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THE EFFECT OF OMEPRAZOLE ON PHARMACOKINETICS OF METHADONE IN THE RABBITS

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ABSTRACT

Omeprazole is a gastric H^+ K^+ ATPase acid pump inhibitor, increases gastric pH and metabolized in microsomal enzyme system in liver. Pharmacokinetic interaction of methadone with omeprazole was investigated first time in rabbits. Fifteen male New Zeeland White rabbits weighing 4.5 kg of 9-15 months age were grouped, comprising of 8 & 7 animals in test group (Methadone + Omeprazole) and control (Methadone) respectively. The test group of rabbits were given omeprazole (60 umol/kg), suspended in normal saline orally by gavage for one week and methadone (10 mg/kg) orally after one hour of omeprazole dose only on seventh day while the control group of rabbits were given physiological 0.9% of normal saline instead of omeprazole.

Omeprazole delayed the oral absorption of methadone with average peak time of 2.4 hrs as compared to mean 1.38 hrs in controls (>0.05) and increased its AUC by 26 percent. The elimination half life and mean residence time were increased while total clearance reduced by 29 percent in omeprazole treated rabbits ($P<0.01$).

It is concluded that omeprazole slows elimination phase of methadone, so patients talking omeprazole for peptic ulcer, should be followed for any symptoms of methadone toxicity and the dose must be adjusted.

INTRODUCTION

Methadone is a long acting narcotic analgesic, possesses many of the pharmacological properties of morphine. It was first synthesized in Germany during the world war II and was made clinically available in the United States in 1947 (Sullivan, 1973). Methadone is the only narcotic analgesic approved by the FDA to be used for detoxification and treatment of chronic pain. The cardiovascular and central nervous system (CNS) effects of methadone may be enhanced both in magnitude and duration when administered in combination with other CNS depressants such as barbiturates and tranquilizers. Methadone in high dosage, may depress respiration. In some cases pulmonary edema has been reported following the use of methadone in usual therapeutic doses (Kjeldgaard, 1971). Methadone has been reported to cause hepatotoxicity in few cases, characterized by alterations in liver function tests (Walter, 1969).

Omeprazole is an acid pump inhibitor which controls gastric acid secretion by

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inhibitory gastric H^+ K^+ ATPase (the acid pump) responsible for the final step in the secretion of Hydrochloric acid by parietal cells and use for treatment of peptic ulcer (Lindberg et al., 1986). It increases intragastric pH 1 to 2, to value around 3 to 5. This might potentially influence the absorption of drugs because of their ionization within the stomach and passive diffusion. The absorption of some drugs like digoxin, phenytoin and nifedipine are increased by 10-12% through gastrointestinal tract in combination with Omeprazole. The increased AUC was suggestive of increased absorption, resulting from decreased hydrolysis within the stomach as a consequence of the elevated pH obtained by omeprazole (Gault et al., 1980 and Anderson, 1990). Prichard et al. (1987) demonstrated significant increased from 121.6 to 151.4 mg/L h in phenytoin AUC because of increased elimination half-life with omeprazole. These findings have potential clinical importance because in view of the narrow therapeutic window of these drugs.

Cimetidine-methadone interaction has been reported by Eugene et al. in 1983. Cimetidine decreases the hepatic clearance of methadone by inhibiting hepatic microsomal enzyme activity. It is entirely possible that inhibition of methadone metabolism by Cimetidine contribute methadone toxicity in patients using cimetidine for treatment of peptic ulcer.

Since methadone and omeprazole are mainly metabolized by P-450 enzymes system in the liver, the saturation of this enzyme with omeprazole may result in longer terminal half-life. These finding has potential clinical importance in view of the therapeutic and methadone toxicity in narcotic addicts. Cytochrome P450 converts lipophilic substrates to more hydrophilic derivatives, which are then more easily excreted from the body via urine or bile (Pichard et al., 1990 and Watkins et al., 1985). The effect of omeprazole on the pharmacokinetics of the benzodiazepine especially diazepam has shown slow metabolism in liver, exhibiting decreased in the mean clearance and the increased in elimination half-life of by 130% (Anderson, 1990).

The pharmacokinetic parameters of methadone have varied considerably in different drug interactions studies and depend on the route of administration, metabolism in liver and pH of urine. Some drugs increase serum level and effect of methadone in the body while other drugs enhanced the metabolism and its excretion from body. There is hardly any study carried out to see drug interaction of methadone with omeprazole. The widespread use of omeprazole and increasing number of patients who receive methadone for detoxification or chronic pain are a matter of concern. This study provides important information for better management of methadone dosage and toxicity in case of combined therapy with omeprazole.

MATERIALS AND METHODS

Experimental Animals:

Fifteen male New Zeeland white rabbits weighing 4.5 kg of 9-15 months age (Lessers Animal Co. II) were kept in BRL, UIC at Chicago. They were maintained under controlled condition of temperature (25 ± 2 degrees centigrade), humidity (50 ± 10% and light (6:00 A.M. to 6:00 P.M.). These animals had free access to food and water. The protocol was approved by animal care committee of University of Illinois at Chicago.

Drugs Administration:

Methadone hydrochloride was obtained from Sigma Corp. (St. Loius, Cat number 0733) and dissolved in 10 mg/ml of 0.9% normal saline. Omeprazole enteric-coated granules were removed from capsules and suspended in 0.9% normal saline. Omeprazole were administered through oral gavage and flushed with 5 ml of normal saline.

Experimental Design and Treatment Schedule:

This study was randomized and placebo controlled. The rabbits were divided into two groups comprising of 7 and 8 animals in control (Methadone) and test group (Methadone + Omeprazole) respectively. The control group of rabbits was given physiological 0.9% of normal saline for one week and 10 mg/kg methadone only on 7th day by gavage. The test group was given omeprazole (60 umol/kg), suspended in normal saline orally by gavage for one week and methadone (10 mg/kg) orally after one hour of omeprazole dose only on seventh day.

Blood Sampling:

Blood samples were collected in 3 ml heparinized vacutainer tubes (Bectori Dickinson, Rutherford NJ) from marginal vein by 25 gauge needle just before dosing and at 1, 2, 4, 8, 12 and 24 h after methadone administration in both groups. The plasma was separated by centrifugation at 3000 g for 10 minutes within 1 h of collection and stored at -20 degree centigrade until analyzed.

Analysis of Plasma Methadone:

Plasma methadone concentrations were determined, using the Coat- A-Count Methadone assay (Diagnostic Products Corporation, Los Angeles, Calif.), a solid=pohase ^{125}I radiommunoassay. Radioactivity was count for 1 minute in a gamma counter (12 channel Gamma Counter Ne 1612 Nuclear Enterprises UK). The sensitivity of the method was 0.5 ng/ml. The day-to-day assay coefficient of variation (CV) was 9.7% and the within-day was 5.2%.

Pharmacokinetic Calculations:

The total areas under the plasma concentration-time curve (AUC 0-∞) of methadone were obtained by trapezoid rule. The apparent volume of the central compartment (Vd), total clearance (CL), rate constants (k10), mean residence time (MRT), absorption rate constant (Ka), absorption ($t_{1/2\alpha}$) and elimination $t_{1/2\beta}$) half-lives, time of peak plasma concentration (tmax) and peak plasma concentration (C_{max}) of methadone. The total plasma systemic clearance (CL) of methadone was calculated from:

$$CL = \frac{Dose}{AUC}$$

Statistical Analysis:

The plasma methadone concentration after oral administration were expressed as the mean and the SD. The statistical analysis of pharmacokinetic parameters were analyzed by using unpaired 't' test. P-value less than 0.05 is considered as significant.

RESULTS

The time course of methadone distribution following oral administration in rabbits under influence of omeprazole, to our knowledge, has been undertaken for the first time. The plasma methadone concentration at 1h, 2hrs, 4hrs, 8hrs, 12hrs and 24hrs in test group of eight rabbits taking methadone and omeprazole is shown in Fig.1. The plasma methadone levels at same interval up to 24 hrs in control group of seven rabbits is shown in Fig.2. The very low plasma levels of methadone result from the well- known ability of basic drugs to distribute rapidly from plasma into tissues.

The plasma methadone concentration in test group and control group animals is shown in Table 1. In the initial period, plasma methadone levels were significantly high at one hour and 2 hrs of oral administration with peak levels 55.57 ± 7.86 ng/ml in control and 44.08 ±12.68 ng/ml in test group respectively. In subsequent time period, the methadone levels in test group of animals started raising with significant difference at 8 hrs and 12 hrs as compared to control rabbits ($P < 0.05$).

Gastrointestinal Absorption Kinetics of Methadone:

The computer calculated pharmacokinetic parameters for methadone along with omeprazole is shown in Table 2. There are some variation in pharmacokinetic parameters in this group of the animals. The area under the plasma concentration time curve (AUC) varied from 240-407 mg.h/1 in test group indicate erratic absorption. The mean apparent volume of distribution of methadone was (Vd) 0.15 1/kg. The absorption rate constant (ka) of methadone for the eight data sets ranged

from 0.29 to 2.79 with mean value of 1.036 1/h and the absorption half-lives varied from 0.24 to 2.42 hours. Our study also indicate that omeprazole treated rabbits exhibited lower mean peak plasma concentration of methadone 41.51 mg/1 and more time was required to reach maximum plasma concentration (tmax) ranged 1.114 to 4.14 hours after single oral dose as compared to control. The results of the kinetic studies in control group of rabbits are shown in Table 3.

The gastrointestinal absorption kinetics is shown in Table 4. The AUC of methadone was increased by 26 percent following omeprazole treatment while volume of distribution remain unchanged. The absorption rate constant (Ka) of methadone was much lower while absorption half life increased significantly in Omeprazole treated rabbits ($P < 0.01$). The Omeprazole delayed the oral absorption of methadone and reduced mean C_{max} 41.51 mg/1 in rabbits ($P < 0.01$).

Elimination Kinetic of Methadone in Rabbits:

The disposition pharmacokinetic parameters in Omeprazole pretreated animals showed a slow elimination phase of methadone (Table 5). The total methadone clearance (CL) was lowered with mean of 0.029 1/h and elimination ($t_{1/2\beta}$) half-lives varied from 2.51 to 4.746 hours. Mean residence time ranged from 5.81 to 8.46 hours in this group. The elimination pharmacokinetic parameters in control group of animals is summarized in Table 6.

The elimination pharmacokinetics of oral methadone were determine to ascertain whether omeprazole had any role in metabolism in liver or total clearance from body in rabbits. These results are summarized in Table 7. The elimination half life i.e. 3.56 hours increased significantly in omeprazole treated rabbits while this group had lowered by 29 percent total body clearance ($P < 0.05$). Following oral administration of omeprazole the mean residence time of methadone was increased in the test rabbits.

DISCUSSION

Different types of drug interactions have been studied to determine the narcotic withdrawal effect and toxicity due to alterations in methadone kinetics in animals and humans. Pharmacokinetic interaction of methadone with omeprazole, has not been studied so far. Redfern and Co-workers (1971) produced a marked increase in mean intra gastric pH 5.0 over 12 hours period after 60 umol/kg administration of Omeprazole in rabbits. We use the same dose of omeprazole in these rabbits because prolonged inhibition of gastric acid was required to study the pharmacokinetic of methadone.

Both groups of rabbits had marked variation in the plasma methadone levels at 1h, 2hrs, 4hrs, 8hrs, 12hrs and 24 hrs (Fig. 1-2). The very low plasma levels of methadone result from the well-known ability of basic drugs to distribute rapidly from plasma into tissues. Rabinson and Williams (1971) found that the concentration of methadone in human lung, liver and kidney greatly exceeded the amount in blood. This is consistent with Paalzow and Co-worker (1982) who demonstrated large inter individual differences in plasma concentration with average plasma level of 80 ng/ml after optimal methadone dose in cancer patients.

The plasma concentration of methadone at different interval upto 24 hours was compared with and without pretreatment with Omeprazole in rabbits (Table 1). Methadone concentration was lower till 2 hour and started raising after 4 hour in omeprazole treated animals; might be due to delayed absorption from intestines or decreased total clearance from body. Based on our original hypothesis that omeprazole might increase absorption of methadone from stomach due to raised pH was not proven with this data. There are lot of factors which determine the extent, rate of absorption and variation in plasma levels of methadone such as pH of gastrointestinal tract, rate of gastric emptying of contents into intestine, microbial flora and metabolizing enzymes in gastrointestinal tract. The gastric emptying of methadone appeared to be a rate limiting step in its overall gastrointestinal absorption (Walsh et al., 1975). The omeprazole upto 80 umol/kg has shown no effect on gastric emptying in rats but reduced pancreatic bicarbonate secretion probably due to diminished duodenal acidification following the inhibited gastric acid secretion (Larsson et al., 1985). These above mentioned factors can cause decreased rate of methadone absorption from intestines in omeprazole pretreated rabbits.

The area under the plasma concentration time curve was significantly high in omeprazole treated rabbits as compared to control animals ($P < 0.05$) and the AUC of methadone was increased by 26 percent while volume of distribution remain unchanged (Table 4). Gault et al. (1980) reported similar finding and noted increase of 10 percent AUC of digoxin following omeprazole treatment due to increased absorption, resulting from decreased hydrolysis of digoxin within stomach. Prichard et al. (1987) demonstrated significant increased from 121.6 to 151.4 mg/L h in phenytoin AUC with omeprazole. The amount of nifedipine absorbed was increased by 21 percent after the 7-days pretreatment of omeprazole could be due either to decreased first-pass elimination or an increased absorption as a consequence of the elevated pH in stomach compared with the control (Anderson et al., 1991). These finding has potential clinical importance in view of the narrow therapeutic window of digoxin and phenytoin. Patients talking omeprazole treatment for peptic ulcer, should be followed for any symptoms of methadone toxicity and the dose must be adjusted. Although there was a slight delay in absorption of bacampicillin but no effect of omeprazole on

AUC of amoxycillin and bacampicillin was noted (Paulsen et al., 1989).

The mean 1.04 1/h absorption rate constant (Ka) and Cmax 41.51 mg/1 of methadone was much lower in omeprazole treated rabbits as compared to controls ($P < 0.01$). The difference in the absorption rates might be due to the difference in the stomach emptying times and pH in gastrointestinal tract. The slowed gastric emptying and difference in pH, could there delay the transfer of methadone to small intestine which is the main site of absorption because of its large surface area the basic characteristics of methadone. The omeprazole also delayed the oral absorption of methadone. Decreased gastrointestinal absorption of methadone during omeprazole administration could not be evaluated fully without measuring the other metabolites of and fecal collections of methadone (Tong et al., 1981).

The average peak time after single oral dose of methadone was 2.4 hours in omeprazole treated animals as compared to 1.38 hours in controls. This is consistent with those reported by Nilsson and Co-worker (1982) that methadone peak plasma occurred at 3 hours (range 1-5 hours) after single dose in human. After omeprazole pretreatment, mean bacampicillin Cmax was slightly lower and tmax was delayed to 1.1 h.

Elimination Kinetic of Methadone in Rabbits:

It is well known that both biotransformation and renal excretion are important determinants of the disposition of methadone. The disposition pharmacokinetic parameters describe in Table 7, showed a slow elimination phase and increased the mean residence time of methadone after oral administration of omeprazole. Similar results were reported by Gugler and Jensen (1984). They noted the increased elimination half-life of diazeparm from 36.9 to 85.0 h and the total body clearance was reduced from 1.34 to 0.61 L h/ kg after a 6-day course of omeprazole treatment. Phenytoin clearance was also reduced from 0.025 to 021 L h/kg after omeprazole and mean elimination half-life was increased from 20.7 to 26.3 hours (Gugler and Jensen, 1984). From these results it might be possible that omeprazole has the potential to interfere with the metabolism of methadone mainly by cytochrome p-450 enzymes. omeprazole can bind to cytochrome p-450 and inhibit the oxidative metabolism of these drugs and thus decreases the clearances from body and increases the mean residence time of methadone in omeprazole pre-treated rabbits.

The other reason of decreased clearance and increase mean residence time of methadone could be the similarity in action of omeprazole between H, K-ATPase in stomach and Na, K-ATPase, in renal tubules. Since methadone is a basic drug and urinary pH can influence the elimination kinetics of methadone. Garrett (1978) reported that the renal clearance of methadone range 3-33 ml/min was urine pH

dependent and had a profound effect on the terminal half-life of methadone. Thus same dose of methadone with a fixed interval may accumulate due to its long terminal half-life and causes toxicity in patient using omeprazole.

It is concluded that omeprazole has a interaction with methadone and affect pharmacokinetics of methadone by increasing AUC, MRT, terminal half-life and decreasing total body clearance in rabbits. These finding has potential clinical importance in view of the therapeutic and methadone toxicity in narcotic addicts. Practitioner should be aware of the potential hazards of this combination and should monitor closely for evidence of excessive opiate action in their patients.

Table 1
Plasma methadone concentrations (ng/ml) at different interval, after oral administrations of methadone at 10 mg/kg of body weight alone and with omerprazole 60 mg/kg of body in rabbits (n = 15)

Time (hours)	Methadone Mean ± SD	Methadone + Omeprezole Mean ± SD	P-value
1	41.45 ± 7.82	28.69 ± 8.5	< 0.05
2	55.57 ± 7.86	44.08 ± 12.68	< 0.05
4	28.49 ± 7.59	33.47 ± 8.80	NS
8	14.84 ± 4.72	18.63 ± 66.69	< 0.05
12	6.57 ± 1.98	10.11 ± 3.45	< 0.05
24	2.53 ± 1.80	3.67 ± 1.85	NS

Table 2
Gastrointestinal absorption kinetics calculations from the eight rabbits data sets following oral administration of methadone hydrochloride (10 mg/kg body weight) with omeprazole

Rabbit No.	Pharmacokinetic parameters					
	AUC (h.mg/l)	Vd (l/kg)	ka (l/h)	t½ abs α (h)	T_{max} (h)	C_{max} (mg/l)
T1	311.9	0.165	1.61	0.430	1.497	45.01
T2	250.77	0.273	2.79	0.247	1.114	31.12
T3	388.2	0.128	0.29	2.421	4.144	33.92
T4	314.4	0.109	0.32	2.290	3.362	34.41
T5	399.99	0.114	0.63	1.103	2.571	49.93
T6	240.1	0.107	0.497	1.396	2.663	44.98
T7	398.8	0.164	0.930	0.774	2.322	42.75
T8	407.0	0.146	1.236	0.560	1.871	50.02
Mean	351.64	0.150	1.045	1.15	2.443	41.517
SD	55.64	0.054	0.848	0.827	0.986	7.417

Area under the plasma concentration-time curve (AUC 0-∞), apparent volume of distribution (Vd), absorption rate constant (Ka), absorption (t½α) and time of peak plasma concentration (tmax) and peak plasma concentration (C_{max}) of methadone.

Table 3
Gastrointestinal absorption kinetics calculation from the seven rabbits data sets following oral administration of methadone hydrochloride alone (10 mg/kg body weight)

Rabbit No.	Pharmacokinetic parameters					
	AUC (h mg/l)	Vd (1/kg)	ka 1/h)	t½ abs α (h)	T_{max} (h)	C_{max} (mg/l)
C1	346.0	0.1181	2.026	0.3421	1.731	63.32
C2	194.7	0.1063	11.83	0.0586	1.247	82.10
C3	308.5	0.1709	10.13	0.0684	1.242	65.25
C5	236.5	0.1239	10.89	0.06366	1.242	72.13
C6	249.0	0.1635	10.53	0.0658	1.208	55.92
C8	263.9	0.1677	2.077	0.3347	1.687	44.54
C9	342.3	0.1342	12.25	0.0566	1.288	69.28
Mean	277.27	0.1407	8.533	0.141	1.377	63.217
SD	56.84	0.0263	4.487	0.134	0.227	12.397

Area under the plasma concentration-time curve (AUC 0-∞), apparent volume of distribution (Vd), absorption rate constant (Ka), absorption ($t_{1/2\alpha}$) and time of peak plasma concentration (T_{max}) and peak plasma concentration (C_{max}) of methadone.

Table 4
Gastrointestinal absorption kinetics parameters following oral administration of methadone alone and with omeprazole in rabbits (n = 15)

Kinetic parameters	Methadone Mean ± SD	Methadone + Omeprezole Mean ± SD	p-value
AUC (h.mg/l)	277.27 ± 56.84	351.64 ± 56.64	< 0.05
Vd (1/kg)	0.1407 ± 0.026	0.150 ± 0.054	NS
ka (1/h)	8.533 ± 4.487	1.036 ± 0.848	< 0.01
t½ abs α (h)	0.141 ± 0.134	1.153 ± 0.827	< 0.01
T_{max} (h)	1.377 ± 0.228	2.443 ± 0.986	< 0.05
C_{max} (mg/l)	63.217 ± 12.397	41.517 ± 7.417	< 0.01

Area under the plasma concentration-time curve (AUC 0 - ∞), apparent volume of distribution (Vd), absorption rate constant (Ka), absorption ($t_{1/2\alpha}$) and time of peak plasma concentration (t_{max}) and peak plasma concentration (C_{max}) of methadone.

Table 5
Pharmacokinetic calculations from the eight data sets of disposition kinetic following oral administration of methadone hydrochloride (10 mg/kg body weight) with omeprezole in rabbits

Rabbit No.	Pharmacokinetic parameters				
	AUC (h.mg/l)	CL (1/h)	T1/2b (h)	K10 (1/h)	MRT (h)
T1	311.9	0.0321	3.600	0.1925	5.814
T2	250.77	0.0399	4.746	0.1461	7.204
T3	388.2	0.0258	3.446	0.2011	8.464
T4	314.4	0.0318	2.370	0.2925	6.723
T5	399.99	0.0250	3.156	0.2196	6.144
T6	340.1	0.0294	2.514	0.2757	5.641
T7	398.8	0.0251	4.533	0.1529	7.615
T8	409.0	0.0244	4.144	0.1673	6.788
Mean	351.64	0.0290	3.562	0.205	6.799
SD	56.64	0.0053	0.875	0.054	0.952

Area under the plasma concentration-time curve (AUC 0 - ∞), total clearance (CL), mean residence time (MRT) and elimination ($t_{1/2\beta}$) half-lives of methadone.

Table 6
Pharmacokinetic calculations from the seven data sets of disposition kinetic following oral administration of methadone hydrochloride alone (10 mg/kg body weight) in rabbits

Rabbit No.	Pharmacokinetic parameters				
	AUC (h.mg/l)	CL 1/h)	T½β (h)	k10 (1/h)	MRT (h)
C1	346.0	0.0289	2.833	0.2447	5.124
C2	194.7	0.0514	1.434	0.4833	3.119
C3	308.5	0.0323	3.653	0.1897	6.212
C5	236.5	0.0422	0.032	0.3412	3.937
C6	249.0	0.0402	2.032	0.2456	5.008
C8	263.9	0.0377	3.069	0.2259	5.396
C9	342.3	0.0292	3.183	0.2177	5.627
Mean	277.27	0.0374	2.718	0.2783	4.917
SD	56.84	0.00807	0.748	0.1020	1.053

Area under the plasma concentration-time curve (AUC 0 - ∞), total clearance (CL), mean residence time (MRT) and elimination (t½β) half-lives of methadone.

Table 7
Elimination kinetics parameters following oral administration of methadone alone and with omeprazole in rabbits (n = 15)

Kinetic parameters	Methadone Mean ± SD	Methadone ± Omeprezole Mean ± SD	p-value
AUC (mg.h/1)	277.27 ± 56.84	351.64 ± 56.64	< 0.05
Cl (1/h)	0.0374 ± 0.0080	0.029 ± 0.0053	< 0.05
t 1/2 elim b (h)	2.718 ± 0.7480	3.562 ± 0.875	NS
MRT (h)	4.917 ± 1.053	6.799 ± 0.952	< 0.01
k10 (h^{-1})	0.2783 ± 0.1020	0.2050 ± 0.054	NS

Area under the plasma concentration-time curve (AUC 0 - ∞), total clearance (CL), rate constants (k10), mean residence time (MRT) and elimination (t½β) half-lives of methadone.

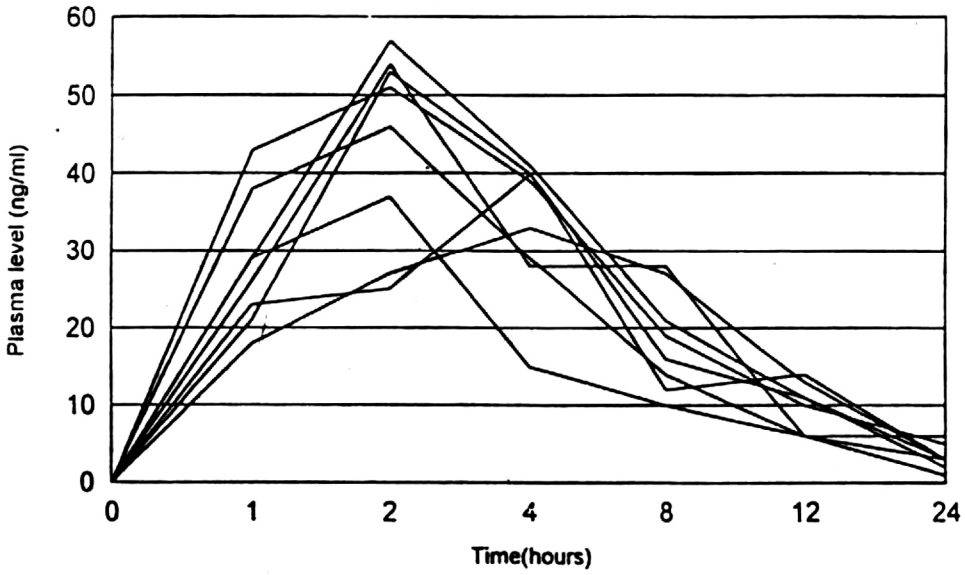

Fig.1: Plasma methadone concentrations after oral administration of methadone and omeprazole at 60 mg/kg of body weight in eight test rabbits.

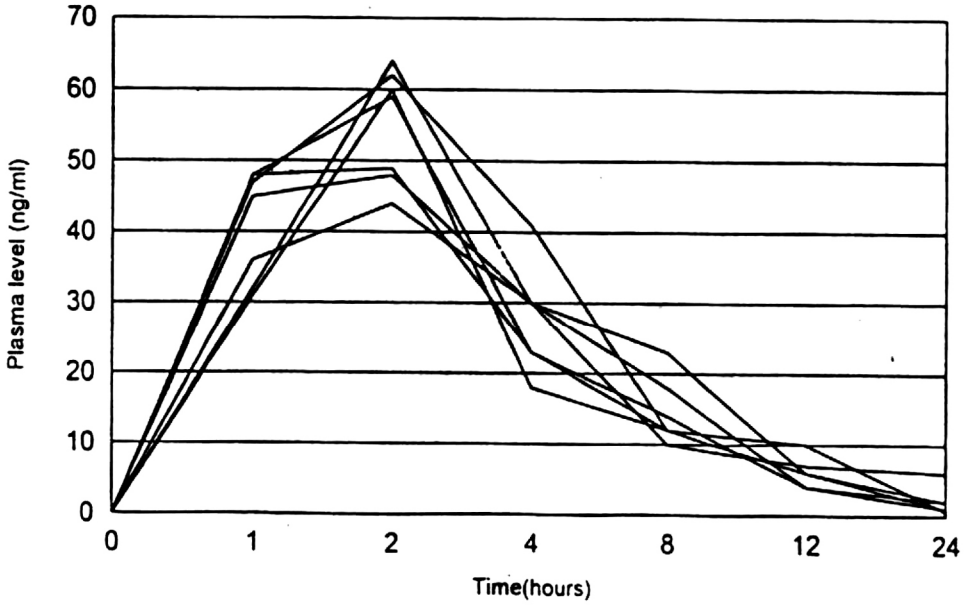

Fig.2: Plasma methadone concentrations after oral administration of methadone at 10 mg/kg of body weight in seven control rabbits.

REFERENCES

Andersson T., Lagerstrom P.O. and Unge P. (1990a). *Therapeutic Drug Monitoring.* 12: 329.

Andersson T., Cederberg C., Edvardsson G., Heggelund A. and Lundborg P. (1990b). *Clin. Pharmacology and Therapeutics.* 47: 79.

Andersson T., Lundborg P. and Regardh C.G. (1991). *European Journal of Clinical Pharmacology.* 40: 61.

Eugene M., Sorkin, Gary S. and Ogawa (1983). *Drug Intelligence and Clinical Pharmacy.* 17: 60.

Garrett E.R. (1978). *Int. J. Clin. Pharmacol.* 16: 155.

Gault H., Kalra J., Ahmed M. and Kephay D. (1980). *Clin. Pharmacol. Ther.* 27: 16.

Gugler R. and Jensen J.C. (1984). *Lancet.* 1: 96.

Kjeldgaard J.M., Hahn G.W., Heckenlively J.R. et al. (1971). *JAMA.* 218: 882.

Larsson H., Mattsson H., Sundell G. and Carlsson E. (1985). *Scand J. Gastroenterol.* 20 (Suppl. 198): 23.

Lindberg P., Nordberg P., Alminger T., Brandstrom A. and Wallmark B. (1986). *Journal of Medicinal Chemistry.* 29: 1327.

Nilssom M.I., Meresaar U. and Anggard E. (1982). *Acta Anaesth Scand.* 74: 66.

Paalzow I., Nilsson L. and Stenberg P. (1982). *Acta Anaesth Scand.* 74: 55.

Pichard L., Gillet G. and Fabre I. et al. (1990). *Drug Metabolism and Disposition.* 18: 711.

Prichard P.J., Walt R.P., Kitchhingman G.K. and Somerville K.M. (1987). *Br. J. Clin. Pharm.* 24: 543.

Paulsen O., Hoglund P. and Walder M. (1989). *Scand J. Infect. Dis.* 21: 219.

Redfern J.S., Lin H.J., Mcarthur K.E., Prince M.D. and Feldman M. (1991). *Am. J. Physiol.* 261: G295.

Robinson A.E. and William F.M. (1971). *J. Pharm. Pharmacol.* 23: 352.

Sullivan H.R., Due S.L. and McMohan R.E. (1973). *J. Pharmacol.* 25: 1009.

Tong T.G., Susan M. and Kreek M.J. (1981). *Annal of Med.* 94: 349.

Walter A.J. (1969). *Can Med. Assoc. J.* 100.

Walsh C.T., Levine R.R. and Squires C. (1975). *Drug Metab. Disp.* 3: 525.