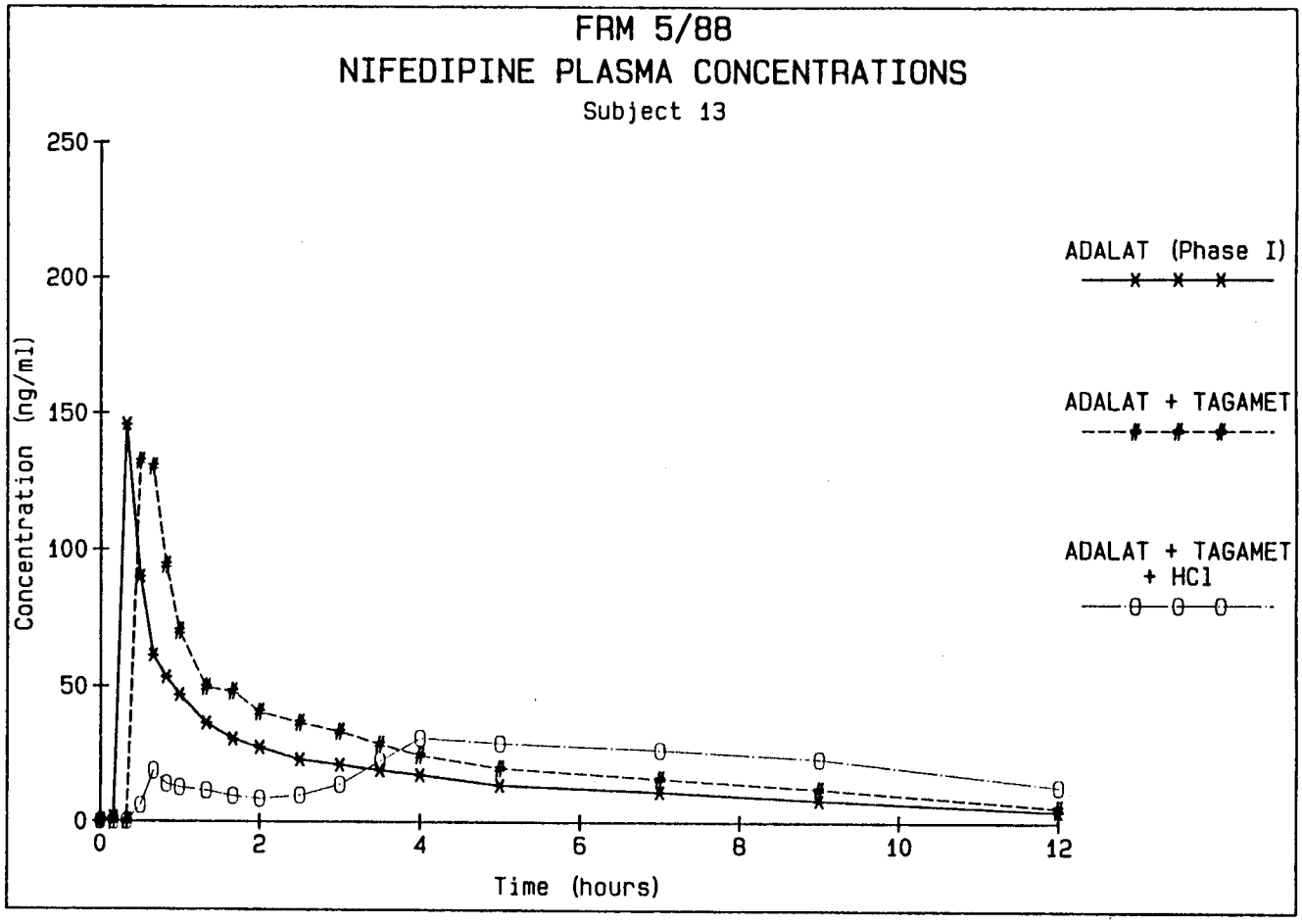
Fig. 3.19

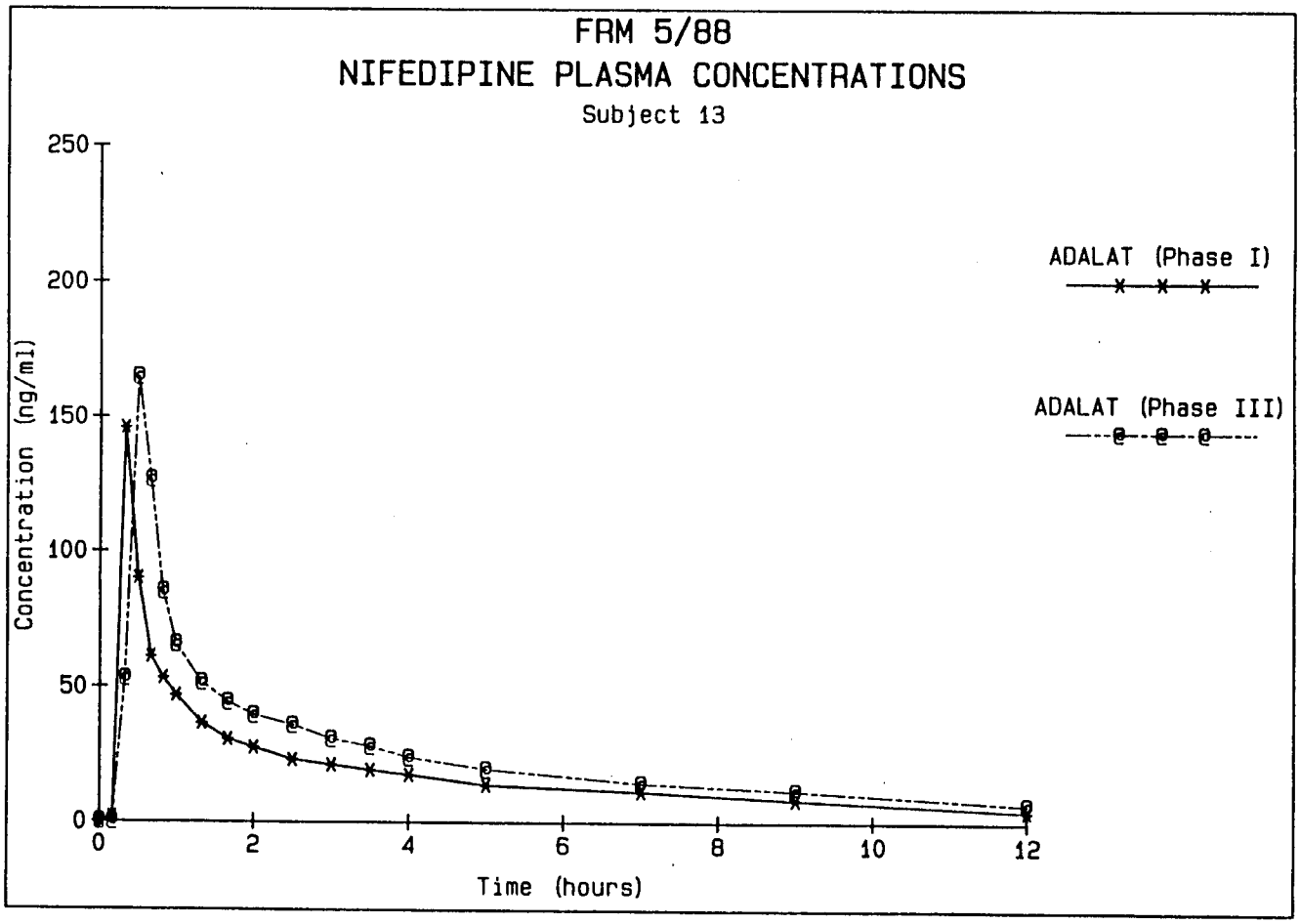

FRM 5/88
NIFEDIPINE PLASMA CONCENTRATIONS
Subject 12
Concentration (ng/ml)
250
200
150
100
50
0
0
2
4
6
8
10
12
Time (hours)
ADALAT (Phase I)
ADALAT + TAGAMET
ADALAT + TAGAMET + HCl


FRM 5/88
NIFEDIPINE PLASMA CONCENTRATIONS
Subject 12
Concentration (ng/ml)
250
200
150
100
50
0
0
2
4
6
8
10
12
Time (hours)
ADALAT (Phase I)
ADALAT (Phase III)

NM

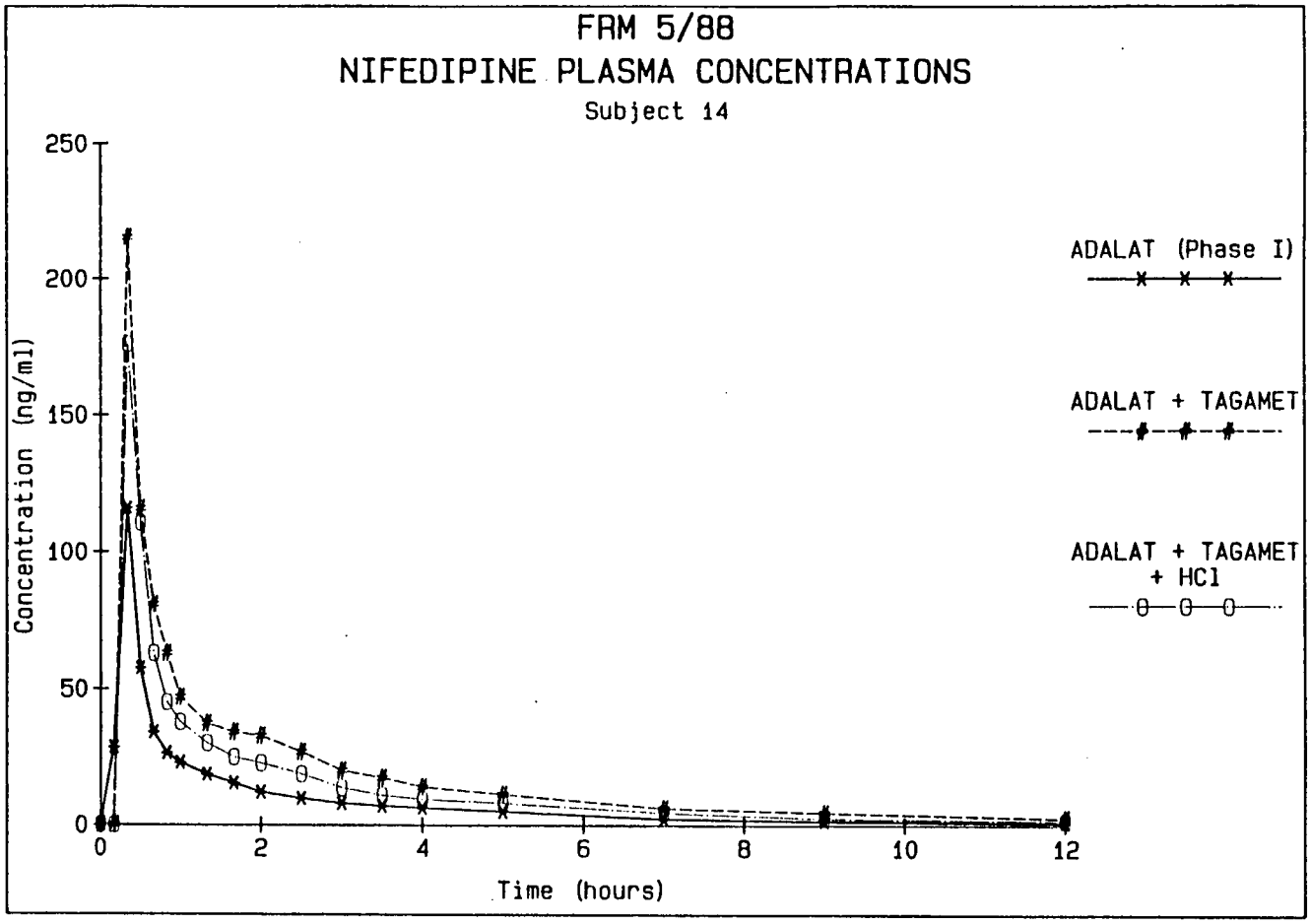
Fig. 3.20

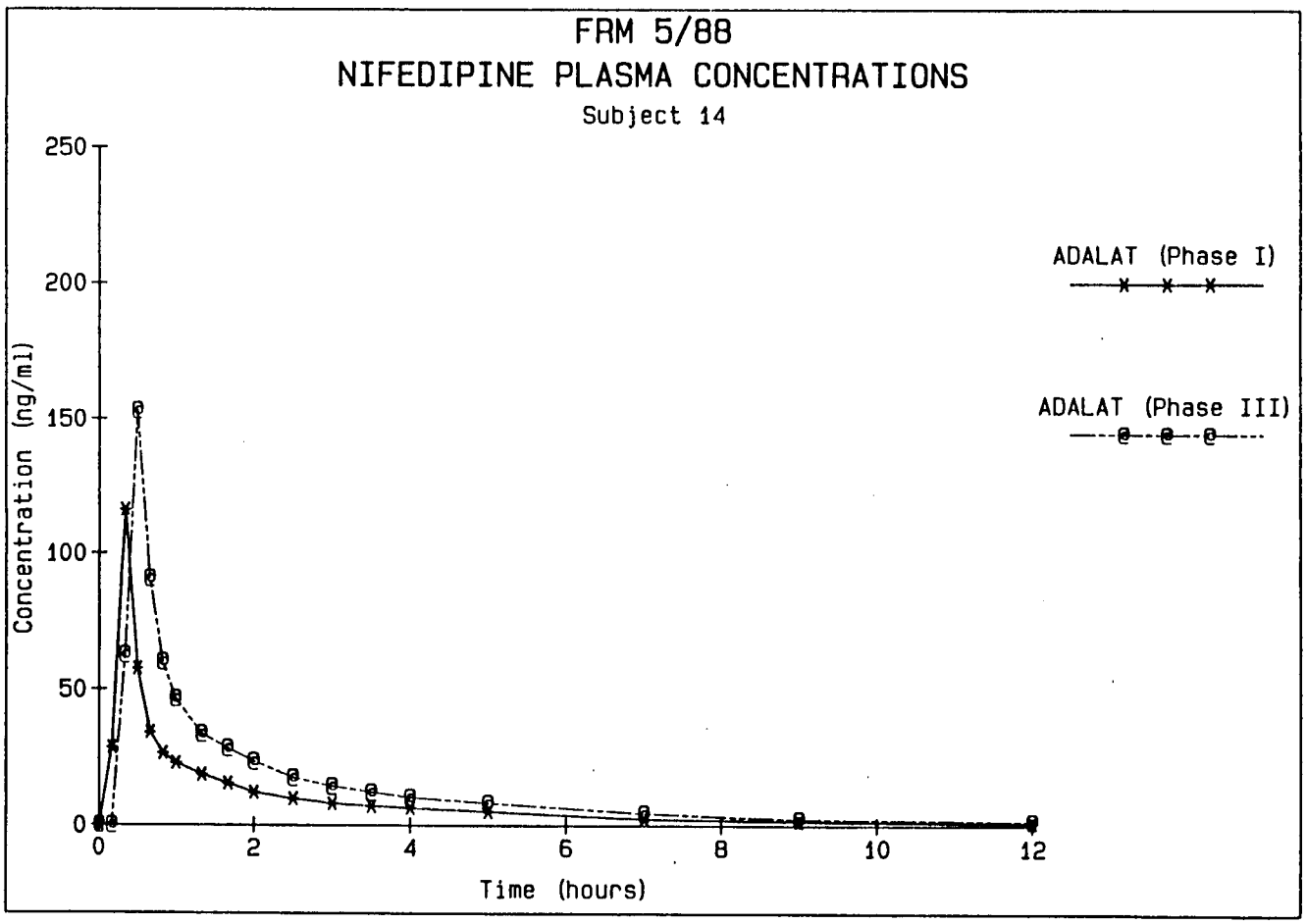

FRM 5/88
NIFEDIPINE PLASMA CONCENTRATIONS
Subject 13
Concentration (ng/ml)
250
200
150
100
50
0
0
2
4
6
8
10
12
Time (hours)
ADALAT (Phase I)
ADALAT + TAGAMET
ADALAT + TAGAMET + HCl


FRM 5/88
NIFEDIPINE PLASMA CONCENTRATIONS
Subject 13
Concentration (ng/ml)
250
200
150
100
50
0
0
2
4
6
8
10
12
Time (hours)
ADALAT (Phase I)
ADALAT (Phase III)

PM

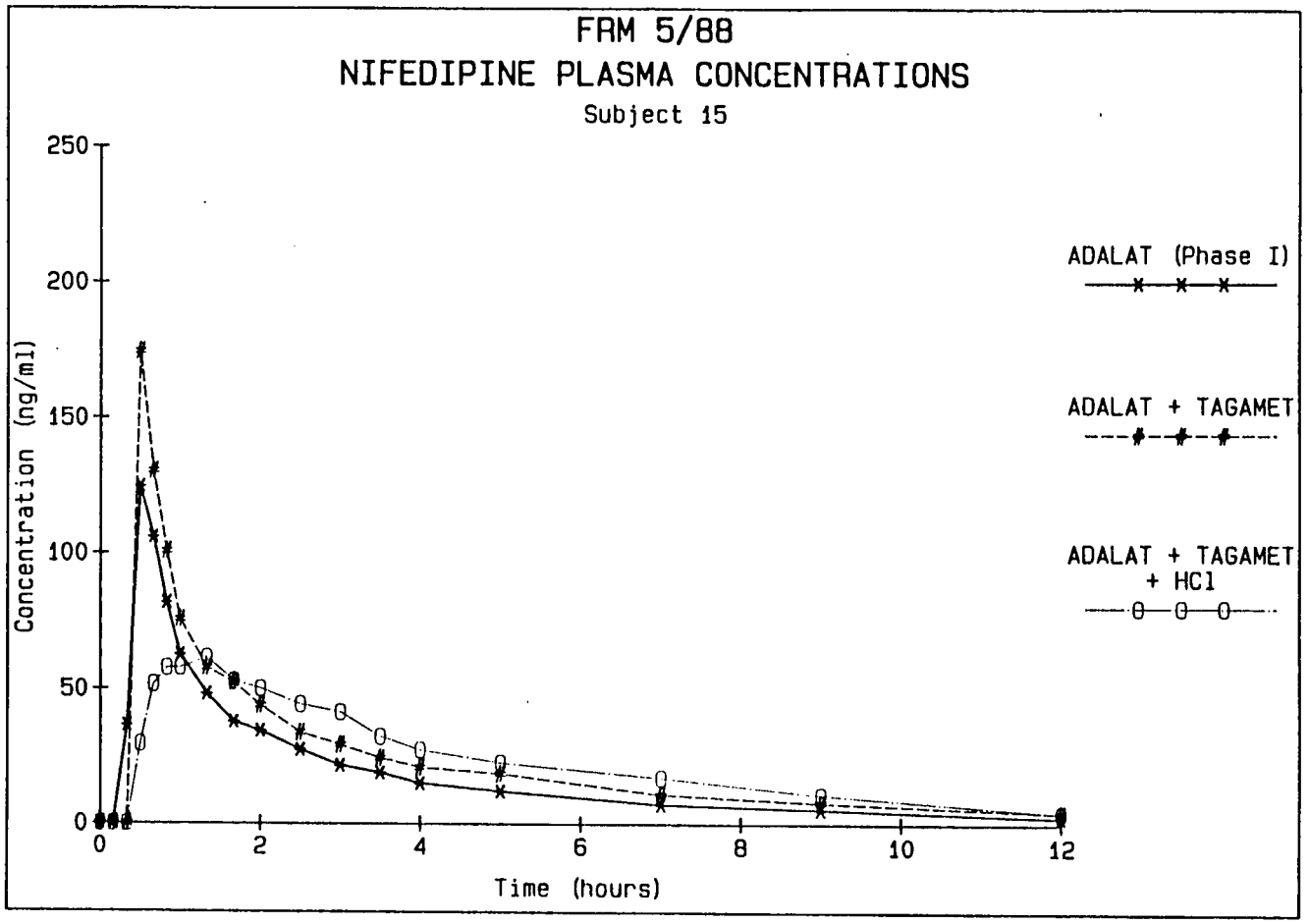
Fig. 3.21

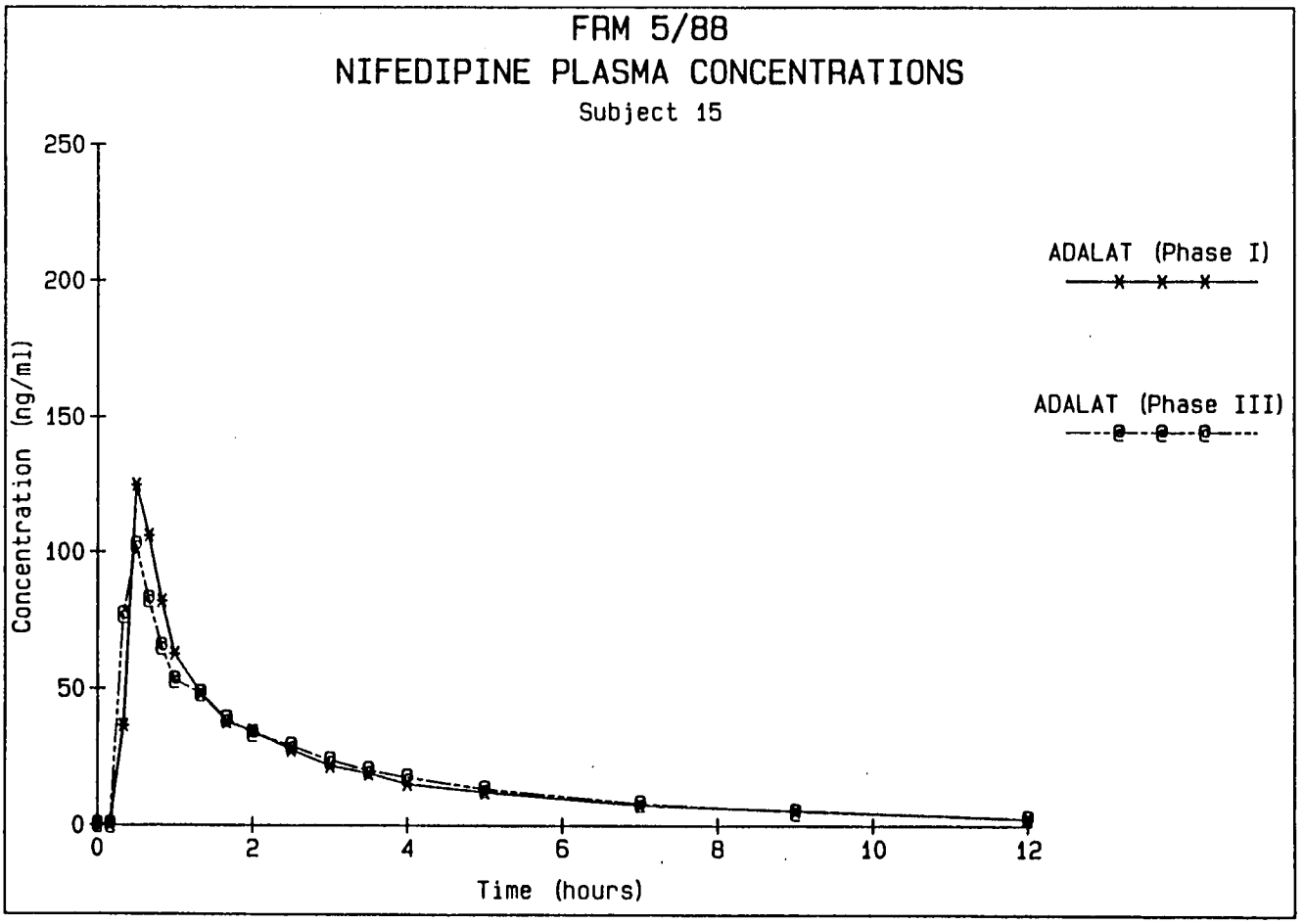

FRM 5/88
NIFEDIPINE PLASMA CONCENTRATIONS
Subject 14
Concentration (ng/ml)
250
200
150
100
50
0
0
2
4
6
8
10
12
Time (hours)
ADALAT (Phase I)
ADALAT + TAGAMET
ADALAT + TAGAMET + HCl


FRM 5/88
NIFEDIPINE PLASMA CONCENTRATIONS
Subject 14
Concentration (ng/ml)
250
200
150
100
50
0
0
2
4
6
8
10
12
Time (hours)
ADALAT (Phase I)
ADALAT (Phase III)

EO

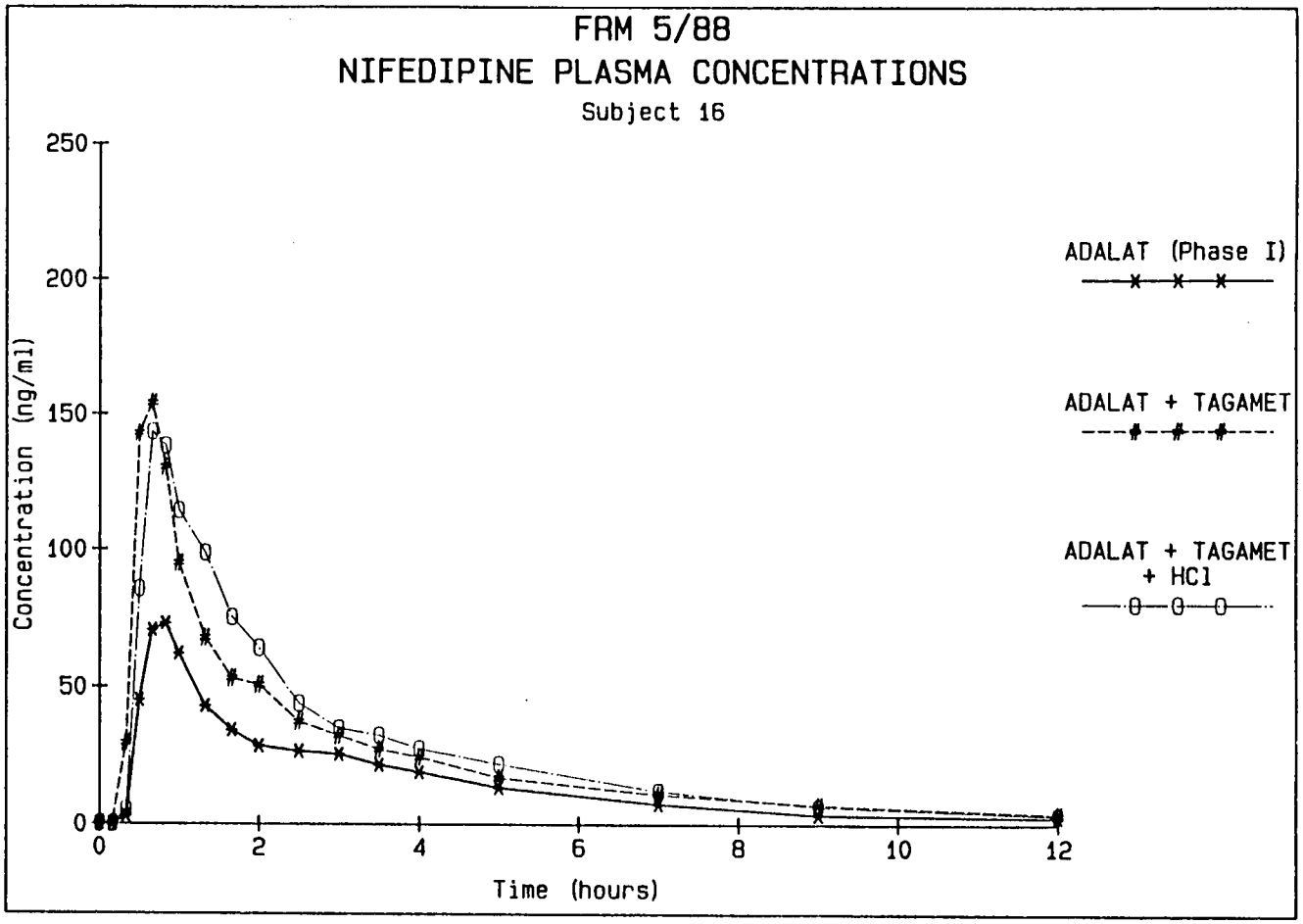
Fig. 3.22

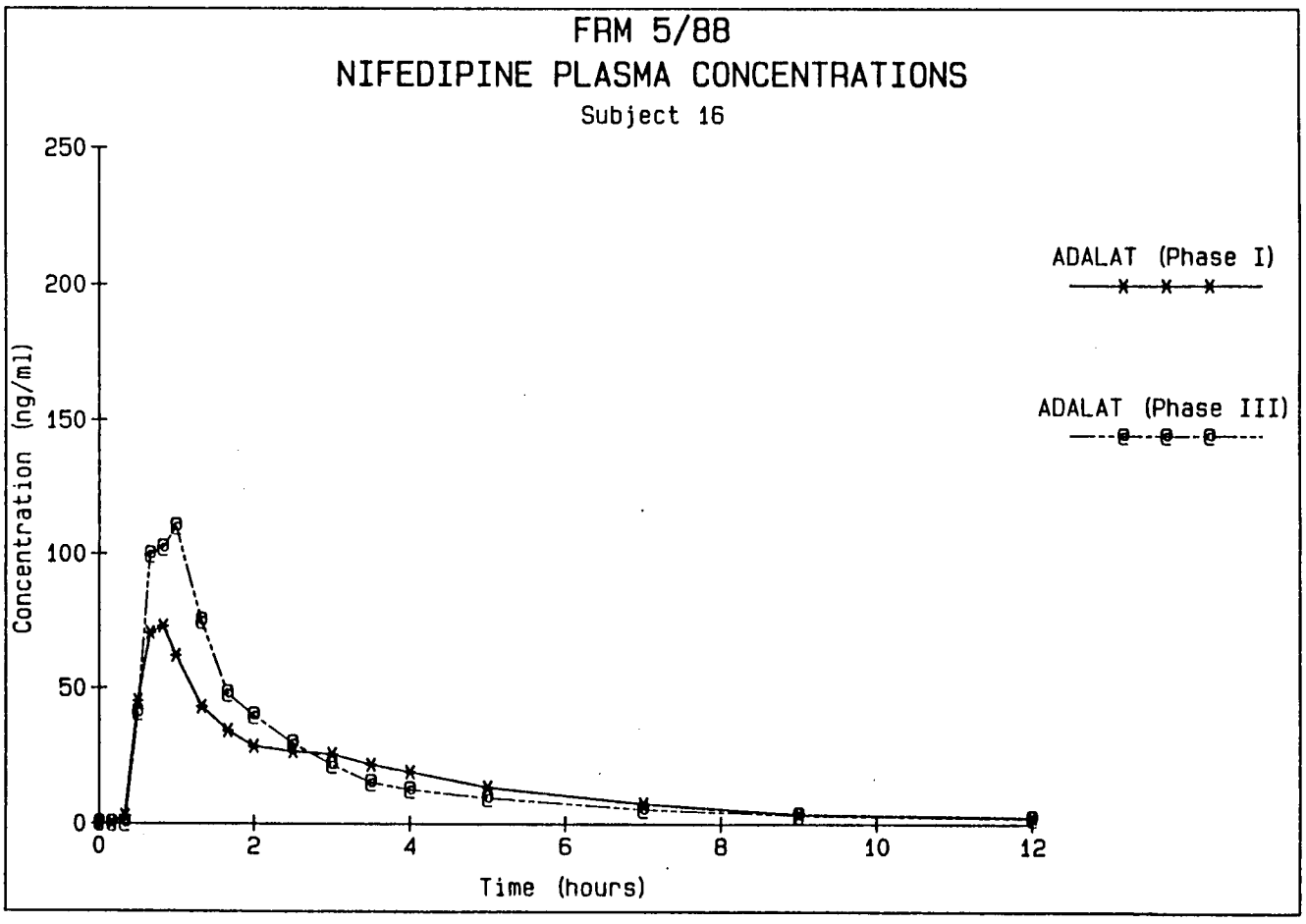

FRM 5/88
NIFEDIPINE PLASMA CONCENTRATIONS
Subject 15
Concentration (ng/ml)
250
200
150
100
50
0
0
2
4
6
8
10
12
Time (hours)
ADALAT (Phase I)
ADALAT + TAGAMET
ADALAT + TAGAMET + HCl


FRM 5/88
NIFEDIPINE PLASMA CONCENTRATIONS
Subject 15
Concentration (ng/ml)
250
200
150
100
50
0
0
2
4
6
8
10
12
Time (hours)
ADALAT (Phase I)
ADALAT (Phase III)

EO

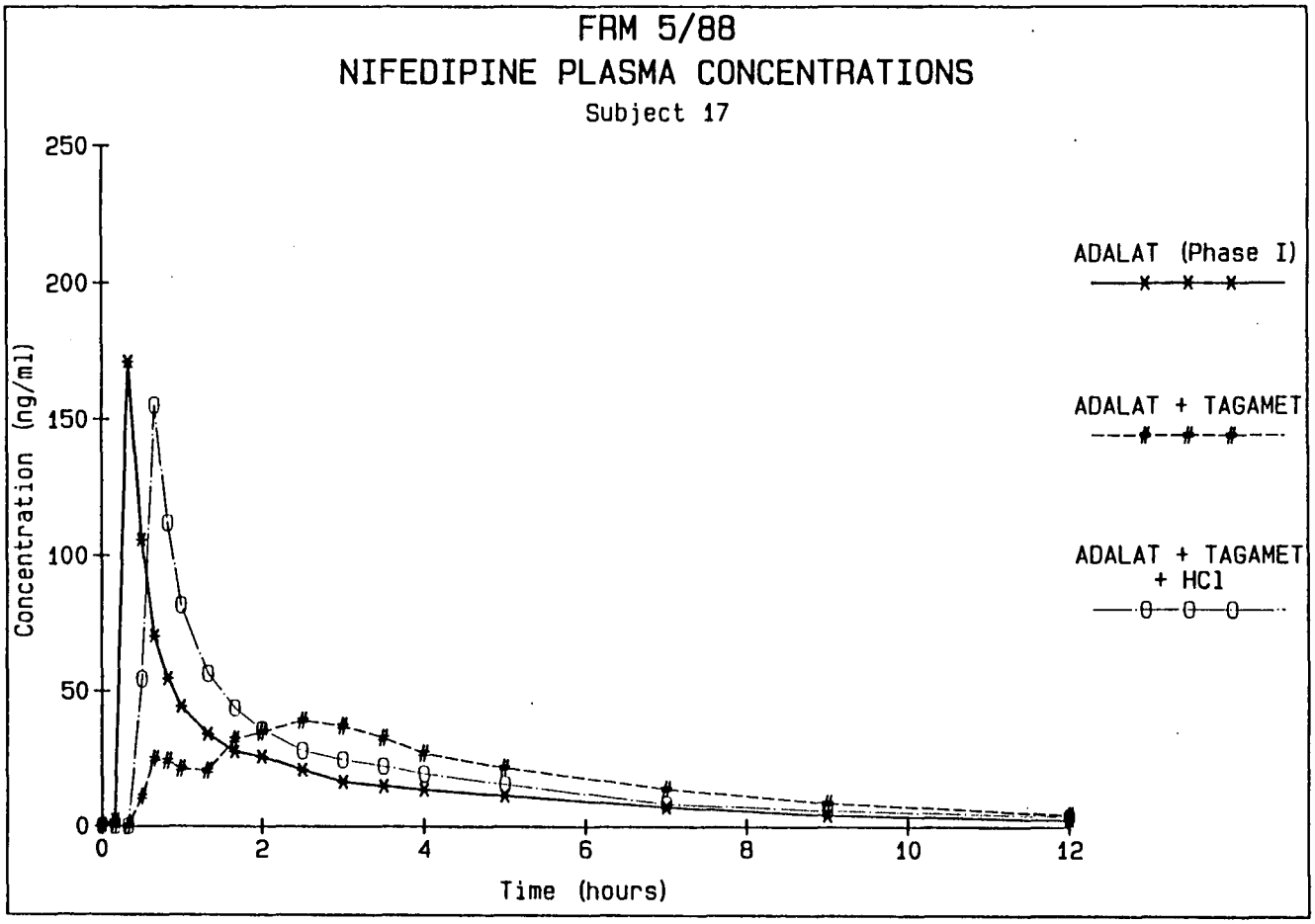
Fig. 3.23

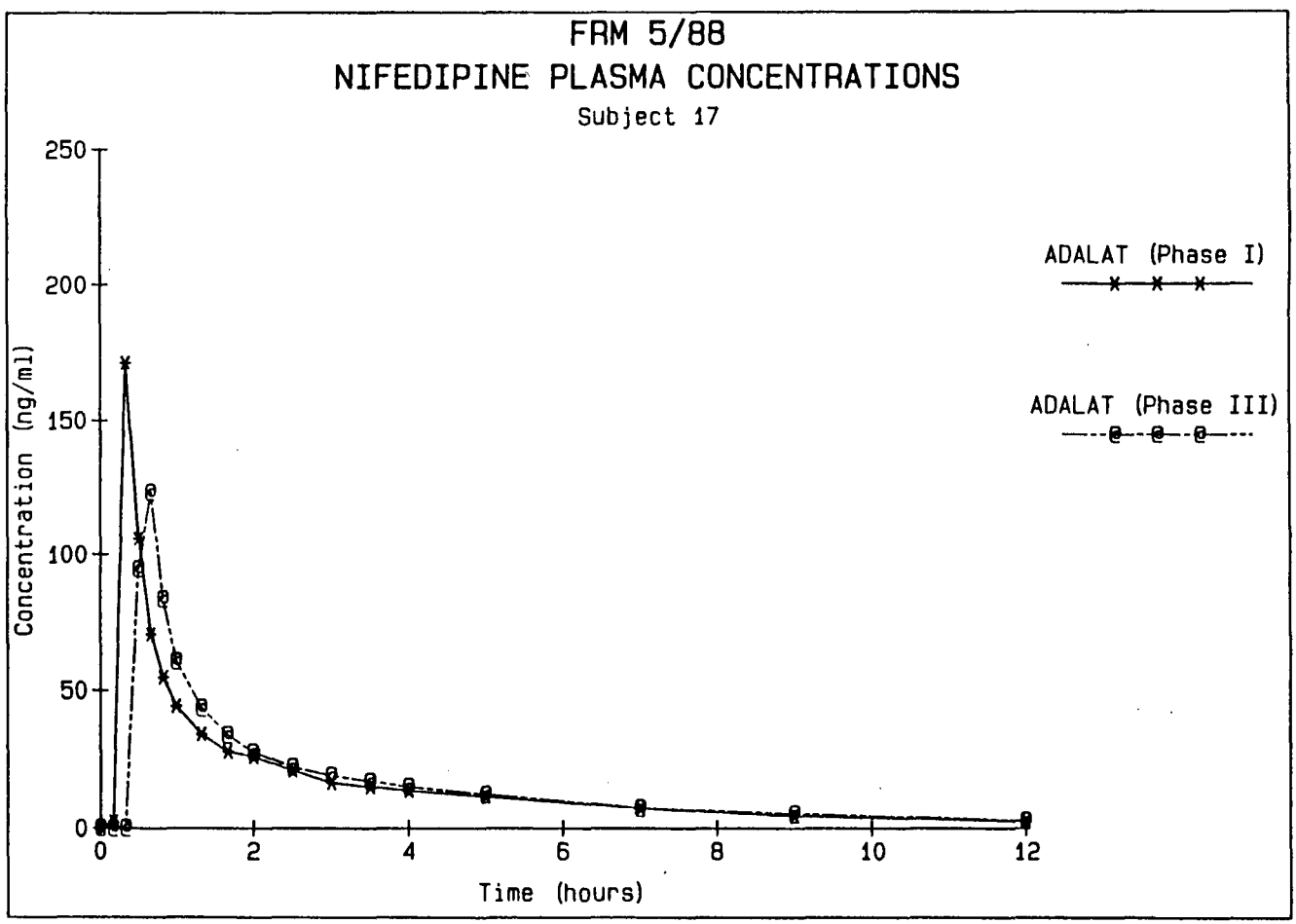

FRM 5/88
NIFEDIPINE PLASMA CONCENTRATIONS
Subject 16
Concentration (ng/ml)
250
200
150
100
50
0
0
2
4
6
8
10
12
Time (hours)
ADALAT (Phase I)
ADALAT + TAGAMET
ADALAT + TAGAMET + HCl


FRM 5/88
NIFEDIPINE PLASMA CONCENTRATIONS
Subject 16
Concentration (ng/ml)
250
200
150
100
50
0
0
2
4
6
8
10
12
Time (hours)
ADALAT (Phase I)
ADALAT (Phase III)

NM

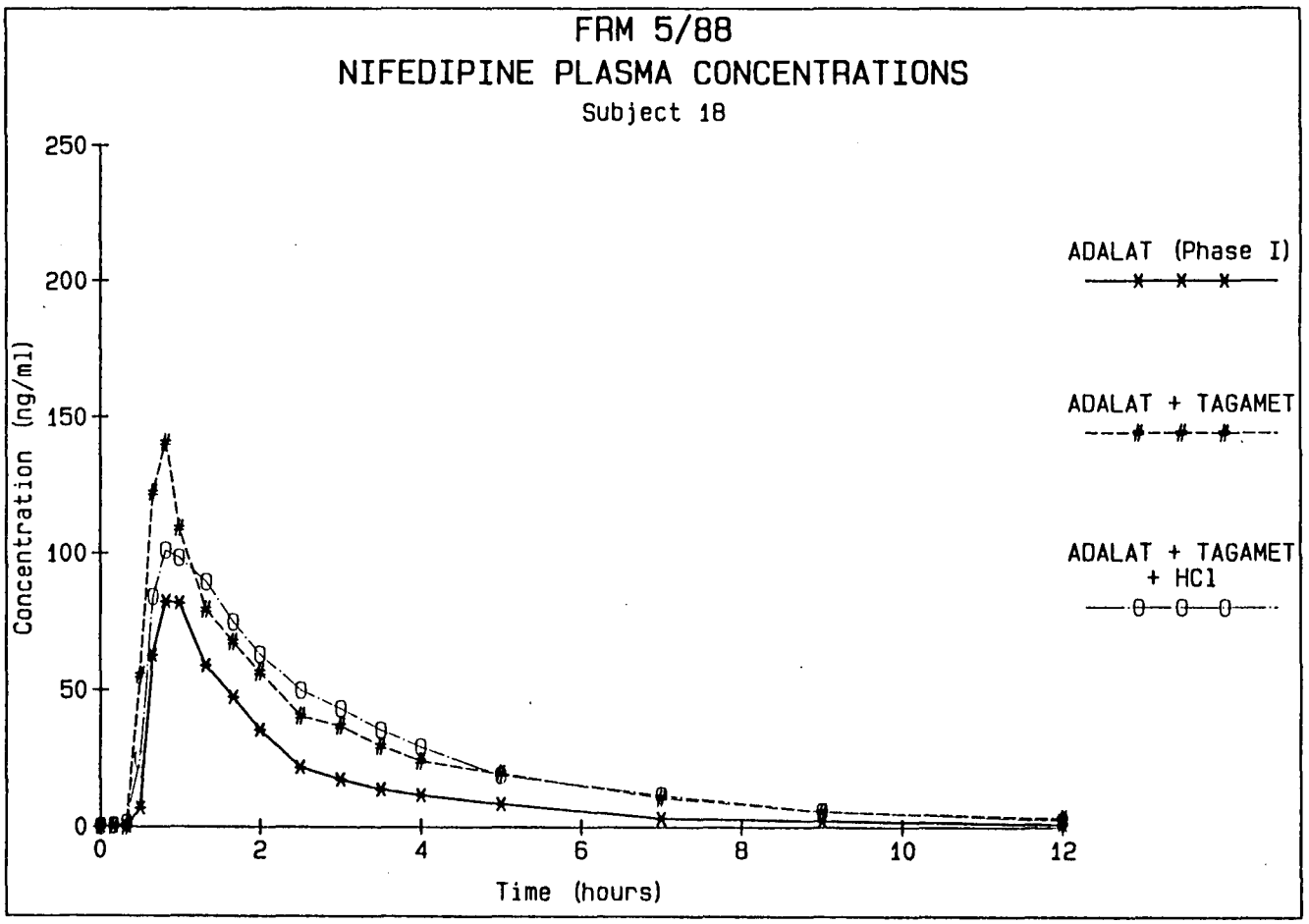
Fig. 3.24

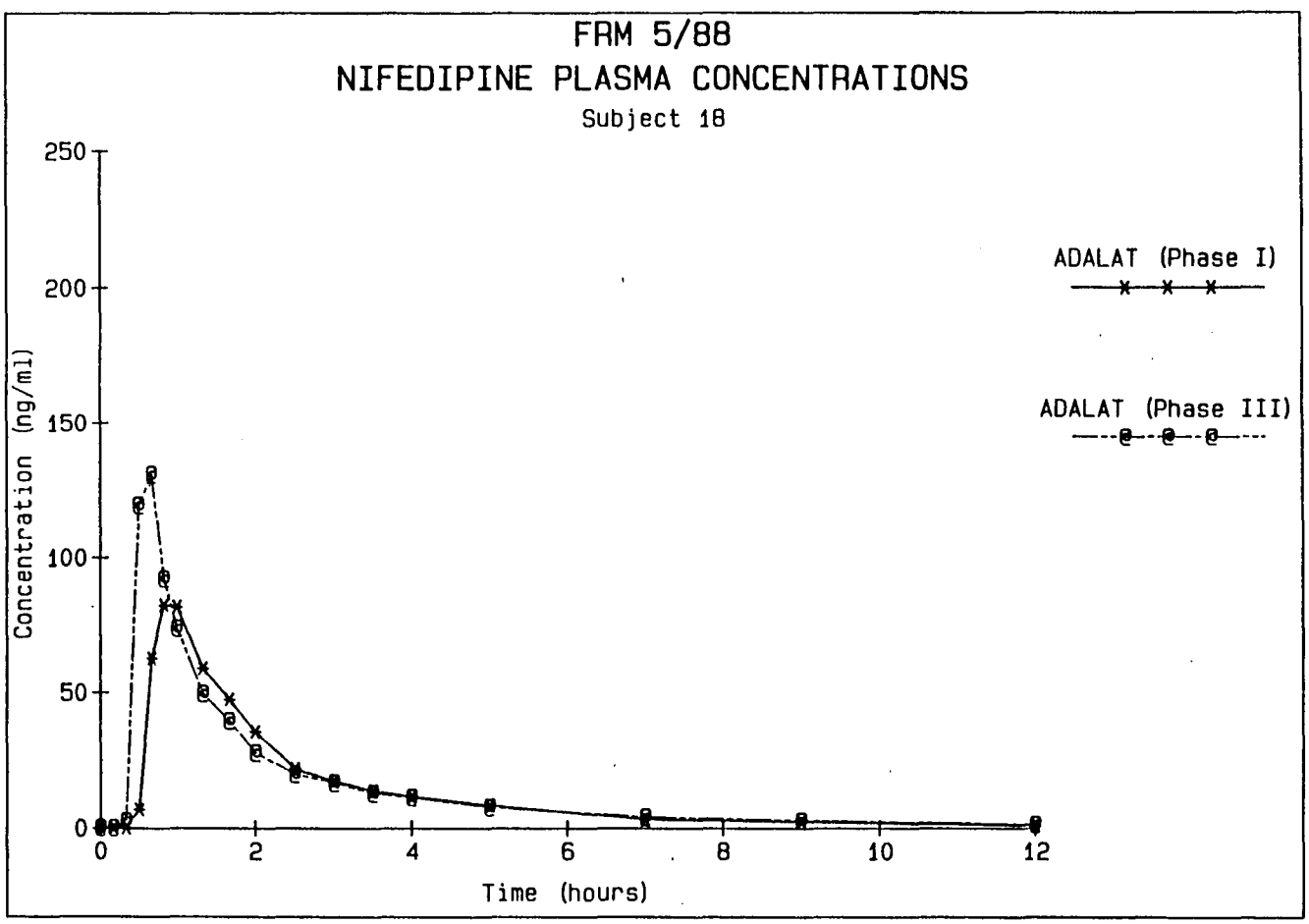

FRM 5/88
NIFEDIPINE PLASMA CONCENTRATIONS
Subject 17
Concentration (ng/ml)
250
200
150
100
50
0
0
2
4
6
8
10
12
Time (hours)
ADALAT (Phase I)
ADALAT + TAGAMET
ADALAT + TAGAMET + HCl


FRM 5/88
NIFEDIPINE PLASMA CONCENTRATIONS
Subject 17
Concentration (ng/ml)
250
200
150
100
50
0
0
2
4
6
8
10
12
Time (hours)
ADALAT (Phase I)
ADALAT (Phase III)

EO

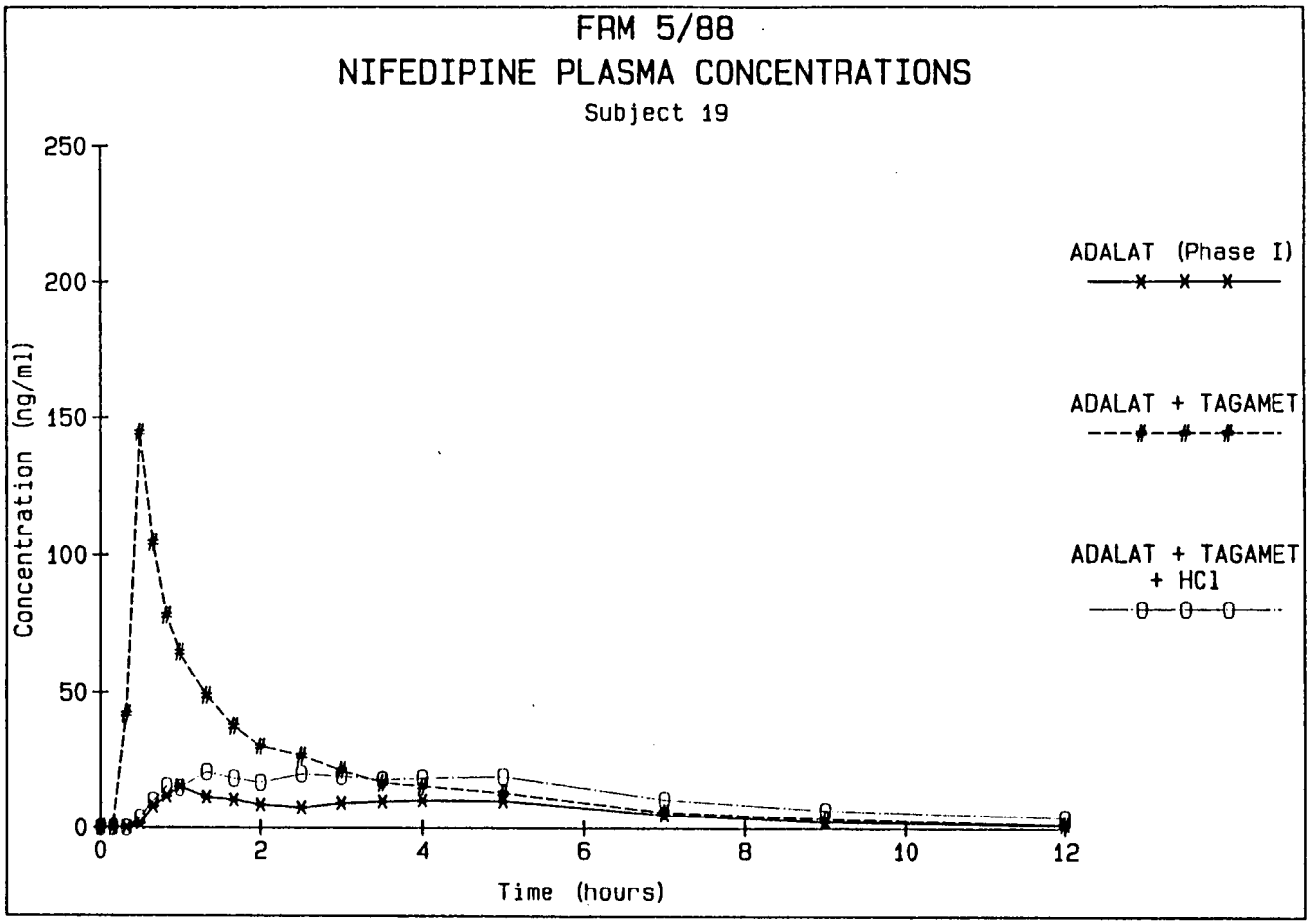
Fig. 3.25

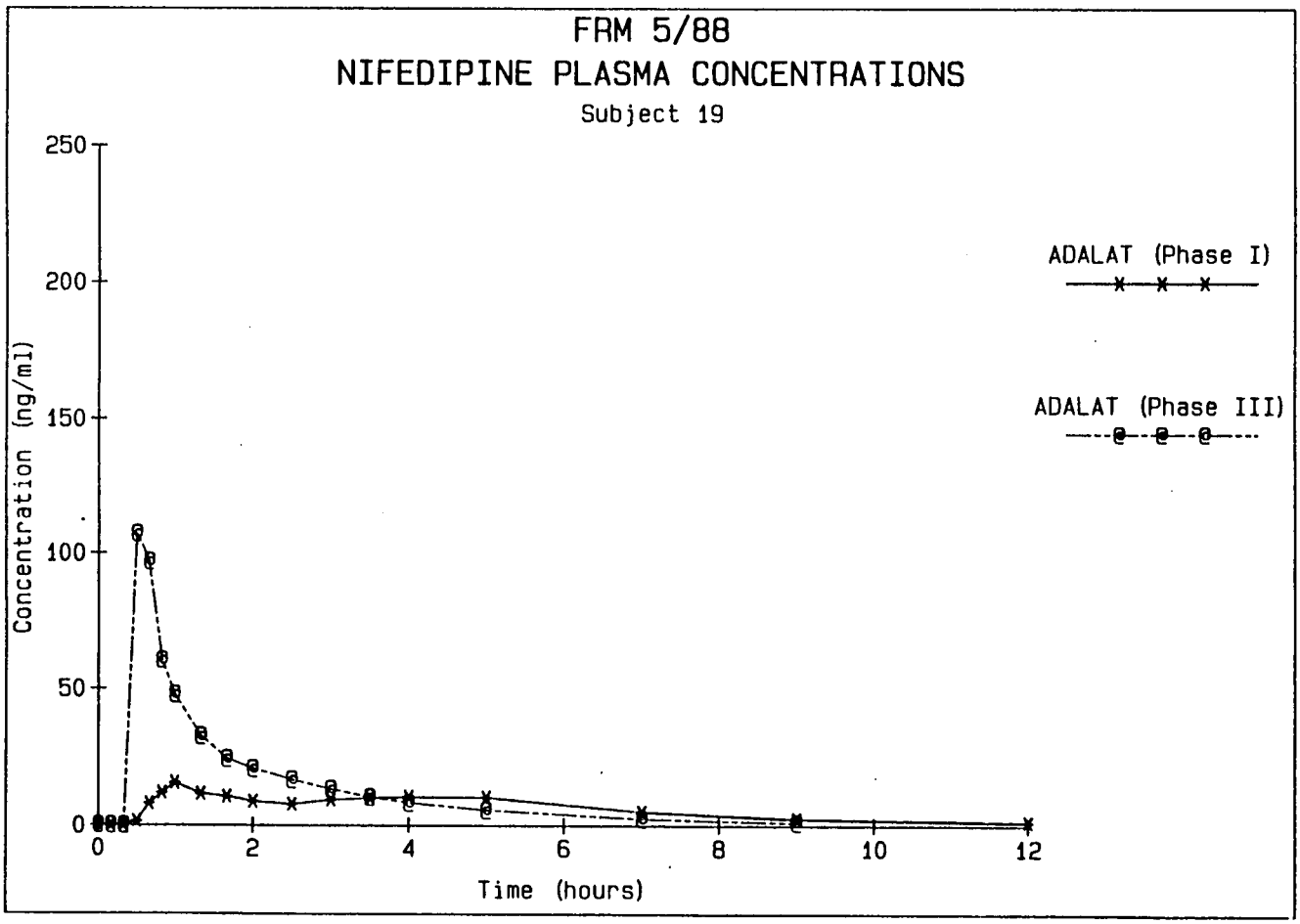

FRM 5/88
NIFEDIPINE PLASMA CONCENTRATIONS
Subject 18
Concentration (ng/ml)
250
200
150
100
50
0
0
2
4
6
8
10
12
Time (hours)
ADALAT (Phase I)
ADALAT + TAGAMET
ADALAT + TAGAMET + HCl


FRM 5/88
NIFEDIPINE PLASMA CONCENTRATIONS
Subject 18
Concentration (ng/ml)
250
200
150
100
50
0
0
2
4
6
8
10
12
Time (hours)
ADALAT (Phase I)
ADALAT (Phase III)

NM

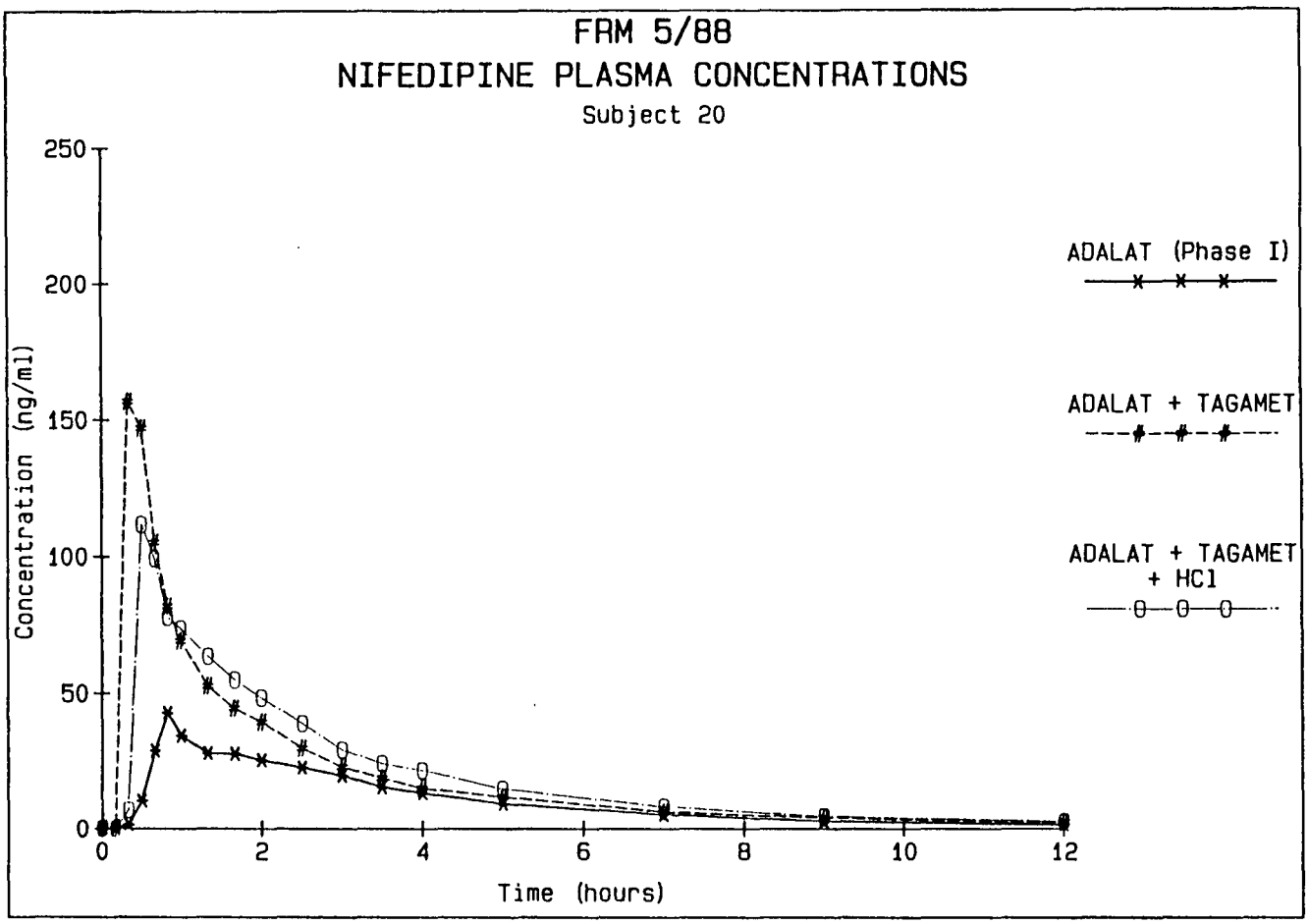
Fig. 3.26

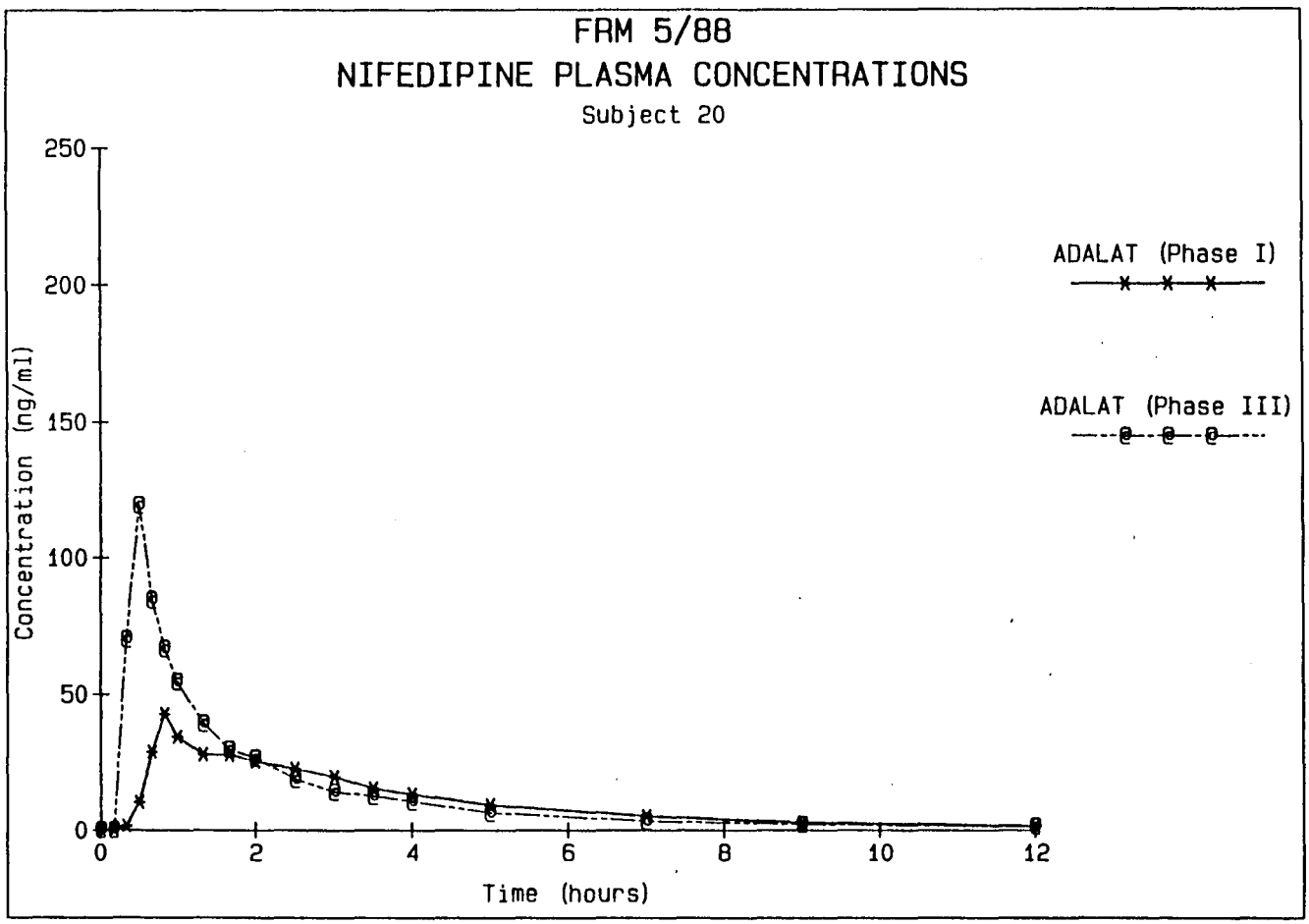

FRM 5/88
NIFEDIPINE PLASMA CONCENTRATIONS
Subject 19
Concentration (ng/ml)
250
200
150
100
50
0
0
2
4
6
8
10
12
Time (hours)
ADALAT (Phase I)
ADALAT + TAGAMET
ADALAT + TAGAMET + HCl


FRM 5/88
NIFEDIPINE PLASMA CONCENTRATIONS
Subject 19
Concentration (ng/ml)
250
200
150
100
50
0
0
2
4
6
8
10
12
Time (hours)
ADALAT (Phase I)
ADALAT (Phase III)

NM

Fig. 3.27


FRM 5/88
NIFEDIPINE PLASMA CONCENTRATIONS
Subject 20
Concentration (ng/ml)
250
200
150
100
50
0
0
2
4
6
8
10
12
Time (hours)
ADALAT (Phase I)
ADALAT + TAGAMET
ADALAT + TAGAMET + HCl


FRM 5/88
NIFEDIPINE PLASMA CONCENTRATIONS
Subject 20
Concentration (ng/ml)
250
200
150
100
50
0
0
2
4
6
8
10
12
Time (hours)
ADALAT (Phase I)
ADALAT (Phase III)

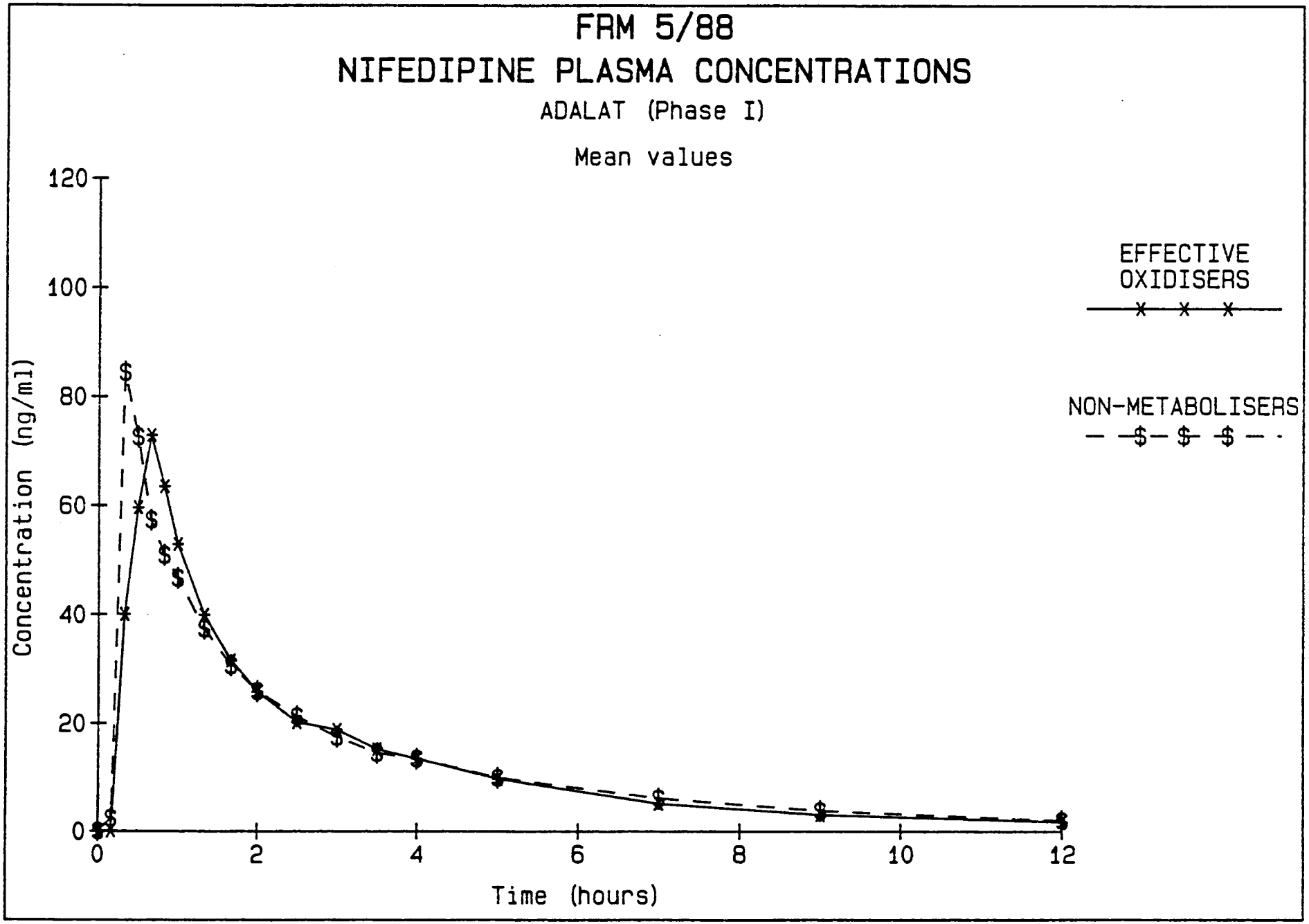

FRM 5/88
NIFEDIPINE PLASMA CONCENTRATIONS
ADALAT (Phase I)
Mean values
EFFECTIVE OXIDISERS
NON-METABOLISERS
Concentration (ng/ml)
120
100
80
60
40
20
0
0
2
4
6
8
10
12
Time (hours)

Fig. 3.28

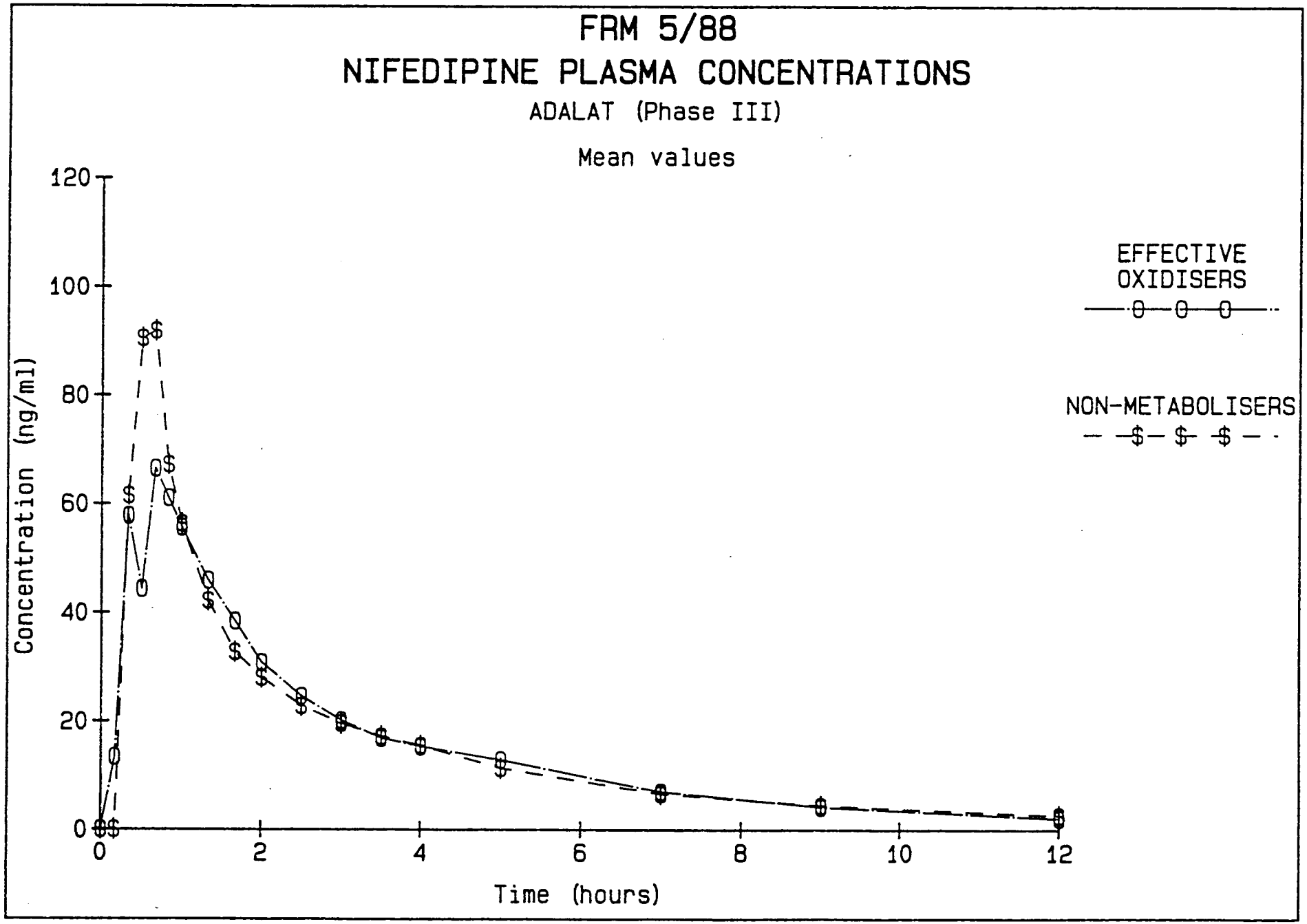

FRM 5/88
NIFEDIPINE PLASMA CONCENTRATIONS
ADALAT (Phase III)
Mean values
EFFECTIVE OXIDISERS
NON-METABOLISERS
Concentration (ng/ml)
120
100
80
60
40
20
0
0
2
4
6
8
10
12
Time (hours)

Fig. 3.27

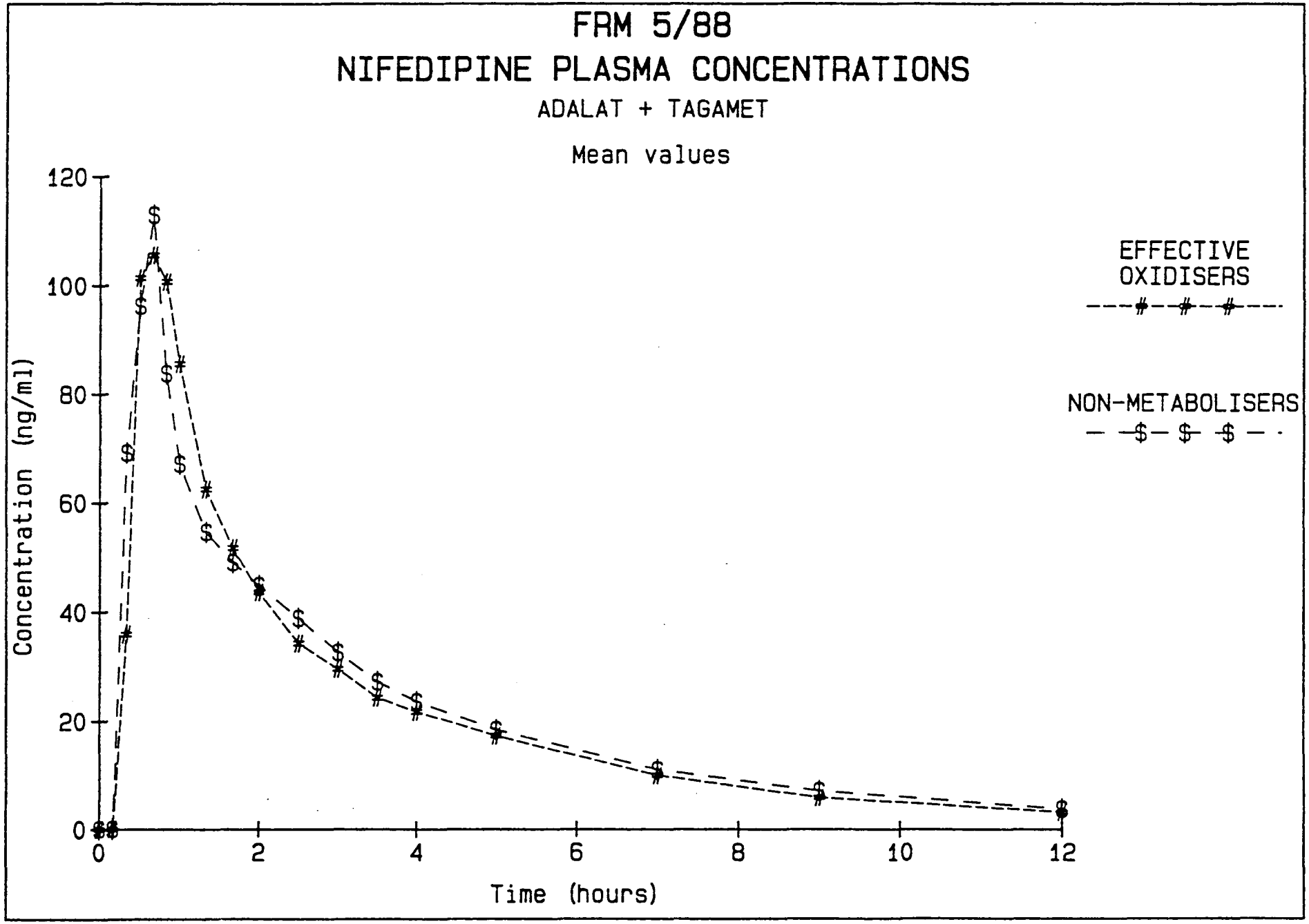

FRM 5/88
NIFEDIPINE PLASMA CONCENTRATIONS
ADALAT + TAGAMET
Mean values
EFFECTIVE OXIDISERS
NON-METABOLISERS
Concentration (ng/ml)
120
100
80
60
40
20
0
0
2
4
6
8
10
12
Time (hours)

Fig. 3.30

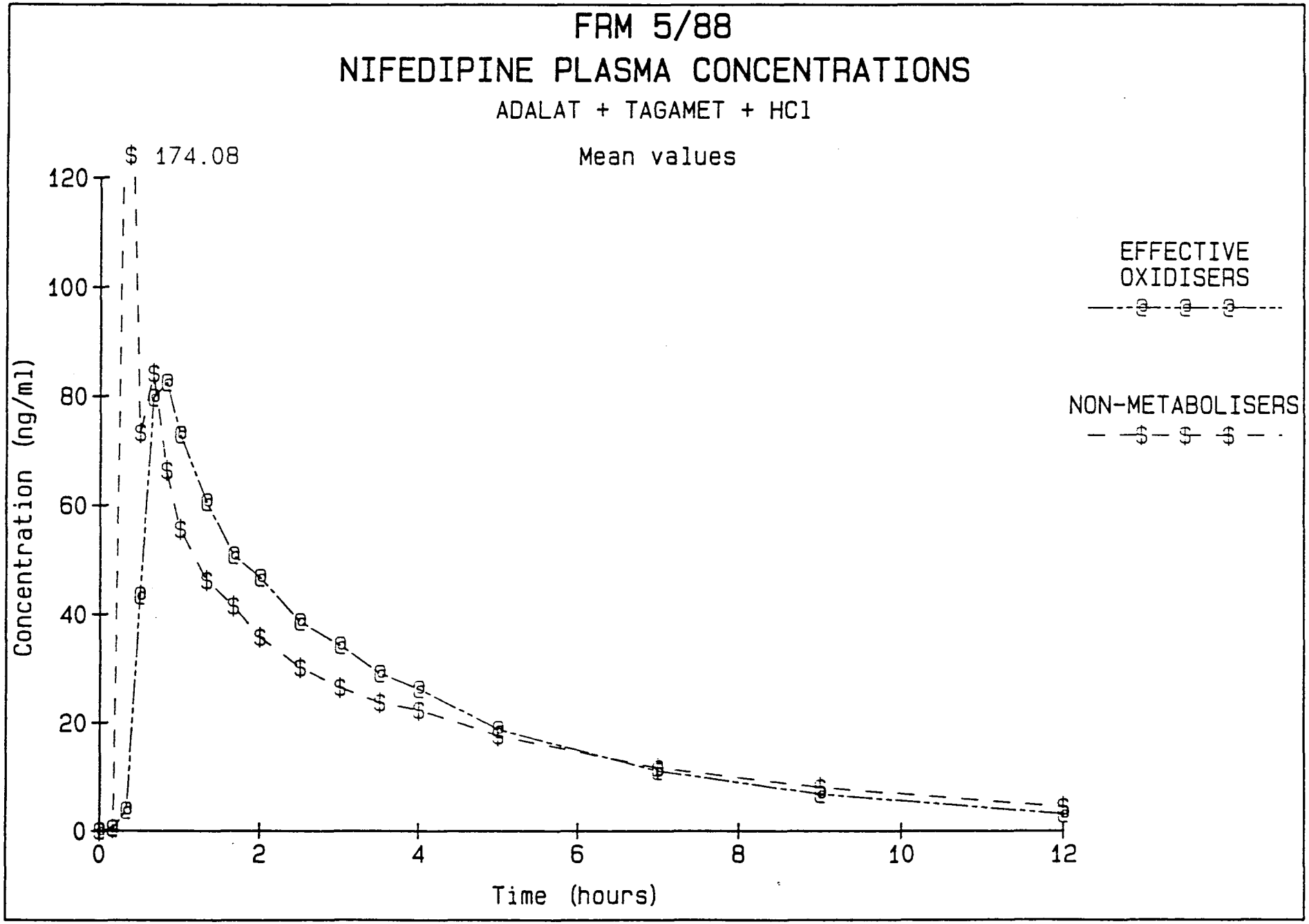

FRM 5/88
NIFEDIPINE PLASMA CONCENTRATIONS
ADALAT + TAGAMET + HCl
Mean values
$ 174.08
EFFECTIVE OXIDISERS
NON-METABOLISERS
Concentration (ng/ml)
120
100
80
60
40
20
0
0
2
4
6
8
10
12
Time (hours)

Fig. 3.31

3.3.1 Pharmacokinetic parameters of nifedipine

3.3.1.1 Effective oxidisers and non-metabolisers of sparteine

The mean and individual nifedipine values of C_{max}, T_{max}, AUD, AUDC, %Extr, $t_{\frac{1}{2}};z$, Cl-tot/f, MT-vsys and V-sys/f of the four different phases are summarised in Tables 3.15 - 3.18 (Cl-tot/f and V-sys/f are only expressed per body mass). Mean (SD) values of each parameter are summarised in Table 3.19. See Table 3.24 for a frequency table and Fig. 3.32 for a histogram of T_{max}.

Table 3.15 **NIFEDIPINE PHARMACOKINETIC PARAMETERS**
PHASE I: Nifedipine

Subj No	C_{max} (ng/ml)	T_{max} (h)	AUD (ng.h/ml)	AUDC (ng.h/ml)	%Extr	t½;z (h)	Cl-tot/f (ml/min/kg)	MT-vsys (h)	V-sys/f (l/kg)
1	101	0.50	122	127	3.27	2.83	16.2	2.80	2.73
2	101	0.50	257	263	2.40	2.10	9.90	3.38	2.01
3	76.2	0.50	112	115	3.03	1.84	17.0	2.39	2.44
4	125	0.50	236	249	5.17	3.10	8.36	3.67	1.84
5	109	0.50	115	118	2.92	2.40	16.4	2.67	2.62
6	24.6	1.33	79.4	83.4	4.75	2.40	22.2	3.91	5.22
7	50.5	0.67	77.1	79.3	2.81	2.30	27.3	3.32	5.44
8	19.7	1.00	73.5	77.3	4.91	2.62	26.3	4.62	7.29
9	129	0.33	153	157	2.60	2.20	14.3	2.47	2.12
10	160	0.50	271	278	2.70	2.51	7.68	2.88	1.33
11	123	0.67	241	253	4.96	2.89	9.14	3.87	2.12
12	26.3	3.00	106	110	4.28	2.05	19.9	5.23	6.23
13	146	0.33	218	240	9.41	3.78	8.16	4.87	2.39
14	116	0.33	99.9	103	3.15	2.53	20.4	2.74	3.37
15	124	0.50	211	222	4.75	3.09	9.39	3.65	2.06
16	72.8	0.83	183	190	4.10	2.22	11.4	3.79	2.58
17	171	0.33	191	202	5.69	3.26	10.1	3.66	2.21
18	82.2	0.83	157	159	1.87	1.94	14.5	2.91	2.54
19	15.5	1.00	72.8	76.4	4.76	2.00	30.3	5.03	9.13
20	42.6	0.83	123	127	3.56	2.21	17.5	3.91	4.10
MEAN	90.7	0.75	155	162	4.05	2.51	15.8	3.59	3.49
SD	48.1	0.59	66.1	69.6	1.67	0.51	6.85	0.85	2.10
MIN	15.5	0.33	72.8	76.4	1.87	1.84	7.68	2.39	1.33
MAX	171	3.00	271	278	9.41	3.78	30.3	5.23	9.13
N	20	20	20	20	20	20	20	20	20

Table 3.16 **NIFEDIPINE PHARMACOKINETIC PARAMETERS**
PHASE III: Nifedipine

Subj No	Cmax (ng/ml)	Tmax (h)	AUD (ng.h/ml)	AUDC (ng.h/ml)	%Extr	t½;z (h)	Cl-tot/f (ml/min/kg)	MT-vsys (h)	V-sys/f (l/kg)
1	33.0	0.83	124	132	5.80	2.58	15.6	4.61	4.31
2	37.5	2.00	227	247	8.34	2.91	10.5	5.55	3.50
3	26.6	1.00	111	115	3.60	2.00	17.1	4.55	4.65
4	183	0.50	180	183	1.78	2.07	11.4	2.48	1.69
5	151	0.33	185	189	2.25	2.07	10.3	2.46	1.51
6	55.7	0.67	94.4	105	10.0	3.83	17.7	4.94	5.24
7	17.4	0.83	95.0	102	6.42	2.66	21.3	5.64	7.22
8	91.6	1.00	171	177	2.84	2.42	11.5	3.21	2.22
9	139	0.67	151	153	1.79	2.82	14.7	2.51	2.21
10	102	1.67	324	336	3.59	2.31	6.36	4.00	1.53
11	126	0.67	243	254	4.33	2.63	9.12	3.77	2.06
12	22.1	1.00	122	126	3.46	1.79	17.4	4.83	5.05
13	165	0.50	298	337	11.4	3.98	5.82	5.29	1.85
14	153	0.50	161	166	2.90	2.24	12.7	2.85	2.17
15	102	0.50	212	222	4.41	2.70	9.39	3.67	2.07
16	110	1.00	203	210	3.38	2.45	10.3	3.12	1.92
17	123	0.67	192	203	5.71	3.05	10.0	3.92	2.35
18	130	0.67	178	182	2.11	2.22	12.7	2.71	2.07
19	107	0.50	124	127	2.06	1.70	18.3	2.29	2.51
20	119	0.50	158	164	3.23	2.63	13.6	2.80	2.28
MEAN	99.8	0.80	178	186	4.47	2.55	12.8	3.76	2.92
SD	51.0	0.41	62.1	67.6	2.73	0.59	4.12	1.12	1.55
MIN	17.4	0.33	94.4	102	1.78	1.70	5.82	2.29	1.51
MAX	183	2.00	324	337	11.4	3.98	21.3	5.64	7.22
N	20	20	20	20	20	20	20	20	20

Table 3.17 **NIFEDIPINE PHARMACOKINETIC PARAMETERS**
Nifedipine + Cimetidine

Subj No	Cmax (ng/ml)	Tmax (h)	AUD (ng.h/ml)	AUDC (ng.h/ml)	%Extr	t½;z (h)	Cl-tot/f (ml/min/kg)	MT-vsys (h)	V-sys/f (l/kg)
1	45.7	2.00	183	197	6.86	2.56	10.5	5.03	3.16
2	243	0.50	350	365	4.05	2.59	7.14	3.44	1.47
3	148	0.50	212	218	2.48	1.96	9.00	2.89	1.56
4	184	0.67	387	413	6.41	2.93	5.04	4.30	1.30
5	115	0.50	191	198	3.56	2.79	9.77	3.13	1.83
6	83.5	0.67	144	152	5.52	2.78	12.2	3.97	2.90
7	47.2	1.00	185	195	5.08	2.19	11.1	4.91	3.27
8	110	0.67	176	183	4.17	2.50	11.1	4.03	2.68
9	192	0.67	334	348	4.11	2.53	6.47	3.63	1.41
10	204	0.83	455	477	4.59	2.70	4.48	3.97	1.07
11	189	0.50	260	274	5.02	2.89	8.46	3.68	1.87
12	118	0.67	266	274	3.08	2.43	8.00	3.50	1.68
13	132	0.50	296	325	9.02	3.56	6.04	5.05	1.83
14	215	0.33	216	227	4.97	2.99	9.30	3.39	1.89
15	174	0.50	277	296	6.48	3.12	7.04	4.15	1.76
16	154	0.67	298	311	4.42	2.58	6.95	3.63	1.51
17	38.9	2.50	210	229	8.46	3.07	8.88	5.59	2.98
18	141	0.83	293	303	3.51	2.28	7.63	3.55	1.62
19	144	0.50	205	208	1.73	2.17	11.1	2.95	1.96
20	156	0.33	237	245	3.26	2.39	9.09	2.98	1.62
MEAN	142	0.77	259	272	4.84	2.65	8.46	3.89	1.97
SD	57.1	0.54	79.1	83.7	1.87	0.38	2.13	0.76	0.65
MIN	38.9	0.33	144	152	1.73	1.96	4.48	2.89	1.07
MAX	243	2.50	455	477	9.02	3.56	12.2	5.59	3.27
N	20	20	20	20	20	20	20	20	20

Table 3.18 **NIFEDIPINE PHARMACOKINETIC PARAMETERS**
Nifedipine + Cimetidine + HCl

Subj No	Cmax (ng/ml)	Tmax (h)	AUD (ng.h/ml)	AUDC (ng.h/ml)	%Extr	t½;z (h)	Cl-tot/f (ml/min/kg)	MT-vsys (h)	V-sys/f (l/kg)
1	53.5	1.67	225	237	5.03	2.51	8.69	4.31	2.25
2	177	0.33	293	304	3.77	2.94	8.57	3.28	1.69
3	112	0.83	200	206	2.98	2.37	9.51	3.35	1.91
4	339	0.33	445	474	5.99	3.43	4.40	3.89	1.03
5	117	0.83	218	225	2.94	2.89	8.63	3.21	1.66
6	75.1	0.50	159	169	6.32	3.06	10.9	4.48	2.94
7	99.6	0.50	163	170	3.92	2.84	12.7	3.55	2.71
8	131	0.67	188	195	3.29	2.69	10.4	3.31	2.07
9	26.8	1.67	133	149	10.95	3.23	15.1	5.67	5.14
10	65.5	1.00	314	335	6.08	2.79	6.39	4.84	1.85
11	113	0.83	305	328	6.95	2.87	7.06	4.66	1.98
12	46.3	2.00	261	274	4.68	2.33	8.00	4.73	2.27
13	30.9	4.00	241	345	30.06	5.41	5.68	10.51	3.58
14	176	0.33	161	167	3.56	2.62	12.6	2.94	2.22
15	61.4	1.33	277	297	6.84	3.42	7.00	4.99	2.10
16	143	0.67	329	341	3.51	2.46	6.34	3.54	1.35
17	155	0.67	235	251	6.28	2.87	8.11	4.05	1.97
18	101	0.83	296	305	3.00	2.50	7.58	3.63	1.65
19	20.7	1.33	145	161	10.1	2.77	14.4	6.09	5.26
20	112	0.50	242	250	3.17	2.19	8.89	3.42	1.82
MEAN	108	1.04	242	259	6.47	2.91	9.05	4.42	2.37
SD	72.1	0.85	76.8	83.2	6.00	0.68	2.88	1.67	1.11
MIN	20.7	0.33	133	149	2.94	2.19	4.40	2.94	1.03
MAX	339	4.00	445	474	30.1	5.41	15.1	10.5	5.26
N	20	20	20	20	20	20	20	20	20

Table 3.19 PHARMACOKINETIC PARAMETERS OF NIFEDIPINE (Effective oxidisers and non-metabolisers of sparteine) [Mean (SD) values]

PARAMETER	NIFED (I)	NIFED (III)	NIFED CIMET	NIFED CIMET HCl
Cmax (ng/ml)	90.8 (48.1)	99.8 (51.0)	142 (57.1)	108 (72.1)
Tmax (h)	0.75 (0.59)	0.80 (0.41)	0.77 (0.54)	1.04 (0.85)
AUD (ng.h/ml)	155 (66.1)	178 (62.1)	259 (79.1)	242 (76.8)
AUDC (ng.h/ml)	162 (69.6)	186 (67.6)	272 (83.7)	259 (83.2)
%Extr	4.05 (1.67)	4.47 (2.73)	4.84 (1.87)	6.47 (6.00)
$t_{\frac{1}{2}};z$ (h)	2.51 (0.51)	2.55 (0.59)	2.65 (0.38)	2.91 (0.68)
Cl-tot/f (ml/min)	1243 (548)	1001 (336)	666 (192)	707 (222)
Cl-tot/f (ml/min/kg)	15.8 (6.85)	12.8 (4.12)	8.46 (2.13)	9.05 (2.88)
MT-vsys (h)	3.59 (0.85)	3.76 (1.12)	3.89 (0.76)	4.42 (1.67)
V-sys/f (l)	273 (162)	230 (127)	156 (57.6)	185 (83.9)
V-sys/f (l/kg)	3.49 (2.09)	2.92 (1.55)	1.97 (0.65)	2.37 (1.11)

NIFED = Nifedipine
CIMET = Cimetidine (steady-state)
HCl = Diluted Hydrochloric Acid
I = Phase I
III = Phase III
(See Appendix 1 : Protocol)

The mean values of each pharmacokinetic parameter are compared for the different phases and given in Table 3.20 - 3.23.

Table 3.20 MEAN PHARMACOKINETIC PARAMETERS OF NIFEDIPINE (Effective oxidisers and non-metabolisers of sparteine)

Parameter	Nifedipine (Phase I)	Nifedipine (Phase III)	PE*	CI*
C_{max} (ng/ml)	90.8	99.8	110	81-139
T_{max} (h)	0.75	0.80		
AUD (ng.h/ml)	155	178		
AUDC (ng.h/ml)	162	186	115	102-128
%Extr	4.05	4.47		
$t_{\frac{1}{2}};z$ (h)	2.51	2.55	102	95-109
Cl-tot/f (ml/min)	1243	1001		
Cl-tot/f (ml/min/kg)	15.8	12.8	81	71-90
MT-vsys (h)	3.59	3.76	105	90-120
V-sys/f (l)	273	230		
V-sys/f (l/kg)	3.49	2.92	84	65-102

*

PE = Point estimate for the ratio nifedipine (Phase III) relative to nifedipine (Phase I) [expressed as a percentage]

CI = 90% confidence intervals for the ratio mentioned above [expressed as a percentage]

It is interesting to note a difference in the pharmacokinetic parameters when the two phases during which nifedipine was given as only drug, are compared. The values of AUDC are discussed as an example. All the other parameters can be interpreted in the same way.

The sample mean for AUDC of nifedipine in phase III of this study was 15% above that of nifedipine in phase I. The true mean for AUDC of nifedipine (Phase III) lies, with 90% certainty, between 2% and 28% above that of nifedipine (Phase I).

Table 3.21 MEAN PHARMACOKINETIC PARAMETERS OF NIFEDIPINE (Effective oxidisers and non-metabolisers of sparteine)

Parameter	Nifedipine (Phase I)	Nifedipine + Cimetidine	PE*	CI*
C_{max} (ng/ml)	90.8	142	156	128-185
T_{max} (h)	0.75	0.77		
AUD (ng.h/ml)	155	259		
AUDC (ng.h/ml)	162	272	168	155-181
%Extr	4.05	4.84		
$t_{\frac{1}{2}};z$ (h)	2.51	2.65	105	98-112
Cl-tot/f (ml/min)	1243	666		
Cl-tot/f (ml/min/kg)	15.8	8.46	53	44-63
MT-vsys (h)	3.59	3.89	108	94-123
V-sys/f (l)	273	156		
V-sys/f (l/kg)	3.49	1.97	56	38-75

*

PE = Point estimate for the ratio nifedipine + cimetidine (steady-state) relative to nifedipine (Phase I) [expressed as a percentage]

CI = 90% confidence intervals for the ratio mentioned above [expressed as a percentage]

Table 3.22 MEAN PHARMACOKINETIC PARAMETERS OF NIFEDIPINE (Effective oxidisers and non-metabolisers of sparteine)

Parameter	Nifedipine (Phase I)	Nifedipine + Cimetidine + HCl	PE*	CI*
C_{max} (ng/ml)	90.8	108	119	90-147
T_{max} (h)	0.75	1.04		
AUD (ng.h/ml)	155	242		
AUDC (ng.h/ml)	162	259	160	147-173
%Extr	4.05	6.47		
$t_{½};z$ (h)	2.51	2.91	116	109-123
Cl-tot/f (ml/min)	1243	707		
Cl-tot/f (ml/min/kg)	15.8	9.05	57	48-67
MT-vsys (h)	3.59	4.42	123	108-138
V-sys/f (l)	273	185		
V-sys/f (l/kg)	3.49	2.37	68	49-87

*

PE = Point estimate for the ratio nifedipine + cimetidine (steady-state) + diluted HCl relative to nifedipine (Phase I) [expressed as a percentage]

CI = 90% confidence intervals for the ratio mentioned above [expressed as a percentage]

Table 3.23 MEAN PHARMACOKINETIC PARAMETERS OF NIFEDIPINE (Effective oxidisers and non-metabolisers of sparteine)

Parameter	Nifedipine + Cimetidine	Nifedipine + Cimetidine + HCl	PE*	CI*
C_{max} (ng/ml)	142	108	76	58-94
T_{max} (h)	0.77	1.04		
AUD (ng.h/ml)	259	242		
AUDC (ng.h/ml)	272	259	95	88-103
%Extr	4.84	6.47		
$t_{\frac{1}{2};z}$ (h)	2.65	2.91	110	103-116
Cl-tot/f (ml/min)	666	707		
Cl-tot/f (ml/min/kg)	8.46	9.05	107	89-125
MT-vsys (h)	3.89	4.42	114	100-127
V-sys/f (l)	156	185		
V-sys/f (l/kg)	1.97	2.37	120	87-154

*

PE = Point estimate for the ratio nifedipine + cimetidine (steady-state) + diluted HCl relative to nifedipine + cimetidine (steady-state) [expressed as a percentage]

CI = 90% confidence intervals for the ratio mentioned above [expressed as a percentage]

An apparent difference in the rate of nifedipine absorption is seen when these two phases are compared. Adding diluted HCl attenuated the rate of absorption. The degree of absorption was not affected by addition of HCl.

The time to maximum concentration (Tmax)

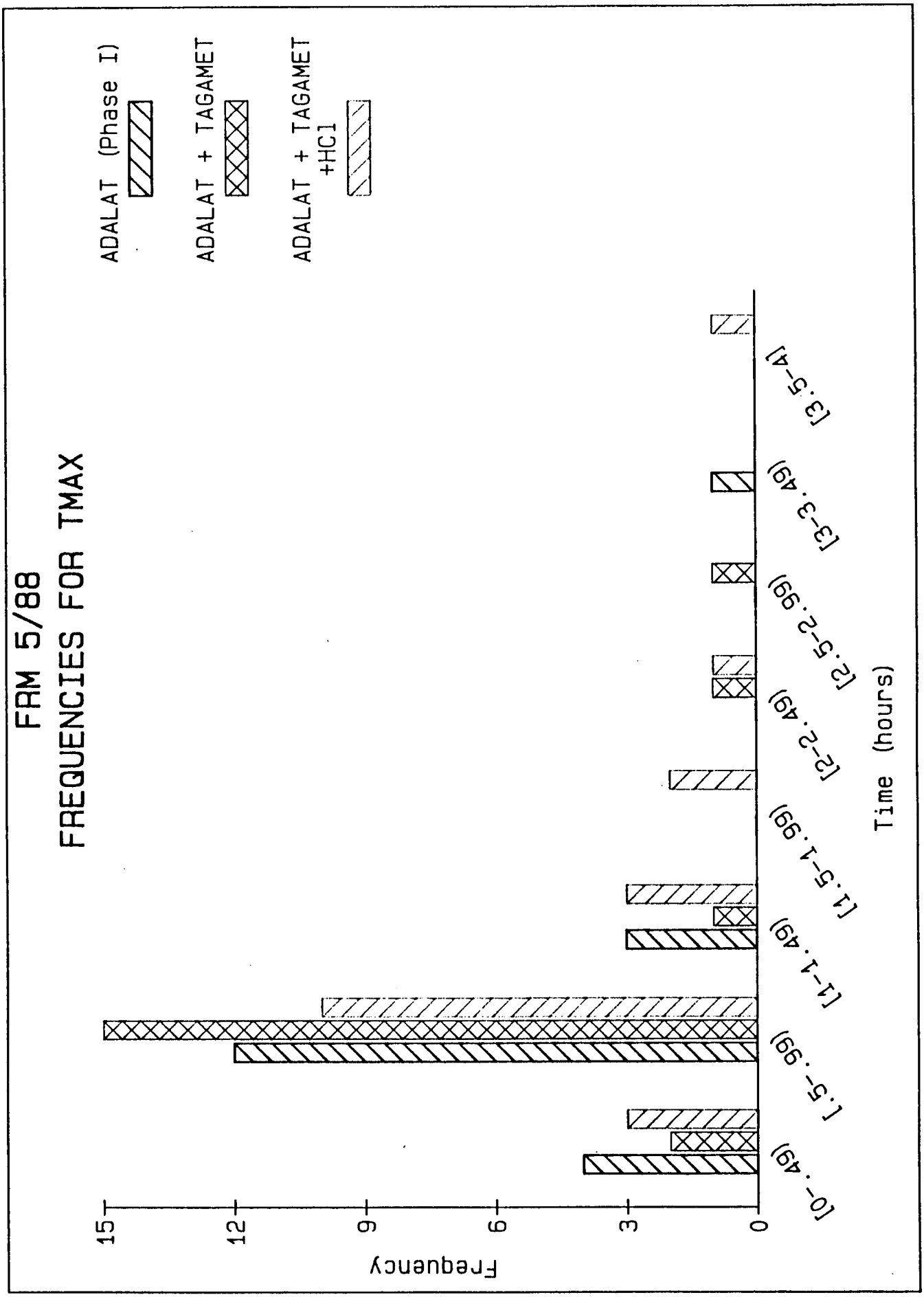
	Mean (h)	Median	Range
Nifedipine Phase I	0.75	0.50	0.33-3.00
Nifedipine + Cimetidine	0.77	0.67	0.33-2.50
Nifedipine + Cimetidine + HCl	1.04	0.83	0.33-4.00

Table 3.24 FREQUENCY TABLE FOR T_{max}

Time interval (h)	Nifedipine (Phase I)	Nifedipine + Cimetidine	Nifedipine + Cimetidine + HCl
0.00 - 0.49	4	2	3
0.50 - 0.99	12	15	10
1.00 - 1.49	3	1	3
1.50 - 1.99	0	0	2
2.00 - 2.49	0	1	1
2.50 - 2.99	0	1	0
3.00 - 3.49	1	0	0
3.50 - 4.00	0	0	1
TOTAL	20	20	20

See Fig. 3.32 for histogram.

Fig. 3.32


FRM 5/88
FREQUENCIES FOR TMAX
ADALAT (Phase I)
ADALAT + TAGAMET
ADALAT + TAGAMET +HCl
Frequency
0
3
6
9
12
15
Time (hours)
[0-.49)
[.5-.99)
[1-1.49)
[1.5-1.99)
[2-2.49)
[2.5-2.99)
[3-3.49)
[3.5-4]

3.3.1.2 Effective oxidisers of sparteine

The mean and individual nifedipine values of C_{max}, T_{max}, AUD, AUDC, %Extr, $t_{\frac{1}{2}}.z$, Cl-tot/f, MT-vsys and V-sys/f of the four different phases are summarised in Tables 3.26 - 3.29 (Cl-tot/f and V-sys/f are only expressed per body mass). Mean (SD) values of each parameter are summarised in Table 3.25. See Table 3.34 for a frequency table and Fig. 3.33 for a histogram of T_{max}.

Table 3.25 PHARMACOKINETIC PARAMETERS OF NIFEDIPINE (Effective oxidisers of sparteine) [Mean (SD) values]

PARAMETER	NIFED (I)	NIFED (III)	NIFED CIMET	NIFED CIMET HCl
Cmax (ng/ml)	84.9 (44.4)	84.4 (49.6)	137 (48.1)	93.4 (30.2)
Tmax (h)	0.93 (0.77)	0.83 (0.37)	0.67 (0.18)	0.93 (0.45)
AUD (ng.h/ml)	155 (68.6)	177 (73.8)	258 (86.2)	252 (63.1)
AUDC (ng.h/ml)	161 (71.5)	184 (75.6)	270 (90.5)	265 (67.3)
%Extr	3.62 (1.08)	4.36 (2.32)	4.37 (1.22)	4.72 (1.67)
$t_{\frac{1}{2}};z$ (h)	2.36 (0.40)	2.46 (0.57)	2.57 (0.36)	2.75 (0.34)
Cl-tot/f (ml/min)	1240 (540)	1050 (414)	677 (213)	673 (194)
Cl-tot/f (ml/min/kg)	15.5 (6.35)	13.2 (4.87)	8.46 (2.21)	8.42 (2.10)
MT-vsys (h)	3.46 (0.82)	3.97 (1.03)	3.74 (0.56)	4.10 (0.70)
V-sys/f (l)	260 (139)	267 (166)	152 (58.3)	163 (46.3)
V-sys/f (l/kg)	3.26 (1.70)	3.33 (2.02)	1.91 (0.67)	2.04 (0.49)

NIFED = Nifedipine
CIMET = Cimetidine (steady-state)
HCl = Diluted Hydrochloric Acid
I = Phase I
III = Phase III
(See Appendix 1 : Protocol)

Table 3.26 **NIFEDIPINE PHARMACOKINETIC PARAMETERS**
(Effective oxidisers of sparteine)
PHASE I: Nifedipine

Subj No	C_{max} (ng/ml)	T_{max} (h)	AUD (ng.h/ml)	AUDC (ng.h/ml)	%Extr	t½;z (h)	Cl-tot/f (ml/min/kg)	MT-vsys (h)	V-sys/f (l/kg)
3	76.2	0.50	112	115	3.03	1.84	17.0	2.39	2.44
5	109	0.50	115	118	2.92	2.40	16.4	2.67	2.62
6	24.6	1.33	79.4	83.4	4.75	2.40	22.2	3.91	5.22
7	50.5	0.67	77.1	79.3	2.81	2.30	27.3	3.32	5.44
10	160	0.50	271	278	2.70	2.51	7.68	2.88	1.33
11	123	0.67	241	253	4.96	2.89	9.14	3.87	2.12
12	26.3	3.00	106	110	4.28	2.05	19.9	5.23	6.23
15	125	0.50	211	222	4.75	3.09	9.39	3.65	2.06
16	72.8	0.83	183	190	4.10	2.22	11.4	3.79	2.58
18	82.2	0.83	157	159	1.87	1.94	14.5	2.91	2.54
MEAN	84.9	0.93	155	161	3.62	2.36	15.5	3.46	3.26
SD	44.4	0.77	68.6	71.5	1.08	0.40	6.35	0.82	1.70
MIN	24.6	0.50	77.1	79.3	1.87	1.84	7.68	2.39	1.33
MAX	160	3.00	271	278	4.96	3.09	27.3	5.23	6.23
N	10	10	10	10	10	10	10	10	10

Table 3.27 **NIFEDIPINE PHARMACOKINETIC PARAMETERS**
(Effective oxidisers of sparteine)
PHASE III: Nifedipine

Subj No	Cmax (ng/ml)	Tmax (h)	AUD (ng.h/ml)	AUDC (ng.h/ml)	%Extr	t½;z (h)	Cl-tot/f (ml/min/kg)	MT-vsys (h)	V-sys/f (l/kg)
3	26.6	1.00	111	115	3.60	2.00	17.1	4.55	4.65
5	151	0.33	185	189	2.25	2.07	10.3	2.46	1.51
6	55.7	0.67	94.4	105	10.0	3.83	17.7	4.94	5.24
7	17.4	0.83	95.0	102	6.42	2.66	21.3	5.64	7.22
10	102	1.67	324	336	3.59	2.31	6.36	4.00	1.53
11	126	0.67	243	254	4.33	2.63	9.12	3.77	2.06
12	22.1	1.00	122	126	3.46	1.79	17.4	4.83	5.05
15	102	0.50	212	222	4.41	2.70	9.39	3.67	2.07
16	110	1.00	203	210	3.38	2.45	10.3	3.12	1.92
18	130	0.67	178	182	2.11	2.22	12.7	2.71	2.07
MEAN	84.4	0.83	177	184	4.36	2.46	13.2	3.97	3.33
SD	49.6	0.37	73.8	75.6	2.32	0.57	4.87	1.03	2.02
MIN	17.4	0.33	94.4	102	2.11	1.79	6.36	2.46	1.51
MAX	151	1.67	324	336	10.0	3.83	21.3	5.64	7.22
N	10	10	10	10	10	10	10	10	10

Table 3.28 **NIFEDIPINE PHARMACOKINETIC PARAMETERS**
(Effective oxidisers of sparteine)
Nifedipine + Cimetidine

Subj No	Cmax (ng/ml)	Tmax (h)	AUD (ng.h/ml)	AUDC (ng.h/ml)	%Extr	t½;z (h)	Cl-tot/f (ml/min/kg)	MT-vsys (h)	V-sys/f (l/kg)
3	148	0.50	212	218	2.48	1.96	9.00	2.89	1.56
5	115	0.50	191	198	3.56	2.79	9.77	3.13	1.83
6	83.5	0.67	144	152	5.52	2.78	12.2	3.97	2.90
7	47.2	1.00	185	195	5.08	2.19	11.1	4.91	3.27
10	204	0.83	455	477	4.59	2.70	4.48	3.97	1.07
11	189	0.50	260	274	5.02	2.89	8.46	3.68	1.87
12	118	0.67	266	274	3.08	2.42	8.01	3.50	1.68
15	174	0.50	277	296	6.48	3.12	7.04	4.15	1.76
16	154	0.67	298	311	4.42	2.58	6.95	3.63	1.51
18	141	0.83	293	303	3.51	2.28	7.63	3.55	1.62
MEAN	137	0.67	258	270	4.37	2.57	8.46	3.74	1.91
SD	48.1	0.18	86.2	90.5	1.22	0.36	2.21	0.56	0.67
MIN	47.2	0.50	144	152	2.48	1.96	4.48	2.89	1.07
MAX	204	1.00	455	477	6.48	3.12	12.2	4.91	3.27
N	10	10	10	10	10	10	10	10	10

Table 3.29 **NIFEDIPINE PHARMACOKINETIC PARAMETERS**
(Effective oxidisers of sparteine)
Nifedipine + Cimetidine + HCl

Subj No	Cmax (ng/ml)	Tmax (h)	AUD (ng.h/ml)	AUDC (ng.h/ml)	%Extr	t½;z (h)	Cl-tot/f (ml/min/kg)	MT-vsys (h)	V-sys/f (l/kg)
3	112	0.83	200	206	2.98	2.37	9.51	3.35	1.91
5	117	0.83	218	225	2.94	2.89	8.63	3.21	1.66
6	75.1	0.50	159	169	6.32	3.06	10.9	4.48	2.94
7	99.6	0.50	163	170	3.92	2.84	12.7	3.55	2.71
10	65.5	1.00	314	335	6.08	2.79	6.39	4.84	1.85
11	113	0.83	305	328	6.95	2.87	7.06	4.66	1.98
12	46.3	2.00	261	274	4.68	2.33	8.00	4.73	2.27
15	61.4	1.33	277	297	6.84	3.42	7.00	4.99	2.10
16	143	0.67	329	341	3.51	2.46	6.34	3.54	1.35
18	101	0.83	296	305	3.00	2.50	7.58	3.63	1.65
MEAN	93.4	0.93	252	265	4.72	2.75	8.42	4.10	2.04
SD	30.2	0.45	63.1	67.2	1.67	0.34	2.10	0.70	0.49
MIN	46.3	0.50	159	169	2.94	2.33	6.34	3.21	1.35
MAX	143	2.00	329	341	6.95	3.42	12.7	4.99	2.94
N	10	10	10	10	10	10	10	10	10

The mean values of each pharmacokinetic parameter are compared for the different phases and given in Table 3.30 - 3.33.

Table 3.30 MEAN PHARMACOKINETIC PARAMETERS OF NIFEDIPINE (Effective oxidisers of sparteine)

Parameter	Nifedipine (Phase I)	Nifedipine (Phase III)	PE*	CI*
C_{max} (ng/ml)	84.9	84.4	99	70-129
T_{max} (h)	0.93	0.83		
AUD (ng.h/ml)	155	177		
AUDC (ng.h/ml)	161	184	114	100-129
%Extr	3.62	4.36		
$t_{½;z}$ (h)	2.36	2.46	104	95-113
Cl-tot/f (ml/min)	1240	1050		
Cl-tot/f (ml/min/kg)	15.5	13.2	85	73-97
MT-vsys (h)	3.46	3.97	115	100-129
V-sys/f (l)	260	267		
V-sys/f (l/kg)	3.26	3.33	102	81-124

*

PE = Point estimate for the ratio nifedipine (Phase III) relative to nifedipine (Phase I) [expressed as a percentage]

CI = 90% confidence intervals for the ratio mentioned above [expressed as a percentage]

The pharmacokinetic differences, highlighted by the confidence intervals, differ from the group as a whole.

Table 3.31 MEAN PHARMACOKINETIC PARAMETERS OF NIFEDIPINE (Effective oxidisers of sparteine)

Parameter	Nifedipine (Phase I)	Nifedipine + Cimetidine	PE*	CI*
C_{max} (ng/ml)	84.9	137	162	132-191
T_{max} (h)	0.93	0.67		
AUD (ng.h/ml)	155	258		
AUDC (ng.h/ml)	161	270	168	153-182
%Extr	3.62	4.37		
$t_{½;z}$ (h)	2.36	2.57	109	100-118
Cl-tot/f (ml/min)	1240	677		
Cl-tot/f (ml/min/kg)	15.5	8.46	55	43-67
MT-vsys (h)	3.46	3.74	108	94-122
V-sys/f (l)	260	152		
V-sys/f (l/kg)	3.26	1.91	59	37-80

*

PE = Point estimate for the ratio nifedipine + cimetidine (steady-state) relative to nifedipine (Phase I) [expressed as a percentage]

CI = 90% confidence intervals for the ratio mentioned above [expressed as a percentage]

The apparent difference between the values of the pharmacokinetic parameters of the group of effective oxidisers of sparteine is in accordance with the group as a whole.

Table 3.32 MEAN PHARMACOKINETIC PARAMETERS OF NIFEDIPINE (Effective oxidisers of sparteine)

Parameter	Nifedipine (Phase I)	Nifedipine + Cimetidine + HCl	PE*	CI*
C_{max} (ng/ml)	84.9	93.4	110	80-140
T_{max} (h)	0.93	0.93		
AUD (ng.h/ml)	155	252		
AUDC (ng.h/ml)	161	265	165	150-179
%Extr	3.62	4.72		
$t_{½;z}$ (h)	2.36	2.75	117	108-125
Cl-tot/f (ml/min)	1240	673		
Cl-tot/f (ml/min/kg)	15.5	8.42	54	42-66
MT-vsys (h)	3.46	4.10	118	104-133
V-sys/f (l)	260	163		
V-sys/f (l/kg)	3.26	2.04	63	41-84

*

PE = Point estimate for the ratio nifedipine + cimetidine (steady-state) + diluted HCl relative to nifedipine (Phase I) [expressed as a percentage]

CI = 90% confidence intervals for the ratio mentioned above [expressed as a percentage]

A similar difference between the pharmacokinetic parameters of nifedipine during these two phases is noted when compared to the group as a whole.

Table 3.33 MEAN PHARMACOKINETIC PARAMETERS OF NIFEDIPINE (Effective oxidisers of sparteine)

Parameter	Nifedipine + Cimetidine	Nifedipine + Cimetidine + HCl	PE*	CI*
C_{max} (ng/ml)	137	93.4	68	50-86
T_{max} (h)	0.67	0.93		
AUD (ng.h/ml)	258	252		
AUDC (ng.h/ml)	270	265	98	89-107
%Extr	4.37	4.72		
$t_{\frac{1}{2};z}$ (h)	2.57	2.75	107	99-115
Cl-tot/f (ml/min)	677	673		
Cl-tot/f (ml/min/kg)	8.46	8.42	99	77-122
MT-vsys (h)	3.74	4.10	110	96-123
V-sys/f (l)	152	163		
V-sys/f (l/kg)	1.91	2.04	107	70-144

*

PE = Point estimate for the ratio nifedipine + cimetidine (steady-state) + diluted HCl relative to nifedipine + cimetidine (steady-state) [expressed as a percentage]

CI = 90% confidence intervals for the ratio mentioned above [expressed as a percentage]

A similar apparent difference between the values of nifedipine's pharmacokinetic parameters as seen with the group as a whole, is seen when these two phases are compared in this homogenous group.

The time to maximum concentration (Tmax)

	Mean (h)	Median	Range
Nifedipine Phase I	0.93	0.67	0.50-3.00
Nifedipine + Cimetidine	0.67	0.67	0.50-1.00
Nifedipine + Cimetidine + HCl	0.93	0.83	0.50-2.00

Table 3.34 FREQUENCY TABLE FOR T_{max}

Time interval (h)	Nifedipine (Phase I)	Nifedipine + Cimetidine	Nifedipine + Cimetidine + HCl
0.00 - 0.49	0	0	0
0.50 - 0.99	8	9	7
1.00 - 1.49	1	1	2
1.50 - 1.99	0	0	0
2.00 - 2.49	0	0	1
2.50 - 2.99	0	0	0
3.00 - 3.50	1	0	0
TOTAL	10	10	10

See Fig. 3.33 for histogram.

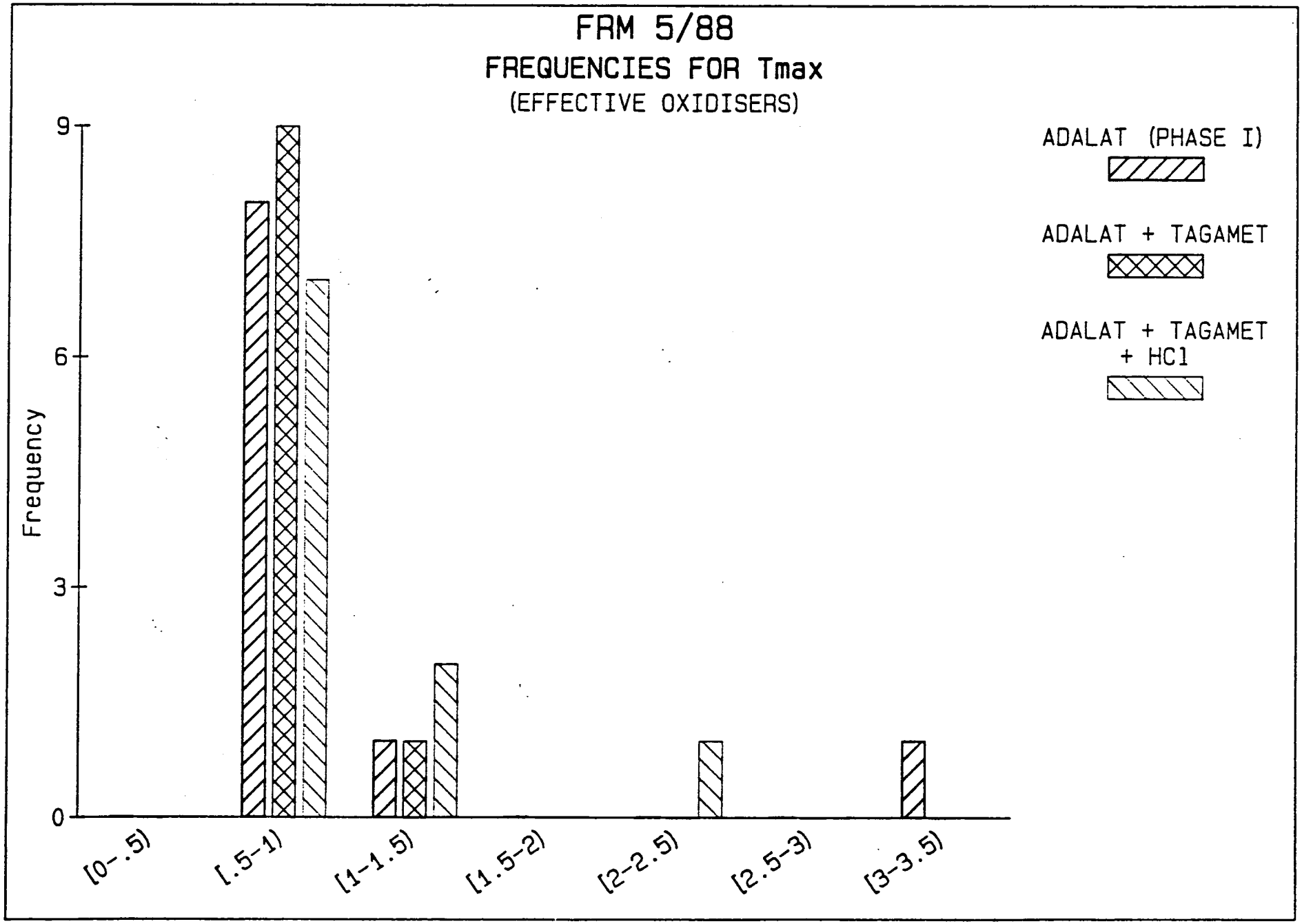

FRM 5/88
FREQUENCIES FOR Tmax
(EFFECTIVE OXIDISERS)
ADALAT (PHASE I)
ADALAT + TAGAMET
ADALAT + TAGAMET + HCl
Frequency
9
6
3
0
[0-.5)
[.5-1)
[1-1.5)
[1.5-2)
[2-2.5)
[2.5-3)
[3-3.5)

Fig. 3.33

3.3.1.3 Non-metabolisers of sparteine

The mean and individual nifedipine values of C_{max}, T_{max}, AUD, AUDC, %Extr, $t_{\frac{1}{2}}.z$, Cl-tot/f, MT-vsys and V-sys/f of the four different phases are summarised in Tables 3.36 - 3.39 (Cl-tot/f and V-sys/f are only expressed per body mass). Mean (SD) values of each parameter are summarised in Table 3.35. See Table 3.44 for a frequency table and Fig. 3.34 for a histogram of T_{max}.

Table 3.35 MEAN PHARMACOKINETIC PARAMETERS OF NIFEDIPINE (NON-METABOLISERS OF SPARTEINE) (Mean (SD) values)

PARAMETER	NIFED (I)	NIFED (III)	NIFED CIMET	NIFED CIMET HCl
Cmax (ng/ml)	94.4 (56.1)	111 (51.2)	138 (66.6)	116 (102)
Tmax (h)	0.59 (0.28)	0.80 (0.48)	0.93 (0.77)	1.24 (1.16)
AUD (ng.h/ml)	161 (68.4)	181 (54.8)	264 (79.0)	239 (92.5)
AUDC (ng.h/ml)	169 (72.6)	191 (65.8)	279 (84.3)	263 (101)
%Extr	4.64 (2.13)	4.77 (3.35)	5.34 (2.46)	8.74 (8.47)
$t_{\frac{1}{2}};z$ (h)	2.68 (0.61)	2.68 (0.64)	2.70 (0.42)	3.12 (0.93)
Cl-tot/f (ml/min)	1205 (604)	947 (264)	646 (188)	714 (251)
Cl-tot/f (ml/min/kg)	15.7 (7.96)	12.4 (3.63)	8.37 (2.28)	9.36 (3.54)
MT-vsys (h)	3.82 (0.89)	3.63 (1.26)	4.11 (0.95)	4.95 (2.32)
V-sys/f (l)	289 (200)	195 (62.8)	160 (63.5)	211 (114)
V-sys/f (l/kg)	3.76 (2.65)	2.55 (0.83)	2.05 (0.71)	2.76 (1.54)

NIFED = Nifedipine
CIMET = Cimetidine (steady-state)
HCl = Diluted Hydrochloric Acid
I = Phase I
III = Phase III
(See Appendix 1 : Protocol)

Table 3.36 **NIFEDIPINE PHARMACOKINETIC PARAMETERS**
(Non-metabolisers of sparteine)
PHASE I: Nifedipine

Subj No	C_{max} (ng/ml)	T_{max} (h)	AUD (ng.h/ml)	AUDC (ng.h/ml)	%Extr	t½;z (h)	Cl-tot/f (ml/min/kg)	MT-vsys (h)	V-sys/f (l/kg)
1	101	0.50	122	127	3.27	2.83	16.2	2.80	2.73
2	101	0.50	257	263	2.40	2.10	9.90	3.38	2.01
4	125	0.50	236	249	5.17	3.10	8.36	3.67	1.84
8	19.7	1.00	73.5	77.3	4.91	2.62	26.3	4.62	7.29
9	129	0.33	153	157	2.60	2.20	14.3	2.47	2.12
13	146	0.33	218	240	9.41	3.78	8.16	4.87	2.39
17	171	0.33	191	202	5.69	3.26	10.1	3.66	2.21
19	15.5	1.00	72.8	76.4	4.76	2.00	30.3	5.03	9.13
20	42.6	0.83	123	127	3.56	2.21	17.5	3.91	4.10
MEAN	94.4	0.59	161	169	4.64	2.68	15.7	3.82	3.76
SD	56.1	0.28	68.4	72.6	2.14	0.61	7.96	0.89	2.65
MIN	15.5	0.33	72.8	76.4	2.40	2.00	8.16	2.47	1.84
MAX	171	1.00	257	263	9.41	3.78	30.3	5.03	9.13
N	9	9	9	9	9	9	9	9	9

Table 3.37 **NIFEDIPINE PHARMACOKINETIC PARAMETERS**
(Non-metabolisers of sparteine)
PHASE III: Nifedipine

Subj No	Cmax (ng/ml)	Tmax (h)	AUD (ng.h/ml)	AUDC (ng.h/ml)	%Extr	t½;z (h)	Cl-tot/f (ml/min/kg)	MT-vsys (h)	V-sys/f (l/kg)
1	33.0	0.83	124	132	5.80	2.58	15.6	4.61	4.31
2	37.5	2.00	227	247	8.34	2.91	10.5	5.55	3.50
4	183	0.50	180	183	1.78	2.07	11.4	2.48	1.69
8	91.6	1.00	171	177	2.84	2.42	11.5	3.21	2.22
9	139	0.67	151	153	1.79	2.82	14.7	2.51	2.21
13	165	0.50	298	337	11.4	3.98	5.82	5.29	1.85
17	123	0.67	192	203	5.71	3.05	10.0	3.92	2.35
19	107	0.50	124	127	2.06	1.70	18.3	2.29	2.51
20	119	0.50	158	164	3.23	2.63	13.6	2.80	2.28
MEAN	111	0.80	181	191	4.77	2.68	12.4	3.63	2.55
SD	51.2	0.48	54.7	65.8	3.35	0.65	3.63	1.26	0.84
MIN	33.0	0.50	124	127	1.78	1.70	5.82	2.29	1.69
MAX	183	2.00	298	337	11.4	3.98	18.3	5.55	4.31
N	9	9	9	9	9	9	9	9	9

Table 3.38 **NIFEDIPINE PHARMACOKINETIC PARAMETERS**
(Non-metabolisers of sparteine)
Nifedipine + Cimetidine

Subj No	Cmax (ng/ml)	Tmax (h)	AUD (ng.h/ml)	AUDC (ng.h/ml)	%Extr	t½;z (h)	Cl-tot/f (ml/min/kg)	MT-vsys (h)	V-sys/f (l/kg)
1	45.7	2.00	183	197	6.86	2.56	10.5	5.03	3.16
2	243	0.50	350	365	4.05	2.59	7.14	3.44	1.47
4	184	0.67	387	413	6.41	2.93	5.04	4.30	1.30
8	110	0.67	176	183	4.17	2.50	11.1	4.03	2.68
9	192	0.67	334	348	4.11	2.53	6.47	3.63	1.41
13	132	0.50	296	325	9.02	3.56	6.04	5.05	1.83
17	38.9	2.50	210	229	8.46	3.07	8.88	5.59	2.98
19	144	0.50	205	208	1.73	2.17	11.1	2.95	1.96
20	156	0.33	237	245	3.26	2.39	9.09	2.98	1.62
MEAN	138	0.93	264	279	5.34	2.70	8.37	4.11	2.05
SD	66.6	0.77	78.9	84.3	2.46	0.42	2.28	0.95	0.71
MIN	38.9	0.33	176	183	1.73	2.17	5.04	2.95	1.30
MAX	243	2.50	387	413	9.02	3.56	11.1	5.59	3.16
N	9	9	9	9	9	9	9	9	9

Table 3.39 **NIFEDIPINE PHARMACOKINETIC PARAMETERS**
(Non-metabolisers of sparteine)
Nifedipine + Cimetidine + HCl

Subj No	Cmax (ng/ml)	Tmax (h)	AUD (ng.h/ml)	AUDC (ng.h/ml)	%Extr	t½;z (h)	Cl-tot/f (ml/min/kg)	MT-vsys (h)	V-sys/f (l/kg)
1	53.5	1.67	225	237	5.03	2.51	8.69	4.31	2.25
2	177	0.33	293	304	3.77	2.94	8.57	3.28	1.69
4	339	0.33	445	474	5.99	3.43	4.40	3.89	1.03
8	131	0.67	188	195	3.29	2.69	10.4	3.31	2.07
9	26.8	1.67	133	149	10.9	3.23	15.1	5.67	5.14
13	30.9	4.00	241	345	30.1	5.41	5.68	10.5	3.58
17	155	0.67	235	251	6.28	2.87	8.11	4.05	1.97
19	20.7	1.33	145	161	10.1	2.77	14.4	6.09	5.26
20	112	0.50	242	250	3.17	2.19	8.89	3.42	1.82
MEAN	116	1.24	239	263	8.74	3.12	9.36	4.95	2.76
SD	102	1.16	92.5	101	8.47	0.93	3.54	2.32	1.54
MIN	20.7	0.33	133	149	3.17	2.19	4.40	3.28	1.03
MAX	339	4.00	445	474	30.1	5.41	15.1	10.5	5.26
N	9	9	9	9	9	9	9	9	9

The mean values of each pharmacokinetic parameter are compared for the different phases and given in Table 3.40 - 3.43.

Table 3.40 MEAN PHARMACOKINETIC PARAMETERS OF NIFEDIPINE (Non-metabolisers of sparteine)

Parameter	Nifedipine (Phase I)	Nifedipine (Phase III)	PE*	CI*
C_{max} (ng/ml)	94.4	111	117	61-174
T_{max} (h)	0.59	0.80		
AUD (ng.h/ml)	161	181		
AUDC (ng.h/ml)	169	191	113	89-137
%Extr	4.64	4.77		
$t_{½};z$ (h)	2.68	2.68	100	88-112
Cl-tot/f (ml/min)	1205	947		
Cl-tot/f (ml/min/kg)	15.7	12.4	79	61-97
MT-vsys (h)	3.82	3.63	95	67-123
V-sys/f (l)	289	195		
V-sys/f (l/kg)	3.76	2.55	68	35-101

*

PE = Point estimate for the ratio nifedipine (Phase III) relative to nifedipine (Phase I) [expressed as a percentage]

CI = 90% confidence intervals for the ratio mentioned above [expressed as a percentage]

Table 3.41 MEAN PHARMACOKINETIC PARAMETERS OF NIFEDIPINE (Non-metabolisers of sparteine)

Parameter	Nifedipine (Phase I)	Nifedipine + Cimetidine	PE*	CI*
C_{max} (ng/ml)	94.4	138	147	90-203
T_{max} (h)	0.59	0.93		
AUD (ng.h/ml)	161	264		
AUDC (ng.h/ml)	169	279	165	141-189
%Extr	4.64	5.34		
$t_{\frac{1}{2}};z$ (h)	2.68	2.70	101	89-113
Cl-tot/f (ml/min)	1205	646		
Cl-tot/f (ml/min/kg)	15.7	8.37	53	36-71
MT-vsys (h)	3.82	4.11	108	80-135
V-sys/f (l)	289	160		
V-sys/f (l/kg)	3.76	2.05	54	21-88

*

PE = Point estimate for the ratio nifedipine + cimetidine (steady-state) relative to nifedipine (Phase I) [expressed as a percentage]

CI = 90% confidence intervals for the ratio mentioned above [expressed as a percentage]

Table 3.42 MEAN PHARMACOKINETIC PARAMETERS OF NIFEDIPINE (Non-metabolisers of sparteine)

Parameter	Nifedipine (Phase I)	Nifedipine + Cimetidine + HCl	PE*	CI*
C_{max} (ng/ml)	94.4	116	123	67-179
T_{max} (h)	0.59	1.24		
AUD (ng.h/ml)	161	239		
AUDC (ng.h/ml)	169	263	156	132-180
%Extr	4.64	8.74		
$t_{½;z}$ (h)	2.68	3.12	116	104-128
Cl-tot/f (ml/min)	1205	714		
Cl-tot/f (ml/min/kg)	15.7	9.36	60	42-77
MT-vsys (h)	3.82	4.95	129	101-157
V-sys/f (l)	289	211		
V-sys/f (l/kg)	3.76	2.76	73	40-106

*

PE = Point estimate for the ratio nifedipine + cimetidine (steady-state) + diluted HCl relative to nifedipine (Phase I) [expressed as a percentage]

CI = 90% confidence intervals for the ratio mentioned above [expressed as a percentage]

Table 3.43 MEAN PHARMACOKINETIC PARAMETERS OF NIFEDIPINE (Non-metabolisers of sparteine)

Parameter	Nifedipine + Cimetidine	Nifedipine + Cimetidine + HCl	PE*	CI*
C_{max} (ng/ml)	138	116	84	45-122
T_{max} (h)	0.93	1.24		
AUD (ng.h/ml)	264	239		
AUDC (ng.h/ml)	279	263	94	80-109
%Extr	5.34	8.74		
$t_{½};z$ (h)	2.70	3.12	115	103-127
Cl-tot/f (ml/min)	646	714		
Cl-tot/f (ml/min/kg)	8.37	9.36	112	79-145
MT-vsys (h)	4.11	4.95	120	94-146
V-sys/f (l)	160	211		
V-sys/f (l/kg)	2.05	2.76	135	74-195

*

PE = Point estimate for the ratio nifedipine + cimetidine (steady-state) + diluted HCl relative to nifedipine + cimetidine (steady-state) [expressed as a percentage]

CI = 90% confidence intervals for the ratio mentioned above [expressed as a percentage]

The time to maximum concentration (Tmax)

	Mean (h)	Median	Range
Nifedipine Phase I	0.59	0.50	0.33-1.00
Nifedipine + Cimetidine	0.93	0.67	0.33-2.50
Nifedipine + Cimetidine + HCl	1.24	0.67	0.33-4.00

Table 3.44 FREQUENCY TABLE FOR T_{max} (Non-metabolisers of sparteine)

Time interval (h)	Nifedipine (Phase I)	Nifedipine + Cimetidine	Nifedipine + Cimetidine + HCl
0.00 - 0.49	3	1	2
0.50 - 0.99	4	6	3
1.00 - 1.49	2	0	1
1.50 - 1.99	0	0	2
2.00 - 2.49	0	1	0
2.50 - 2.99	0	1	0
3.00 - 3.49	0	0	0
3.50 - 4.00	0	0	1
TOTAL	9	9	9

See Fig. 3.34 for histogram.

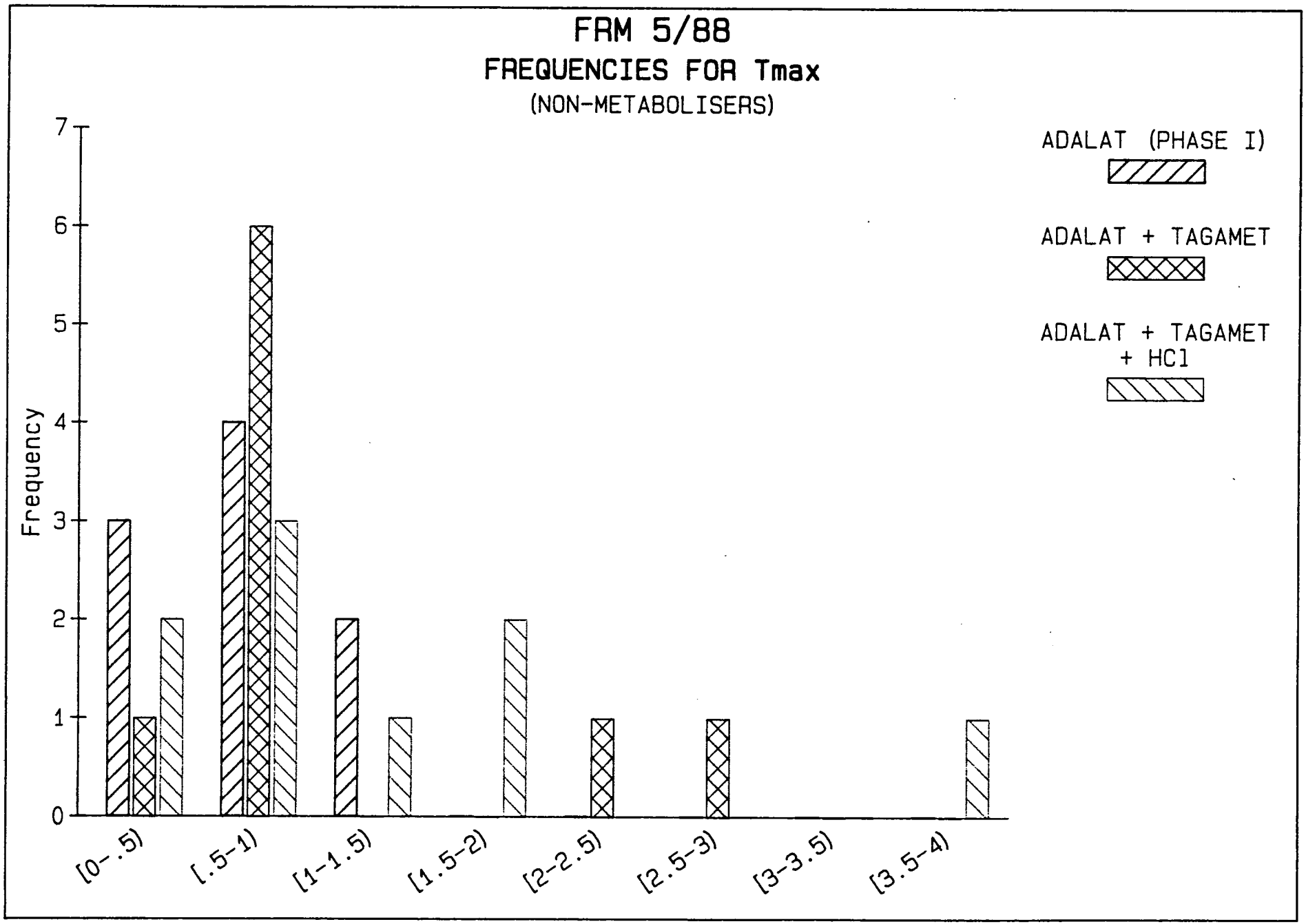

FRM 5/88
FREQUENCIES FOR Tmax
(NON-METABOLISERS)
ADALAT (PHASE I)
ADALAT + TAGAMET
ADALAT + TAGAMET + HCl
Frequency
0
1
2
3
4
5
6
7
[0-.5)
[.5-1)
[1-1.5)
[1.5-2)
[2-2.5)
[2.5-3)
[3-3.5)
[3.5-4)

Fig. 3.34

3.3.1.4 Comparison of effective oxidisers and non-metabolisers of sparteine

The mean (SD) nifedipine values of the afore-mentioned parameters of the four different phases are summarised in Tables 3.45 - 3.48 and compared for the two phenotypic groups of this study. There were 10 effective oxidisers and 9 non-metabolisers of sparteine. Although no specific conclusion can be drawn from these comparisons, there is a tendency for $t_{\frac{1}{2}};z$ to be longer in the non-metaboliser group in all the phases.

Table 3.45 MEAN (SD) PHARMACOKINETIC PARAMETERS OF NIFEDIPINE
Nifedipine (Phase I)

Parameter	EO*	NM*	SR*	CI*
C_{max} (ng/ml)	84.9 (44.4)	94.4 (56.1)	111	54 - 169
T_{max} (h)	0.93 (0.77)	0.59 (0.28)		
AUD (ng.h/ml)	155 (68.6)	161 (68.4)		
AUDC (ng.h/ml)	161 (71.5)	169 (72.6)	105	62 - 148
%Extr	3.62 (1.08)	4.64 (2.13)		
$t_{½;z}$ (h)	2.36 (0.40)	2.68 (0.61)	113	92 - 134
Cl-tot/f (ml/min)	1240 (540)	1205 (604)		
Cl-tot/f (ml/min/kg)	15.5 (6.35)	15.7 (7.96)	101	56 - 146
MT-vsys (h)	3.46 (0.82)	3.82 (0.89)	110	87 - 134
V-sys/f (l)	260 (139)	289 (200)		
V-sys/f (l/kg)	3.26 (1.70)	3.76 (2.65)	115	50 - 181

*
EO = Effective oxidisers of sparteine
NM = Non-metabolisers of sparteine
SR = Sample ratio (%) (NM/EO)
CI = Confidence interval for ratio (%)

Table 3.46 MEAN (SD) PHARMACOKINETIC PARAMETERS OF NIFEDIPINE
Nifedipine (Phase III)

Parameter	EO*	NM*	SR*	CI*
C_{max} (ng/ml)	84.4 (49.6)	111 (51.2)	131	73 - 189
T_{max} (h)	0.83 (0.37)	0.80 (0.48)		
AUD (ng.h/ml)	177 (73.8)	181 (54.8)		
AUDC (ng.h/ml)	184 (75.6)	191 (65.8)	104	67 - 141
%Extr	4.36 (2.32)	4.77 (3.35)		
$t_{\frac{1}{2}};z$ (h)	2.46 (0.57)	2.68 (0.64)	109	85 - 133
Cl-tot/f (ml/min)	1050 (414)	947 (264)		
Cl-tot/f (ml/min/kg)	13.2 (4.87)	12.4 (3.63)	94	62 - 126
MT-vsys (h)	3.97 (1.03)	3.63 (1.26)	91	63 - 119
V-sys/f (l)	267 (166)	195 (62.8)		
V-sys/f (l/kg)	3.33 (2.02)	2.55 (0.83)	76	31 - 122

*
EO = Effective oxidisers of sparteine
NM = Non-metabolisers of sparteine
SR = Sample ratio (%) (NM/EO)
CI = Confidence interval for ratio (%)

Table 3.47 MEAN (SD) PHARMACOKINETIC PARAMETERS OF NIFEDIPINE
Nifedipine + Cimetidine

Parameter	EO*	NM*	SR*	CI*
C_{max} (ng/ml)	137 (48.1)	138 (66.6)	101	60 - 141
T_{max} (h)	0.67 (0.18)	0.93 (0.77)		
AUD (ng.h/ml)	258 (86.2)	264 (79.0)		
AUDC (ng.h/ml)	270 (90.5)	279 (84.3)	103	72 - 135
%Extr	4.37 (1.22)	5.34 (2.46)		
$t_{\frac{1}{2};z}$ (h)	2.57 (0.36)	2.70 (0.42)	105	90 - 120
Cl-tot/f (ml/min)	677 (213)	646 (188)		
Cl-tot/f (ml/min/kg)	8.46 (2.21)	8.37 (2.28)	99	73 - 125
MT-vsys (h)	3.74 (0.56)	4.11 (0.95)	110	90 - 130
V-sys/f (l)	152 (58.3)	160 (63.5)		
V-sys/f (l/kg)	1.91 (0.67)	2.05 (0.71)	107	72 - 142

*
EO = Effective oxidisers of sparteine
NM = Non-metabolisers of sparteine
SR = Sample ratio (%) (NM/EO)
CI = Confidence interval for ratio (%)

Table 3.48 MEAN (SD) PHARMACOKINETIC PARAMETERS OF NIFEDIPINE
Nifedipine + Cimetidine + HCl

Parameter	EO*	NM*	SR*	CI*
C_{max} (ng/ml)	93.4 (30.2)	116 (102)	124	48 - 200
T_{max} (h)	0.93 (0.45)	1.24 (1.16)		
AUD (ng.h/ml)	252 (63.1)	239 (92.5)		
AUDC (ng.h/ml)	265 (67.3)	263 (101)	99	68 - 130
%Extr	4.72 (1.67)	8.74 (8.47)		
$t_{½;z}$ (h)	2.75 (0.34)	3.12 (0.93)	113	89 - 137
Cl-tot/f (ml/min)	673 (194)	714 (251)		
Cl-tot/f (ml/min/kg)	8.42 (2.10)	9.36 (3.54)	111	78 - 144
MT-vsys (h)	4.10 (0.70)	4.95 (2.32)	121	81 - 160
V-sys/f (l)	163 (46.3)	211 (114)		
V-sys/f (l/kg)	2.04 (0.49)	2.76 (1.54)	135	82 - 188

*
EO = Effective oxidisers of sparteine
NM = Non-metabolisers of sparteine
SR = Sample ratio (%) (NM/EO)
CI = Confidence interval for ratio (%)

The tendency for C_{max} to be higher in the non-metaboliser group in this phase of the study, could be misleading. These high values are only because of one of the nine subjects of this group. When the values are calculated without him, they are very similar to the effective oxidiser group, namely a mean (SD) of 88.23 (62.61), sample ratio of 94% and a confidence interval of 44 - 145.

C H A P T E R 4

DISCUSSION

The influence of cimetidine on the bioavailability and pharmacokinetics of nifedipine was investigated, as well as the importance of sparteine metabolic polymorphism on this interaction.

4.1 NIFEDIPINE PLASMA CONCENTRATION vs TIME DATA

A large inter-subject variation of C_{max} and AUDC was noted, even after correction for body mass. This phenomenon has beem described for nifedipine (Foster et al., 1983; Kleinbloesem et al., 1984d).

Comparison of Phases I and III suggests the existence of a large intra-subject variation in regard to C_{max} and AUDC. In the second nifedipine-only phase (Phase III), 50% of subjects exhibited distinctly greater AUDC values, whilst 55% had greater C_{max} values. There are at least two possible explanations for this observation: a period effect, since the study-design did not make provision for randomisation, and/or a carry-over effect of cimetidine on nifedipine clearance which could still have been present after a 6 day wash-out period. In 45% of subjects nifedipine clearance rates had returned to pre-cimetidine values but remained clearly depressed in about 50%, albeit to a lesser degree than observed with cimetidine, indicating a trend to "normalisation" after discontinuation of cimetidine. According to Broughton and Rogers (1981) and Hansten and Horn (1987), the inhibitory effect of cimetidine or its metabolite on the microsomal enzymes continues for at least a week after treatment is stopped.

Cimetidine pre-treatment clearly and significantly increased C_{max} and AUDC values of nifedipine. This is, in all probability, mainly the result of an attenuated first-pass clearance of nifedipine by cimetidine. These data are in accordance with those published by Kirch et al. (1984b) and Smith et al. (1987).

When nifedipine capsules were swallowed with diluted HCl following cimetidine pre-treatment, cimetidine once again appeared to attenuate nifedipine's rate of clearance, resulting in significantly increased AUDC values. In fact, the degree of nifedipine absorption, reflected by AUDC, was very similar in Phases II and IV, with a point estimate of 95% and 90% confidence intervals of 88 - 103 for Phase IV relative to Phase II. However, concomitant ingestion of nifedipine and diluted HCl in the cimetidine pre-treated state, resulted in a significant reduction in the rate of nifedipine absorption as reflected by C_{max} and supported by changes in T_{max}. The point estimate for C_{max} (76%) and the 90% confidence intervals (58-94) for Phase IV relative to Phase II is a clear indication of an attenuated rate of nifedipine absorption. These findings

can be interpreted to differentiate between cimetidine's effects on nifedipine kinetics, given as Adalat^{R} capsules, through inhibition of gastric acid secretion and inhibition of the hepatic monooxygenase system (Wilkinson et al., 1974; Rendic et al., 1979; Pelkonen and Puurunen 1980; Puurunen et al., 1980).

Cimetidine pre-treatment had the effect of narrowing the co-efficients of variation (CV) of nifedipine C_{max} and AUDC from 53% and 43% down to 40% and 31% respectively. On the other hand,concomitant ingestion of diluted HCl, resulted in an exaggeration of the C_{max} co-efficient of variation; i.e. from 53% to 67%. Cimetidine pre-treatment reduced the CV of nifedipine clearance from 43% to 25%.

These findings could serve as a guideline in designing protocols for nifedipine bioavailability studies. Cimetidine pre-treatment could be employed to minimise inter- and intra-subject variability through effecting more comparable intragastric pH's and rates of elimination in participating trial subjects and during the various phases of such studies. This reasoning is based on the assumption that bioavailability studies serve only as in vivo quality control measures. Obviously, the influence of differing intragastric pH on different formulations will have to be investigated. The attenuation of nifedipine absorption by concomitant ingestion of diluted HCl observed in the study under review can only be interpreted with confidence in respect of Adalat^{R} capsules (nifedipine contained in a liquid base within a gelatin capsule).

Altering intragastric pH may result in marked differences in the rate and extent of absorption of nifedipine from different formulations. This may be an approach which could enhance the discriminative value of relative bioavailability studies involving different nifedipine formulations. It may be of interest to repeat the study with ranitidine instead of cimetidine pre-treatment to define more clearly the effects of altering intragastric pH only.

When the subjects were divided into groups of effective oxidisers and non-metabolisers of sparteine and compared, no significant difference could be seen in any phase. Thus, it appears that the ability of subjects to metabolise sparteine oxidatively is not correlated with their ability to eliminate nifedipine.

4.2 TERMINAL HALF-LIFE OF NIFEDIPINE ($t_{\frac{1}{2}};z$)

The mean terminal half-life of orally administered nifedipine in this study was 2.51h (0.51h) and is less than the value of 3.43h (10.4h) reported by Foster *et al.* (1983). Pre-treatment with cimetidine resulted in a slight (5%) increase in the nifedipine elimination half-life, an observation of doubtful clinical significance.

4.3 DRUG-RELATED ADVERSE RESPONSES

Clinically the higher nifedipine C_{max} values encountered with cimetidine pre-treatment were associated with a higher incidence of and also more intense headaches in the subjects who experienced headache as an adverse response during the nifedipine-only phases.

4.4 RELEVANCE OF SPARTEINE OXIDATION STATUS FOR NIFEDIPINE CLEARANCE

Subjects could roughly be subdivided into 3 groups in regard to nifedipine elimination rates. Table 4.1 reflects this data and the corresponding sparteine metabolism status.

No correlation between the ability of trial subjects to metabolise sparteine and eliminate nifedipine could be shown. This is in agreement with Eichelbaum (1982).

Table 4.1: NIFEDIPINE ELIMINATION RATES AND SPARTEINE METABOLISM STATUS

Subject No.	Cl-tot/f ml/min/kg	Sparteine oxidation status (Q values)
	A:7.0-11.9	
2	9.90	85.1 (NM)
4	8.36	190 (NM)
10	7.68	1.07 (EO)
11	9.14	0.67 (EO)
13	8.16	104 (NM)
15	9.39	0.65 (EO)
16	11.4	1.48 (EO)
17	10.1	100 (NM)
	B:12.0-18.9	
1	16.2	132 (NM)
3	17.0	1.12 (EO)
5	16.0	0.88 (EO)
9	14.3	125 (NM)
18	14.5	1.77 (EO)
20	17.5	160 (NM)
	C:19.0-31.0	
6	22.2	1.80 (EO)
7	27.3	0.86 (EO)
8	26.3	163 (NM)
12	19.9	0.42 (EO)
14	20.4	53.8 (PM)
19	30.3	116 (NM)

C H A P T E R 5

CONCLUSION

Cimetidine pre-treatment significantly increased the maximum plasma concentration and the area under curve of nifedipine administered as a single 10mg dose (Adalat^{R} capsule) to 20 healthy male volunteers. Since the terminal half-life of nifedipine remained relatively unaffected by cimetidine pre-treatment, it is assumed that the observed effects on C_{max} and AUDC are attributable to an attenuated first-pass clearance of nifedipine by cimetidine.

Ingestion of nifedipine (Adalat^{R}) with diluted hydrochloric acid by subjects pre-treated with cimetidine, resulted in a slower rate of nifedipine absorption without affecting the above-mentioned influence of cimetidine on nifedipine AUDC. This probably reflects the attenuating influence of HCl on absorption of nifedipine after ingestion of Adalat^{R} capsules. It is uncertain whether this observation can be attributed to an influence of HCl on digestion of the gelatin capsule or to an actual biopharmaceutical effect involving nifedipine as such.

The ability of subjects to metabolise sparteine oxidatively is not correlated with their ability to eliminate nifedipine.

A definite trend for inter-subject variation in regard to nifedipine clearance was observed. This, together with varying intragastric pH, probably explains the large inter-subject variation for C_{max} and AUDC noticed in this study and reported by others.

Cimetidine pre-treatment clearly diminished co-efficients of variation of nifedipine C_{max} and AUDC after ingestion of Adalat^{R} capsules. This may be an approach to minimise inter- and intra-subject variations in the performance of comparative bioavailability studies involving different nifedipine products and formulations.

A B S T R A C T

AN INVESTIGATION INTO THE INFLUENCE OF CIMETIDINE ON THE BIOAVAILABILITY AND PHARMACOKINETICS OF NIFEDIPINE AND THE IMPORTANCE OF METABOLIC POLYMORPHISM ON THIS INTERACTION

Nifedipine is a calcium channel blocker used in the treatment of stable, variant and unstable angina, mild to severe hypertension and Raynaud's phenomenon. Its disposition after oral administration is dependent on rate and extent of absorption, first-pass hepatic metabolism and oxidative phenotype of the subject.

Cimetidine is a third generation H_2-receptor antagonist. It blocks histamine-induced gastric acid secretion and has also been shown to interact with the microsomal cytochrome P-450 linked monooxygenase system, thus inhibiting drug metabolism. It may thus be possible to seperate the inhibitory effect of cimetidine on specific enzyme systems in the liver from its gastric H_2-receptor antagonising effect.

The influence of cimetidine on the bioavailability and pharmacokinetics of nifedipine was investigated as well as the importance of metabolic polymorphism on such an interaction if it existed.

Twenty healthy, non-smoking male volunteers of which ten were known to be effective oxidisers of sparteine, nine non-metabolisers and one poor oxidiser, participated in the study.

Following an overnight fast, each subject was given a single Adalat^R capsule containing 10mg nifedipine. Blood was taken at regular intervals and nifedipine plasma levels were determined by gaschromatography. The study was divided into four different profile days of which two were bioavailability and pharmacokinetic studies of nifedipine. During the other two days, these studies were repeated while the subjects were at steady-state for cimetidine given as Tagamet^R. During the latter two days nifedipine was taken with either 200ml of water or with 200ml of diluted hydrochloric acid (0.1% w/v; 0.028M). These two days were randomised.

The following pharmacokinetic parameters of nifedipine were calculated and compared for the different phases: C_{max}, AUDC, $t_{½};z$, T_{max}, Cl-tot/f, MT-vsys and V-sys/f. Point estimates and 90% confidence intervals were calculated for the different phases.

Comparison of the two nifedipine-only phases suggests the existence of a large intra-subject variation in regard to C_{max} and AUDC. This could be the result of a period effect and/or a carry over effect of cimetidine on nifedipine clearance which could still have been present after a 6 day wash-out period.

Cimetidine pre-treatment clearly and significantly increased C_{max} and AUDC values of nifedipine. This is most probably because of an attenuated first-pass clearance of nifedipine by cimetidine.

Concomitant ingestion of diluted HCl and nifedipine in cimetidine pre-treated subjects, resulted in a significant reduction in the rate of nifedipine absorption when compared to the phase without HCl.

These findings can be interpreted to differentiate between cimetidine's effects on nifedipine kinetics given as Adalat^{R} capsules, i.e. inhibition of gastric acid secretion and inhibition of the hepatic monooxygenase system.

Cimetidine pre-treatment had the effect of narrowing the coefficients of variation (CV) of nifedipine C_{max} and AUDC. This could serve as a guideline in designing protocols for nifedipine bioavailability studies.

The ability of subjects to metabolise sparteine oxidatively is not correlated with their ability to eliminate nifedipine.

O P S O M M I N G

'n ONDERSOEK NA DIE INVLOED VAN SIMETIDIEN OP DIE BIOBESKIKBAARHEID EN FARMAKOKINETIKA VAN NIFEDIPIEN EN DIE BELANG VAN METABOLIESE POLIMORFISME OP HIERDIE INTERAKSIE

Nifedipien is 'n kalsiumkanaal blokeerder wat in die behandeling van stabiele, Prinzmetal en onstabiele angina gebruik word asook vir matig tot erge hipertensie en Raynaud se verskynsel. Nifedipien se metabolisme na orale inname is afhanklik van die spoed en mate van absorpsie, eerste deurgangs effek en oksidatiewe fenotipe van die proefpersoon.

Simetidien is 'n derde generasie H_2-reseptor antagonis. Dit blokkeer histamien-geïnduseerde maagsuur sekresie. Dit is ook aangetoon dat daar 'n wisselwerking met die mikrosomale sitochroom-P-450-gekoppelde mono-oksigenase sisteem is. Sodoende word geneesmiddel metabolisme geïnhibeer. Dit kan dus moontlik wees om die inhibitoriese effek van simetidien op spesifieke ensiemsisteme van die lewer te skei van die gastriese H_2-reseptor antagonisme.

Die invloed van simetidien op die biobeskikbaarheid en farmakokinetika van nifedipien is ondersoek asook die belang van metaboliese polimorfisme op so 'n interaksie indien teenwoordig.

Twintig gesonde, nie-rokende manlike vrywilligers is gebruik. Tien was effektiewe oksideerders van sparteïen, nege was nonmetaboliseerders en een was 'n swak oksideerder.

Nadat al die proefpersone oornag gevas het, het elkeen een Adalat^R kapsule met 10mg nifedipien gekry om te sluk. Bloed is gereeld getrek en nifedipien bloedvlakke is met behulp van 'n gaschromatografiese metode bepaal. Die ondersoek is in vier profieldae ingedeel. Tydens twee van hierdie dae is biobeskikbaarheid- en farmakokinetiese studies gedoen. Tydens die ander twee profieldae is hierdie studies herhaal, maar die proefpersone was op simetidien gelykvlak. Die simetidien is as Tagamet^R gegee. Gedurende hierdie laasgenoemde dae, is die nifedipien met óf 200ml water óf 200ml verdunde soutsuur (0.1% w/v; 0.028M) geneem. Hierdie twee dae was gerandomiseerd.

Die volgende farmakokinetiese parameters van nifedipien is bereken en vergelyk tydens die verskillende fases: C_{max}, AUDC, $t_{½;z}$, T_{max}, Cl-tot/f, MT-vsys en V-sys/f. Puntberamers en 90% vertrouensintervalle is bereken vir die vier fases.

'n Vergelyking van die twee fases waartydens nifedipien as enigste medikasie toegedien is, dui daarop dat daar 'n groot intra-individuele variasie bestaan met betrekking tot C_{max} en AUDC. Dit kan moontlik wees as gevolg van 'n periode effek en/of 'n oordragingseffek van simetidien op nifedipien opruiming wat nog teenwoordig kon wees na 'n uitwasperiode van 6 dae.

Simetidien gelykvlak het die C_{max}- en AUDC-waardes van nifedipien duidelik en beduidend verhoog. Dit is mees waarskynlik as gevolg van 'n verlaagde eerste deurgangseffek op nifedipien wat deur simetidien veroorsaak is.

Die gelyktydige inname van verdunde soutsuur en nifedipien in die persone wat op gelykvlak vir simetidien was, het tot 'n beduidende vermindering in die tempo van nifedipien absorpsie gelei wanneer dit met die fase sonder soutsuur vergelyk is.

Volgens hierdie bevindings kan 'n mens die afleiding maak dat daar onderskei kan word tussen simetidien se effekte op nifedipien kinetika wanneer dit as Adalat^{R} gegee word, naamlik dat maagsuursekresie sowel as die hepatiese mono-oksigenase sisteem geïnhibeer word.

Die vooraf behandeling met simetidien het daartoe gelei dat nifedipien se koëffisiënt van variasie ten opsigte van C_{max} en AUDC verminder het. Dit kan as moontlike riglyn gebruik word wanneer 'n protokol vir nifedipien biobeskikbaarheidstudies opgestel moet word.

Die vermoë van die proefpersone om sparteïen oksidatief te metaboliseer stem nie ooreen met hulle vermoë om nifedipien te elimineer nie.

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APPENDIX 1

P R O T O C O L

AN INVESTIGATION INTO THE INFLUENCE OF CIMETIDINE ON THE BIOAVAILABILITY AND PHARMACOKINETICS OF NIFEDIPINE AND THE IMPORTANCE OF METABOLIC POLYMORPHISM ON THIS INTERACTION

STUDY NO : FRM 5/88

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C O N F I D E N T I A L

1. INTRODUCTION

Nifedipine is an antagonist of calcium influx through the slow channel of the cell membrane. It has been shown to be an effective and relatively well-tolerated treatment for stable, variant and unstable angina, mild to severe hypertension and Raynaud's phenomenon (Sorkin et al., 1985).

Side effects appear to be dose-related and occur in approximately 20% of patients. These effects, most of which are manifestations of the drug's potent vasodilating activity, include headache, flushing and dizziness (Sorkin et al., 1985).

Disposition of nifedipine after oral administration is dependent on rate and extent of absorption, first-pass hepatic metabolism (Waller et al., 1984) and oxidative phenotype of the subject (Kleinbloesem et al., 1984d).

Cimetidine is a third-generation H_2-receptor antagonist. Its competitive inhibitory effect on the action of histamine on H_2-receptors is highly specific and reversible. Its ability to block histamine-induced gastric acid secretion is attributed to an antagonistic effect on parietal cell H_2-receptors. It should also be noted that cimetidine contains an imidazole nucleus, long regarded as essential for H_2-receptor blockade (Gerber et al., 1985).

Cimetidine has also been shown to interact with the microsomal cytochrome P-450 linked monooxygenase system, thus inhibiting drug metabolism (Taylor et al., 1978; Pelkonen & Puurunen, 1980; Puurunen et al., 1980; Henry et al., 1980; Borm et al., 1981; Röllinghof & Paumgartner, 1982). Many imidazole compounds have been found to inhibit microsomal oxidation (Wilkinson et al., 1974). It does not impair glucuronidation mediated by glucuronyl transferase (Gerber et al., 1985; Röllinghof & Paumgartner, 1982). It may thus be possible to separate the inhibitory effect of cimetidine on specific enzyme systems in the liver from its gastric H_2-receptor antagonizing effect.

Because of nifedipine's extensive metabolism in the liver by oxidation and hydroxylation (Kleinbloesem et al., 1984) and cimetidine's inhibition of the oxidative pathway, (Hansten & Horn, 1987; Somogyi & Gugler, 1982) it could be expected that cimetidine would increase plasma concentrations of nifedipine as proven by Smith et al. (1987). Their results could not support any influence of gastric acidity on nifedipine bioavailability (Raemsch & Sommer, 1983).

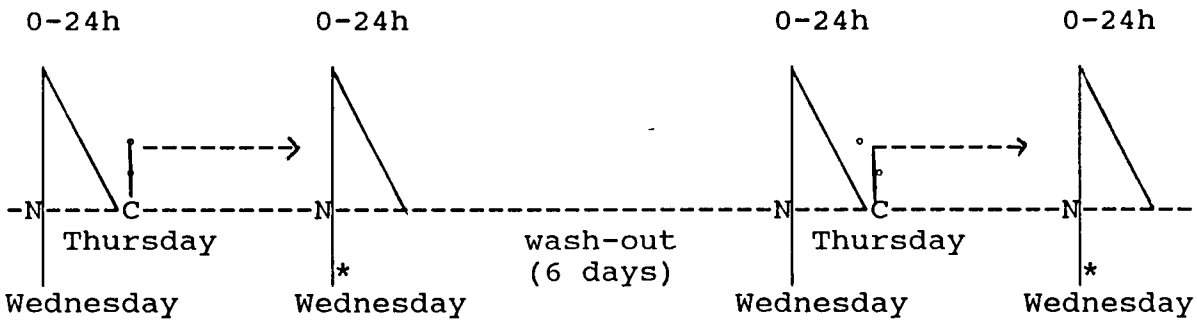
2. OBJECTIVES

To investigate the influence of cimetidine on the bio-availability and pharmacokinetics of nifedipine and the importance of metabolic polymorphism on this interaction.

3. STUDY DESIGN

A single-blind, randomized, cross-over study will be performed. Each subject will take nifedipine (single dose) four times and cimetidine (multiple doses) twice. The two trial periods will be separated by a wash-out period of six (6) days. (See flow-diagram)

Flow-diagram of study design.



N: Nifedipine 10mg
C: Cimetidine 400mg q12h x 6½ days
*: Nifedipine taken with either 200 ml water or 200 ml HCl (0.1% w/v, 0.028M) [Randomised]

4. STUDY POPULATION

4.1 Number of subjects

Twenty (20) healthy, non-smoking, male volunteers of which 10 will be effective oxidizers of sparteine and 10 non-metabolizers, will be included in the study.

Volunteers who meet the inclusion criteria, who do not fall under any of the exclusion criteria and after having given informed consent, may be entered into the study.

4.2 Inclusion criteria

Male subjects between 18 and 40 years of age.

Caucasian.

Body weight not more than 10% above or below their normal weight for height and age according to the 1983 Metropolitan height and mass tables (Geigy Scientific Tables, 1984, Vol.3, p325).

Normal findings in medical history, physical examination and laboratory screens, unless the investigator considers an abnormality to be clinically irrelevant.

Normal ECG and vital signs.

Mental competence and reliability to give informed consent.

4.3 Exclusion criteria

Alcohol abuse and regular use of medication, up to two weeks before the study, or participation in another trial with an investigational drug in the 8 weeks preceding the study.

Treatment within the previous 3 months with any drug known to have a well-defined toxicity potential in regard to a major organ or system (e.g. chloramphenicol and bone marrow suppression).

A major illness during the 3 months preceding the study.

History of hypersensitivity to the trial drugs or to drugs with similar chemical structures.

History or presence of gastrointestinal, liver or kidney disease, or other conditions known to interfere with the absorption, distribution, metabolism or excretion of drugs.

History of bronchial asthma.

4.4 Withdrawal criteria

Volunteers not wishing to continue with the study for reasons other than unwanted effects from the study drug, e.g. unavailability or intolerance of the study procedure.

Unwanted effects from the study drug.

Abnormal biomedical or physical examination.

Intercurrent illness requiring medication.

4.5 Medical and Clinical Laboratory Examination

The subjects will be examined within 2 weeks before drug administration and assessed for their ability to participate. The examinations and tests will include:

Medical history and physical examination.

Height and weight.

Vital signs: radial pulse rate, systolic (1st Korotkoff-sound) and diastolic (5th Korotkoff-sound) blood pressure in recumbent and standing position, respiratory rate and body temperature.

Haematological status: leucocytes, erythrocyte count, haemoglobin, hematocrit, MCV, MCH, MCHC, platelets, differential white cell count, sedimentation rate, reticulocytes, PT, PTT.

Clinical Chemistry (serum): sodium, potassium, chloride, CO_2, urea, creatinine, urate, calcium, phosphate, protein, albumin, total bilirubin, conjugated bilirubin, alkaline phosphatase, GGT, AST, ALT, LD, cholesterol, triglyceride, glucose.

Urinalysis: pH, protein, glucose, ketones, bilirubin, blood, nitrite, urobilinogen.

Electrocardiogram (Standard 12-lead)

4.6 End of study evaluation

Haematological and clinical chemistry profiles will be repeated within 48 hours of completion of the final phase of the trial. In the event of the occurrence of abnormal laboratory results, follow-up determinations will be performed to ascertain if and when they return to pretrial values.

4.7 Restriction on subjects

All subjects must refrain from taking any medications, including those sold over the counter, for two weeks before the study and, except for the test drugs, for the duration of the study. Ingestion of alcoholic and caffeine containing beverages and foods will not be permitted 48 hours before each profile day and until the last sample has been taken on the profile day. Strenuous physical activity will not be allowed for the duration of each trial period. On the dosing days, food and fluid intake will be standardized to minimize intra- and interindividual variances.

4.8 Drop-outs

Subjects who fail to complete the study are to be replaced.

4.9 Volunteers' obligation

Each volunteer should adhere to the instructions given in the protocol and appendices and is obliged to notify the investigator if he is unable to follow the procedures or if he suffers any adverse event. In particular, he should make every effort to contact the investigator if he suffers a more serious adverse event or if he requires to take additional medication of any kind. This applies equally out of hours as to normal working time.

5. TRIAL MEDICATION

5.1 Treatments and dosages

Subjects will be allocated to the treatments according to the randomization plan in Appendix A. Each subject will receive treatment one 4 times and treatment 2 twice.(See study flow-diagram)

Treatment 1	
Generic name:	Nifedipine
Trade name:	Adalat^{R}
Manufacturer:	Bayer-Miles (Pty)Ltd
Dosage form and strength:	Capsules containing 10mg nifedipine
Dose:	10mg (1 x capsule)
Treatment 2	
Generic name:	Cimetidine
Trade name:	Tagamet^{R}
Manufacturer:	Smith Kline & French (Pty)Ltd
Dosage form and strength:	Tablets containing 400mg cimetidine
Dose:	400mg bd x 6½ days (1 tablet twice daily)

5.2 Dosage instruction

Volunteers will take the relevant medication sitting upright, either with 200ml of tap water or with 200ml HCl (0,1% w/v; 0.028M) (Martindale,1982) after an overnight fast of 10 hours whereupon they will lie down on their left sides.

5.3 Randomization

Randomization will be carried out by a biometrician, the dispensing pharmacist and the clinical investigator conducting the trial.

5.4 Supply, storage and dispensing

Drugs for all volunteers will be obtained by the Department of Pharmacology, UOFS, prior to the study. All material for the study will be stored in a limited access area free from environmental extremes. Dispensing thereof on trial days will be done by the nursing staff.

5.5 Packaging and labelling

Each single dose will be retained in a separate container with a label indicating the volunteers' number and trial phase.

5.6 Drug inventory

The investigator shall maintain adequate records of the receipt and disposition of all drugs supplied. Under no circumstances is the investigator to allow the study drugs to be used for purposes other than as directed by this protocol.

6. STUDY PERFORMANCE

6.1 Profile day

The study will be performed in the Farmovs Clinical Pharmacology Unit (CPU) at the Department of Pharmacology. University of the Orange Free State, Bloemfontein.

Volunteers will receive detailed instructions concerning the trial performance, restrictions and possible adverse reactions which may be experienced after the ingestion of the study drugs. There will be two trial periods with a wash-out period of 7 days between them and 4 profile days. On the morning of each profile day, volunteers are to report to the Farmovs CPU, after an overnight fasting period of at least 10 hours.

Having inserted an indwelling venous cannula and after blank pre-dose blood samples have been drawn, subjects will receive 10mg (1 x 10mg capsule) nifedipine as Adalat^{R} with 200ml of tap water on the first profile day. During the following 6½ days they will take 400mg cimetidine every 12 hours (1 x 400mg tablet) and on day 7 the same dose of nifedipine will be given. (second profile day) After the wash-out period of 7 days, the same sequence will be followed. (Profile day 3 and 4) The nifedipine on profile day 2 and 4 will be taken with either 200ml of tap water or 200ml of 0,1% HCl (0,028M) (Martindale,1982) and on profile day 3 with 200ml of tap water. Nifedipine will always be swallowed as intact Adalat^{R} capsules. (See randomization plan in Appendix A. for water/HCl sequence on profile day 2 and 4) Subjects will remain recumbent until four (4) hours after medication.

Food intake will not be permitted until 4 hours after medication, when a standardized lunch will be served. Subjects will drink 200ml of tap water every 2 hours for the first 4 hours (beginning 2 hours post dose), where-after fluid intake will be ad libitum.

6.2 Blood sampling

Heparinised venous blood samples, 10ml each, drawn in Vacutest tubes (green stopper), will be collected according to the following time schedule:

Before drug administration (0) and at 10, 20, 30, 40, 50, 60, 80, 100 and 120 minutes and at 2½, 3, 3½, 4, 5, 7, 9 and 12 hours after drug administration. (18 samples per subject per phase)

The blood samples for nifedipine assays will be centrifuged immediately and from each sample two aliquots will be transferred to labelled tubes and stored at -20°C pending drug assay.

NB : Since nifedipine is light-sensitive, all sample handling and preparation for assay must be done in a darkened room under sodium-light illumination.

7. METHODS

7.1 Special investigations

All biochemical and haematological determinations will be performed in the Departments of Chemical Pathology and Haematology of the University of the Orange Free State, Bloemfontein.

7.2 Drug assay method

Quantitative analysis of plasma-nifedipine in the collected samples will be performed by the Department of Pharmacology, University of the Orange Free State, by means of gas chromatography.

8. BIOMETRICS

The individual plasma-concentration values of every volunteer at each sampling time for all the treatments will be tabulated together with the mean, standard deviation, coefficient of variation, standard error of the mean, minimum, maximum, median and the number of observations.

A graphical presentation of each individual concentration versus time profile for all treatments will be given together with a mean plot. The rate and extent of absorption of nifedipine will be compared by means of the maximum concentration (Cmax), the time to maximum concentration (Tmax) and the area under the concentration-time curve (AUC). Cmax and Tmax will be read directly from the observed concentrations, while AUC will be calculated by the linear trapezoidal rule between the first and last concentration-time data pairs. AUC will also be extrapolated to infinity by using apparent terminal rate constants from the adjustment of a single exponential function to the log-linear terminal phase of the concentration-time profile.

These variables will be listed for each subject and each treatment, together with the descriptive statistics mentioned above. The variables will be listed for each treatment period together with the treatment period means. In addition, a frequency table will be provided for the values of Tmax.

The individual ratios of "test/standard" for each variable, together with the mean, will be listed as well as the power of the test based on Cmax and AUC and a difference of 20% in the treatment means.

The variables Cmax and AUC will be subjected to an analysis of variance for testing the null hypothesis that all the treatments have equal true means. The analysis of variance will take into account treatment, subject and period effects. The subject sum of squares will be partitioned to give a term for sequence and a term for subject within sequence (a residual term).

From this analysis of variance, t-confidence intervals will be constructed for the true difference between treatment means and approximated for the ratio "test/standard" (expressed as a percentage) for each variable.

The symmetrical and t-confidence intervals for the difference in the treatment means will also be calculated after a logarithmic transformation on the data. These limits will be back-transformed to give limits for the ratio of the treatment means on the original scale.

9. ETHICAL SAFEGUARDS

9.1 Ethical and institutional review

Approval by the Ethics Committee of the University of the Orange Free State, Bloemfontein will be required before the study can commence.

9.2 Patient information and informed consent

Preceding the trial, the nature, purpose and risk of the research involved will be explained to all subjects. (Appendix B) They will also be informed that they may withdraw from the study at any time. They will sign the Institute's informed consent form in the presence of a witness. (Appendix C)

9.3 Adverse drug reactions

In the event of adverse drug reactions, the investigator will decide whether to withdraw the subject from the trial and to initiate appropriate treatment.

9.4 Declaration of Helsinki

The study will be carried out in conformance with the recommendations for clinical trials in man, as set out in the "Declaration of Helsinki" (1974), the Tokyo Revision (1975), the Venice Amendment (1983) and the local legal requirements. (Appendix D)

9.5 Indemnity

Insurance cover has been arranged to indemnify the volunteers in the event of death or suffering any deterioration in health or well being or any susceptibility or toxicity caused by the participation in the trial.

Indemnification is provided without regard to the question of legal liability as long as causation is existing between the death or suffering and the participation in the trial.

The insurer will indemnify the amount of money which is necessary to cover the difference between the actual financial status after the death or deterioration of health and the supposed financial status should no deterioration of health or death occur. Any compensation received from social insurance schemes or other sources will be deducted from the amount of compensation provided through Farmovs.

The insurer will indemnify, in case of death or in case of permanent disability, up to R225 000,00. The maximum total contribution is limited to R4 500 000,00 for all subjects participating in the trial/study.

During the course of the clinical trial, the volunteer may not participate in any other trial. Any case of deterioration in health, which could be considered as being caused by the clinical trial, must be reported at once.

9.6 Confidentiality

Results from the medical examination(s) and, if appropriate, from laboratory tests will be recorded.

All information obtained during the conduct of the study with regard to the volunteers' state of health will be regarded as confidential and an agreement must be requested from the volunteer prior to disclosure of such information to a third party.

9.7 Subject remuneration

Payment to the volunteers for time and inconvenience during the study will be made. Volunteers not completing the study for whatever reason will be paid on a pro rata basis.

10. DOCUMENTATION

10.1 Report

A detailed report will be prepared by the investigator without undue delay and submitted to the Ethical Committee and study leaders.

10.2 Publication of results

If publication of results in a reputable scientific journal is envisaged, a draft manuscript will be prepared in collaboration with the study leaders.

11. MONITORING THE STUDY

11.1 Deviations from the protocol

As the study progresses, any addition or changes to the protocol that seem necessary will be worked out by mutual written agreement between the investigator and the study leaders.

These amendments will be submitted, if necessary, to the Ethics Committee for approval before continuation of the trial.

APPENDIX A : FRM 5/88

AN INVESTIGATION INTO THE INFLUENCE OF CIMETIDINE ON THE BIOAVAILABILITY AND PHARMACOKINETICS OF NIFEDIPINE AND THE IMPORTANCE OF METABOLIC POLYMORPHISM ON THIS INTERACTION

RANDOMIZATION PLAN

Subject No.	Profile Day I (Red)	Profile Day II (Yellow)	Profile Day III (Green)	Profile Day IV (Blue)
1	A	B	C	D
2	A	D	C	B
3	A	D	C	B
4	A	B	C	D
5	A	D	C	B
6	A	B	C	D
7	A	B	C	D
8	A	B	C	D
9	A	D	C	B
10	A	D	C	B
11	A	D	C	B
12	A	B	C	D
13	A	B	C	D
14	A	D	C	B
15	A	D	C	B
16	A	B	C	D
17	A	B	C	D
18	A	B	C	D
19	A	D	C	B
20	A	D	C	B

Treatment
A : Nifedipine with 200ml tap water
B : Nifedipine with 200ml tap water(Cimetidine steady state)
C : Nifedipine with 200ml tap water
D : Nifedipine with 200ml 0,1% HCl(Cimetidine steady state)

APPENDIX B : FRM 5/88

AN INVESTIGATION INTO THE INFLUENCE OF CIMETIDINE ON THE BIOAVAILABILITY AND PHARMACOKINETICS OF NIFEDIPINE AND THE IMPORTANCE OF METABOLIC POLYMORPHISM ON THIS INTERACTION

VOLUNTEER INFORMATION

Study objectives

To investigate the influence of cimetidine on the bioavailability and pharmacokinetics of nifedipine and the importance of metabolic polymorphism on this interaction.

Procedure

The study will take place during a four week period. Blood samples will be taken, via a small indwelling cannula, throughout a 4 hour period and after that, by venepuncture at the following times: (0), 10, 20, 30, 40, 50, 60, 80, 100 and 120 minutes and at 2½, 3, 3½, 4, 5, 7, 9 and 12 hours after medication (18 samples/phase).

Restrictions on volunteers

Diet

An overnight fast (total abstinence from food and fluids) from 22h00 on the evening before the study will be required. Lunch will be provided after the 4 hour blood sample has been taken.

Alcohol and Caffeine

No alcohol or caffeine containing foods or beverages are permitted from 06h30 two days before each profile day until the last blood samples have been collected on profile days.

Physical activity

Strenuous physical activity will not be allowed for the duration of each trial period.

Drugs

Pharmaceutical preparations should be avoided in the 14 days prior to the study and until the study is completed. If any such preparations are taken, it must be reported to the investigator.

During the first 4 hours on study days the volunteers will remain recumbent on their left sides in the Farmovs CPU under the direct supervision of the clinical investigator or co-investigator.

Withdrawal from the study

While it is the privilege of any volunteer to withdraw from the study at any time, volunteers must agree to obey the instructions of the investigator concerning matters pertaining to the health of the individual after administration of the trial medication.

Information on the study drug

Nifedipine is a calcium channel blocking agent used in the treatment of angina pectoris, hypertension and Raynaud's phenomenon. Side effects are due to the vasodilating activity of the drug and include headache, flushing and dizziness.

Cimetidine is an H_2-receptor antagonist used in the treatment of peptic ulceration. Side effects include mild transient diarrhoea, muscular pains and skin rash.

Location of study:

Farmovs Clinical Pharmacology Unit (CPU)
Department of Pharmacology
University of the Orange Free State
P O Box 339
9300 BLOEMFONTEIN

APPENDIX C : FRM 5/88

AN INVESTIGATION INTO THE INFLUENCE OF CIMETIDINE ON THE BIOAVAILABILITY AND PHARMACOKINETICS OF NIFEDIPINE AND THE IMPORTANCE OF METABOLIC POLYMORPHISM ON THIS INTERACTION

VOLUNTEER CONSENT FORM

I,_____
hereby give permission that the drug(s) mentioned below be administered to me.

I have been fully informed by Dr AD du Plessis regarding the possible side effects of taking the drug(s) mentioned below.

The drug(s) that will be administered are: Adalat^{R} 10mg (Bayer-Miles) as a single dose (1 x capsule) on profile days and Tagamet^{R} 400mg (Smith Kline & French) (1 x tablet) every 12 hours for 6½ days. On one of the profile days, the Adalat^{R} will be taken with 200ml of 0,1% w/v HCl(0.028M) while on the other three days it will be taken with 200ml of tap water.

I realize that the side effects due to these drugs may include the following: headache, flushing, dizziness, mild transient diarrhoea, muscular pains and skin rash.

My consent is given of my own free will and I realize that it may be withdrawn at any time.

I also declare that I have made the necessary arrangements regarding the attendance of lectures and other academic activities with the lecturers involved.

I understand that a policy to cover volunteers in clinical trials against death or disablement arising as a result of participation in such clinical trials has been taken out by the Farmovs Clinic for Clinical Pharmacology. I accept the conditions of the policy as set out on the reverse side of this form.

_____ _____
Volunteer Date

_____
Person who informed participant

_____
Person who conducted the trial

_____
Witness

Conditions and benefits of policy to cover volunteers in clinical trials

Insurance cover has been arranged to indemnify the volunteers in the event of death or suffering any deterioration in health or well being or any susceptibility or toxicity caused by the participation in the experiment/ trial/test

Indemnification is provided without regard to the question of legal liability as long as causation is existing between the death or suffering and the participation in the trial.

The insurer will indemnify the amount of money which is necessary to cover the difference between the actual financial status after the death or deterioration of health and the supposed financial status should no deterioration of health or death occur. Any compensation received from social insurance schemes or other sources will be deducted from the amount of compensation provided through Farmovs.

The insurer will indemnify in case of death or in case of permanent disability up to R225 000,00. The maximum contribution of insurers for all participants in a clinical trial is limited to R4 500 000,00.

During the course of the clinical trial the volunteer is entitled to participate in other trials only with prior agreement of the supervising doctor. Any case of deterioration in health which could be considered as being caused by the clinical trial must be reported at once. The same applies in case of death where the supervising doctor has to notify the Medical Department of Farmovs immediately.

APPENDIX D : FRM 5/88

DECLARATION OF HELSINKI

Recommendations guiding medical physicians in biomedical research involving human subjects

Adopted by the 18th World Medical Assembly
Helsinki, Finland, June 1964
amended by the 29th World Medical Assembly
Tokyo, Japan, October 1975
and
the 35th World Medical Assembly
Venice, Italy, October 1983

INTRODUCTION

It is the mission of the physician to safeguard the health of the people. His or her knowledge and conscience are dedicated to the fulfillment of this mission.

The Declaration of Geneva of the World Medical Association binds the physician with the words: "the health of my patient will be my first consideration", and the International Code of Medical Ethics declares that: "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."

The purpose of biomedical research involving human subjects must be to improve diagnostic, therapeutic and prophylactic procedures and the understanding of the aetiology and pathogenesis of disease.

In current medical practice most diagnostic, therapeutic or prophylactic procedures involve hazards. This applies especially to biomedical research.

Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.

In the field of biomedical research, a fundamental distinction must be recognized between medical research in which the aim is essentially diagnostic or therapeutic for a patient, and medical research, the essential object of which is purely scientific and without implying direct diagnostic or therapeutic value to the person subjected to the research.

Special caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.

Because it is essential that the results of laboratory experiments be applied to human beings to further scientific knowledge and to help suffering humanity, the World Association has prepared the following recommendations as a guide to every physician in biomedical research involving human subjects. They should be kept under review in the future. It must be stressed that the standards as drafted are only a guide to physicians all over the world. Physicians are not relieved from criminal, civil and ethical responsibilities under the laws of their own countries.

1 BASIC PRINCIPLES

1.1 Biomedical research involving human subjects must conform to generally accepted scientific principles and should be based on adequately performed laboratory and animal experimentation and on a thorough knowledge of the scientific literature.

1.2 The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol which should be transmitted to a specially appointed independent committee for consideration, comment and guidance.

1.3 Biomedical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person.

The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given his or her consent.

1.4 Biomedical research involving human subjects cannot legitimately be carried out unless the importance of the objectives is in proportion to the inherent risk to the subject.

1.5 Every biomedical research project involving human subjects should be preceded by careful assessment of predictable risks in comparison with foreseeable benefits to the subject or to others. Concern for the interests of the subject must always prevail over the interest of science and society.

1.6 The right of the research subject to safeguard his or her integrity must always be respected. Every precaution should be taken to respect the privacy of the subject and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.

1.7 Physicians should abstain from engaging in research projects involving human subjects unless they are satisfied that the hazards involved are believed to be predictable. Physicians should cease any investigation if the hazards are found to outweigh the potential benefits.

1.8 In publication of the results of his or her research, the physician is obliged to preserve the accuracy of the results. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

1.9 In any research on human beings, each potential subject must be adequately informed of the aims, methods, anticipated benefits and potential hazards of the study and the discomfort it may entail. He or she should be informed that he or she is at liberty to abstain from participation in the study and that he or she is free to withdraw his or her consent to participation at any time. The physician should then obtain the subject's freely-given informed consent, preferably in writing.

1.10 When obtaining informed consent for the research project, the physician should be particularly cautious if the subject is in a dependent relationship to him or her or may consent under duress. In that case the informed consent should be obtained by a physician who is not engaged in the investigation and who is completely independent of this official relationship.

1.11 In case of legal incompetence, informed consent should be obtained from the legal guardian in accordance with national legislation. Where physical or mental incapacity makes it impossible to obtain informed consent, or when the subject is a minor, permission from the responsible relative replaces that of the subject in accordance with national legislation. Whenever the minor child is in fact able to give consent, the minor's consent must be obtained in addition to the consent of the minor's legal guardian.

1.12 The research protocol should always contain a statement of the ethical considerations involved and should indicate that the principles enunciated in the present Declaration are complied with.

2 MEDICAL RESEARCH COMBINED WITH PROFESSIONAL CARE (Clinical Research)

2.1 In the treatment of the sick person, the physician must be free to use a new diagnostic and therapeutic measure, if in his or her judgement it offers hope of saving life, re-establishing health or alleviating suffering.

2.2 The potential benefits, hazards and discomfort of a new method should be weighed against the advantages of the best current diagnostic and therapeutic methods.

2.3 In any medical study, every patient - including those of a control group, if any - should be assured of the best proven diagnostic and therapeutic method.

2.4 The refusal of the patient to participate in a study must never interfere with the physician-patient relationship.

2.5 If the physician considers it essential not to obtain informed consent, the specific reasons for this proposal should be stated in the experimental protocol for transmission to the independent committee. (1.2)

2.6 The physician can combine medical research with professional care, the objective being the acquisition of a new medical knowledge, only to the extent that medical research is justified by its potential diagnostic or therapeutic value for the patient

3 NON-THERAPEUTIC BIOMEDICAL RESEARCH INVOLVING HUMAN SUBJECTS
(Non-clinical biomedical research)

3.1 In the purely scientific application of medical research carried out on a human being, it is the duty of the physician to remain the protector of the life and health of that person on whom biomedical research is being carried out.

3.2 The subjects should be volunteers - either healthy persons or patients for whom the experimental design is not related to the patient's illness.

3.3 The investigator or the investigating team should discontinue the research if in his/her or their judgement it may, if continued, be harmful to the individual.

3.4 In research on man, the interest of science and society should never take precedence over considerations related to the well being of the subject.

October 1983