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THE EFFECT OF CHANGES IN GASTRIC pH INDUCED BY OMEPRAZOLE ON THE ABSORPTION AND RESPIRATORY DEPRESSION OF METHADONE

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ABSTRACT

The effect of omeprazole (2 mg kg^{-1} i.v.) on respiratory depression induced in rats by acute oral methadone administration (5 mg kg^{-1}) was examined and compared with control animals that only received methadone.

Quantitative assessments of arterial p_{CO_2}, p_{O_2}, pH, and respiratory rate were employed as criteria for evaluation. Intragastric pH was measured in each rat immediately before and 2 h after methadone.

Plasma concentration of methadone was measured for 3 h. The relationship between drug effect and the systemic bioavailability of methadone, measured as the area under the plasma concentration–time curve (AUC_{0-180}), was also evaluated.

The intensity of the methadone-induced respiratory depression was significantly greater in the omeprazole group than in control rats. A significant variation ($p<0{\cdot}01$) in all respiratory parameters was detected from 30 to 120 min after methadone.

Omeprazole caused a significant increase in methadone levels ($C_{max}=156\pm 6{\cdot}5$ ng mL^{-1} against $51\pm 5{\cdot}8$ ng mL^{-1} in control; $p<0{\cdot}05$). AUC_{0-180} was higher ($p<0{\cdot}05$) after omeprazole treatment ($18{\cdot}6\pm 1{\cdot}4$ μg mL^{-1} min) than in control ($6{\cdot}8\pm 0{\cdot}6$ μg mL^{-1} min).

Two hours after treatment with omeprazole, intragastric pH values were significantly elevated ($4{\cdot}7\pm 0{\cdot}1$ against $2{\cdot}2\pm 0{\cdot}04$) and continued increasing, being $6{\cdot}4\pm 0{\cdot}1$ at the end of the experiment. Correlation was observed between intragastric pH and the area under the effect– (respiratory depression–) time curve ($r=0{\cdot}74$; $p<0{\cdot}001$). A relationship between plasma methadone levels at 120 min and gastric pH ($r=0{\cdot}92$; $p<0{\cdot}001$) was detected. A significant correlation between the area under the effect–time curve (0–120 min) and AUC_{0-180} has been also observed ($r=0{\cdot}90$; $p<0{\cdot}01$).

These pharmacokinetic and pharmacodynamic changes could be gastric pH dependent because they were mimicked when gastric pH was experimentally modified by bicarbonate whereas opposite results were obtained with acidic pH 2 solution.

KEY WORDS: omeprazole; absorption; methadone; effect

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INTRODUCTION

Methadone, a synthetic opioid, is the most widely used pharmacologic treatment for opioid dependence because its pharmacokinetic characteristics are an advantage for regular administration by the oral route: methadone is rapidly absorbed from the gastrointestinal tract, it has high oral bioavailability and shows a long elimination half-life.[1] In addition, a relationship between adequate plasma drug concentration and the success of treatment has been observed.[2] However, pharmacokinetic studies have revealed marked inter-individual differences in plasma methadone levels in man.[3] These variations could have been caused because many patients have a poor compliance with treatment, but also due to alterations in any of the pharmacokinetic processes involved, e.g. oral absorption, metabolism, and excretion.

Methadone, as are most orally administered basic drugs, is mainly absorbed in the small intestine, where a relatively alkaline environment ensures that the drug is in the non-ionized form, and therefore available to cross the epithelium. However, the non-ionized form of a drug will be absorbed more rapidly than the ionized moiety at any site in the gastrointestinal tract, so individual differences or changes in the gastric pH might be expected to influence peak plasma methadone (C_{max} or t_{max}). It is known, for example, that changes in urine pH can affect the disposition of methadone as described by Nilsson and co-workers.[1]

Omeprazole is a member of a new class of substituted benzoimidazoles that inhibits the proton pump in the gastric parietal cell, blocking the final step in the gastric acid secretory pathway;[4] consequently, this action mechanism allows for a prolonged reduction in gastric acidity, so we have used this agent to study whether a change in acidic gastric environment may affect methadone absorption, and its pharmacological effect. Additionally, we have modified intragastric pH by acute administration of sodium bicarbonate or pH 2 water solution to elucidate whether the relative contribution of variations in gastric pH could be responsible for individual differences in plasma methadone concentration, and consequently drug response.

We have evaluated the effect of omeprazole on pharmacokinetics and pharmacodynamics of methadone by means of an animal model, using anaesthesized rats. We measured respiratory frequency, arterial blood oxygen tension (p_{O_2}), carbon dioxide tension (p_{CO_2}), and pH, as indicators of its respiratory depressant effect.

METHODS

Animals and surgery

Female Sprague–Dawley rats, weighing 200–300 g, were used in all experiments. Animals were housed (six per cage) and kept in an environment maintained at $21 \pm 0{\cdot}5\,^{\circ}C$, with relative humidity of 50% and 100% fresh air

exchange at the rate of 20 complete changes per hour. The photoperiod was automatically controlled, providing 12 h of light and 12 h of dark. Animals were fasted for 24 h prior to the experiment.

In order to implant arterial and venous catheters each animal was anaesthetized with urethane (1·3 g kg^{-1} i.p.). After 10 min, the trachea was cannulated with a glass cannula and fixed with silk and a transducer tube Fleish pneumotachometer (Hugo Sach Elektronik) was connected to register respiratory frequency. Polyethylene cannulae were inserted into the femoral vein and the carotid artery for drug injection or collection of blood samples, and continuous measurement of blood pressure or periodic blood gasometry, respectively. A gastric probe was introduced for methadone oral administration and to obtain samples of gastric juice.

Experimental design and drug administration

The effect of methadone (respiratory depression) was tested by continuous recording of the respiratory rate from 0 to 120 min. Before methadone administration, a series of pre-tests was performed on each animal, and the drug was only given when the respiratory frequency was stable. A sample of arterial blood (0·2 mL) was taken at different times after methadone administration, for estimation of blood gases as described afterwards. A sample (0·2 mL) of gastric juice was taken at 0 to 120 min after methadone administration to perform pH measurements.

Arterial and venous blood samples (0·2 mL) were drawn according to the following scheme: at 0, 15, 30, 45, 60, 75, 90, and 120 min. The blood gases (p_{CO_2} and p_{O_2}) and blood pH were measured using a blood gas analyser (AVL-900; AVL Confitest).

Serum methadone levels were analysed in five rats in each group at 30, 60, 90, 120, and 180 min. Serum was kept at −70 °C until required for analysis.

In order to keep the rats in good condition throughout the study, a glucose and electrolyte solution was routinely administered into the femoral vein by constant rate infusion, 0·75 mL h^{-1}. No statistical changes in arterial blood pressure were observed.

In a previous experiment, 80 female rats were used to determine the dose of methadone that produced an adequate variation ($p<0·05$) on the respiratory response. Animals were randomly divided into four groups of 20 animals each that received 0, 2·5, 5·0, and 7·5 mg kg^{-1} of methadone (as water solution) by the oral route using a gastric probe. The effect was measured at baseline, and at 15, 30, 60 and 120 min after methadone administration. Each animal received the suitable volume (0·25 mL) to obtain its exact dose. Distilled water was administered to complete a final volume of 2 mL. From this preliminary work the dose of 5 mg kg^{-1} was considered adequate because it produced a suitable degree of respiratory depression. This was chosen for the subsequent experiments.

In order to determine the effect of acute omeprazole pretreatment on methadone-induced respiratory depression, 40 female rats were used. These animals were randomly divided into two groups of 20 animals each. Omeprazole ($2\,mg\,kg^{-1}$ i.v., therapeutic dose in rats)[5] or saline i.v. (control group) was administered 2 h before surgery or methadone administration ($5\,mg\,kg^{-1}$).

To further analyse the role of experimentally altering gastric pH on methadone's response and kinetics, two additional groups of 20 rats were used. One of them received an acidic solution of methadone (final pH = 2); another received methadone followed by sodium bicarbonate solution (1 M), giving a final volume of 2 mL, as before, to obtain an alkaline environment.

Chemicals

D-L-methadone hydrochloride was supplied from Alcaliber (Madrid, Spain); its purity was 99% by TLC. An aqueous stock solution of $5\,mg\,mL^{-1}$ (pH 5·61) was prepared weekly and dilutions were made to obtain the constant volume required. The solution form was chosen because of its generalized utilization in clinical practice and to avoid a possible irregular absorption (due to possible interindividual differences in disintegration or dissolution when using tablets). The solution was kept in the dark.

Omeprazole was used as the commercially available form (Losec® vial, Astra, Sweden), without further manipulation.

Kits for methadone determination were obtained from Abbott. All other solvents and reagents were of analytical grade.

Chemical assays

Methadone concentrations in serum were determined by the fluorescence immunoassay (TDx-Abbott) according to Beck *et al.*[6] The reproducibility and accuracy of the method were determined over a range of $10–500\,ng\,mL^{-1}$ with the CV varying from 6·3 to 2·2%, respectively. Each sample was evaluated 10 times. The methadone detection limit was $10\,ng\,mL^{-1}$.

Pharmacodynamic and pharmacokinetic parameters

The differences found in the respiratory effect of methadone, between pretreated groups and control (administration of methadone in water solution), were estimated by comparing the evolution of respiratory frequency (breaths min^{-1}), blood pH, p_{CO_2}, and p_{O_2} and by calculating the AUEC (area under the effect– (respiratory frequency–) time curve from time 0 to 120 min, for each individual rat. The AUEC was calculated by the linear trapezoidal method.

Differences in the respiratory effect after oral methadone (control and pretreated) were tested with Fisher's *F*-test. The significance level for all tests

was set at $p<0{\cdot}05$. Correlations were determined by multiple regression analysis.

After the oral dose, the AUC_{0-180} (area under the concentration versus time curve) was calculated by the linear trapezoidal method. C_{max} and t_{max} were directly obtained from the log methadone concentration–time curve.

The differences between C_{max} and AUC in the control and the other groups were evaluated by the Student t-test. The significance level for all tests was $p<0{\cdot}05$.

RESULTS

Pharmacodynamic studies

As previously stated in the preliminary study, methadone in aqueous solution produced significant changes in respiratory frequency at the dose of $5\,mg\,kg^{-1}$. This dose was chosen to carry out the study because of the greater significance of respiratory parameters at all time periods considered. A decrease in respiratory frequency was observed after methadone administration from $151\pm3{\cdot}13$ at time 0 min to $123\pm8{\cdot}72$ at 30, $114\pm9{\cdot}17$ at 45, $99\pm11{\cdot}18$ at 60, $96\pm11{\cdot}18$ at 75, and $101\pm11{\cdot}63$ at 120 min.

Omeprazole pretreatment produced a marked and significant ($p<0{\cdot}01$) increase in the depressant effect of methadone. The mean respiratory frequency (breaths min^{-1}) was decreased at 30 min after methadone administration ($p<0{\cdot}01$). This decrease was observed over a period of 120 min (Figure 1).

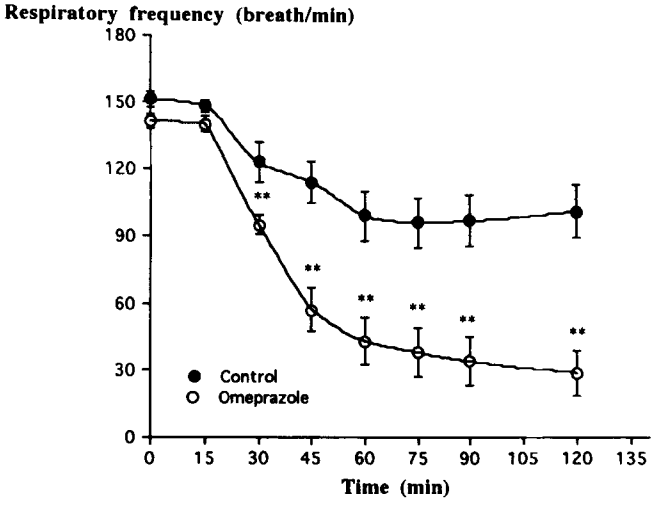

Figure 1. Respiratory frequency (breaths min^{-1}) of orally administered methadone in control (aqueous solution) and omeprazole-pretreated groups ($2\,mg\,kg^{-1}$ i.v., 2 h before methadone administration). $^{**}p<0{\cdot}01$

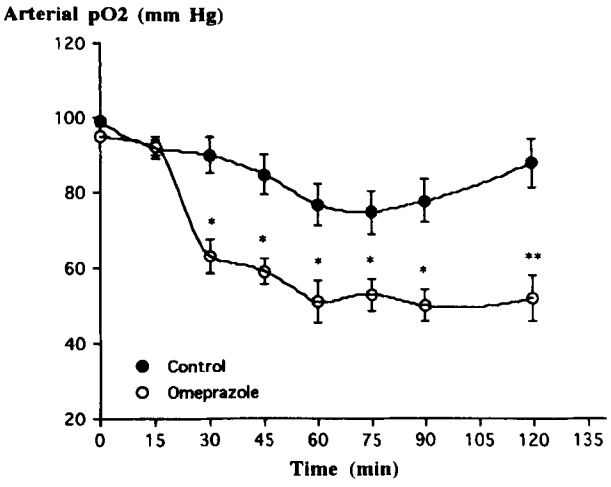

Figure 2. Arterial p_{O_2} of orally administered methadone in control (aqueous solution) and methadone-pretreated groups (2 mg kg^{-1} i.v., 2 h before methadone administration). *$p<0{\cdot}05$; **$p<0{\cdot}01$

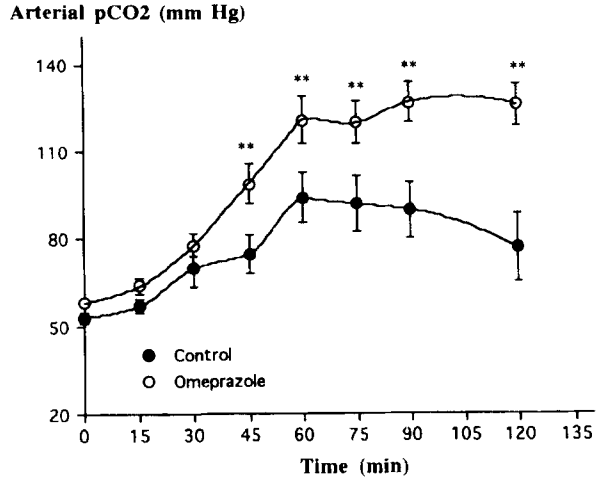

Figure 3. Arterial p_{CO_2} of orally administered methadone in control (aqueous solution) and omeprazole-pretreated groups (2 mg kg^{-1} i.v., 2 h before methadone administration). **$p<0{\cdot}01$

Additionally, a significant decrease of p_{O_2}, an increase of p_{CO_2}, and a decrease of blood pH were observed.

The mean p_{O_2} was significantly decreased ($p<0{\cdot}05$) after 30 min, this change being most pronounced at 120 min ($p<0{\cdot}01$), as represented in Figure 2. The mean p_{CO_2} was significantly increased after 45 min ($p<0{\cdot}01$), being likewise most pronounced at 120 min (Figure 3). Blood pH began to decrease at 60 min

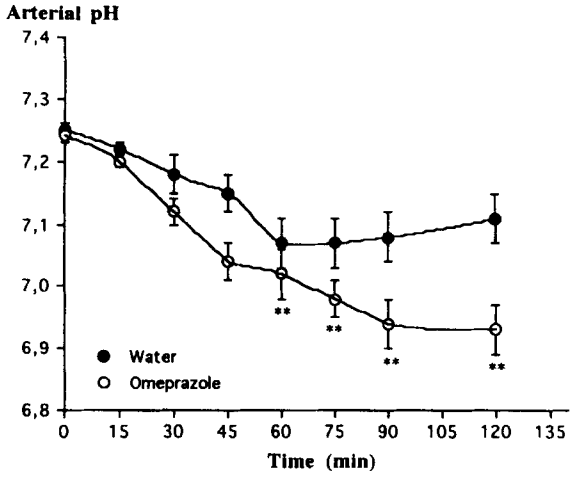

Figure 4. Arterial pH of orally administered methadone in control (aqueous solution) and omeprazole groups (2 mg kg^{-1} i.v., 2 h before methadone administration). **$p<0{\cdot}01$

($p<0{\cdot}01$) after methadone administration in the omeprazole-pretreated group, when compared with controls (the change is shown in Figure 4).

As expected, 2 h after treatment with omeprazole intragastric pH values increased significantly from $2{\cdot}2\pm0{\cdot}04$ to $4{\cdot}7\pm0{\cdot}10$ immediately before methadone administration, and $6{\cdot}4\pm0{\cdot}1$ 2 h after methadone (Table 1). In Table 1 one can also see the values of intragastric pH in control (water solution), bicarbonate-treated rats, and rats receiving pH 2 solution of methadone.

The influence of the alkalinizing effect of bicarbonate solution on methadone respiratory effect can be observed in Table 2. A significant decrease in respiratory frequency, a significant increase in p_{CO_2} and a significant decrease in p_{O_2} can be observed at 30 min. These changes were similar to those found within the omeprazole group (see Figures 1–4).

Table 1. Intragastric pH (mean ± SEM) before and 2 h after methadone in rats with different treatments. Omeprazole was administered 2 h before methadone ClH (pH 5·61)

Group	Baseline	After methadone (2 h)
Control	$2{\cdot}2\pm0{\cdot}09$	$3{\cdot}6\pm0{\cdot}20$
Omeprazole (i.v.)	$4{\cdot}7\pm0{\cdot}10$	$6{\cdot}4\pm0{\cdot}10$**
pH 2	$2{\cdot}2\pm0{\cdot}04$	$2{\cdot}2\pm0{\cdot}04$**
$NaHCO_3$	$2{\cdot}0\pm0{\cdot}02$	$8{\cdot}8\pm0{\cdot}06$**

**$p<0{\cdot}01$ between the different treatments and control.

Table 2. Evolution of respiratory parameters (mean ± SEM) after methadone administration with sodium bicarbonate (1 M)

Time (min)	p_{CO_2} (mmHg)	p_{O_2} (mmHg)	pH arterial	Frequency (breaths min^{-1})
0	55 ± 0·6	99 ± 0·9	7·26 ± 0·004	146 ± 3·6
15	65 ± 2·3	92 ± 1·3	7·22 ± 0·004	142 ± 3·6
30	85 ± 4·1*	63 ± 2·5*	7·12 ± 0·02*	79 ± 12·3**
45	121 ± 8·9**	58 ± 5·0*	6·99 ± 0·04*	41 ± 11·4**
60	125 ± 7·8**	48 ± 2·5*	6·94 ± 0·04*	20 ± 8·5**
75	128 ± 7·1**	49 ± 3·2*	6·91 ± 0·03**	16 ± 7·5**
90	136 ± 7·1**	50 ± 3·6*	6·91 ± 0·03**	15 ± 7·1**
120	142 ± 4·2**	45 ± 2·5**	6·84 ± 0·02**	10 ± 5·9**

*$p < 0·05$; **$p < 0·01$ (statistical significance of differences from control group, methadone in aqueous solution).

On the other hand, as shown in Table 3, changes after acidic methadone administration were similar to those observed following methadone administration with water.

In Figure 5, we can observe a relationship between methadone effect measured as area under the response– (respiratory frequency–) time curve and the mean intragastric pH at 120 min in all groups ($p < 0·001$). Similar results were observed when p_{O_2} and p_{CO_2} were considered.

Pharmacokinetic studies

The extent of methadone absorption was significantly increased by omeprazole because higher plasma levels were observed compared with the control ($C_{max} = 156 \pm 6·5$ against $51 \pm 5·8$ in the control; $p < 0·05$). No changes

Table 3. Evolution of respiratory parameters (mean ± SEM) after methadone administration at pH 2

Time (min)	p_{CO_2} (mmHg)	p_{O_2} (mmHg)	pH arterial	Frequency (breaths min^{-1})
0	62 ± 1·3	94 ± 1·1	7·23 ± 0·01	152 ± 3·4
15	65 ± 1·6	87 ± 2·3	7·22 ± 0·01	151 ± 3·6
30	71 ± 2·3	86 ± 2·3	7·19 ± 0·01	138 ± 3·6
45	72 ± 3·2	80 ± 3·4	7·18 ± 0·02	130 ± 3·4
60	74 ± 3·6	84 ± 3·9	7·17 ± 0·02	131 ± 4·3
75	74 ± 4·6	86 ± 4·3	7·18 ± 0·02	132 ± 4·3**
90	70 ± 4·6	89 ± 4·1	7·18 ± 0·02	134 ± 4·1**
120	63 ± 4·8	93 ± 3·4	7·21 ± 0·02	140 ± 3·9**

**$p < 0·01$ (statistical significance of differences from control, methadone in aqueous solution).

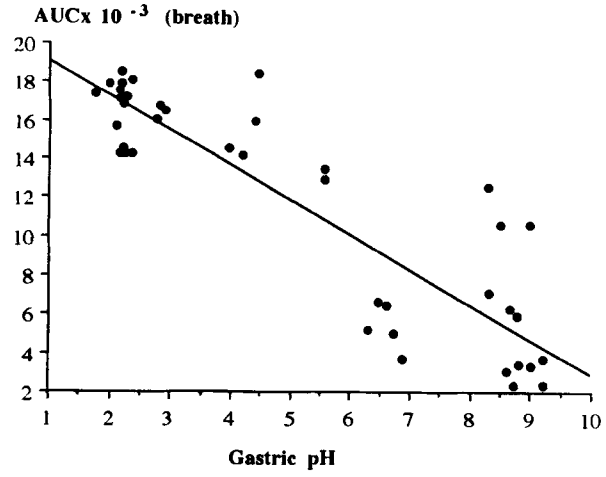

Figure 5. The relationship between the area under the response– (respiratory frequency–) time curve of methadone and the mean inragastric pH at 120 min in all groups ($r = 0{\cdot}74$; $p < 0{\cdot}001$)

in t_{max} were observed. When these results were expressed as AUC_{0-180}, we also observed a marked difference between the omeprazole and control groups ($18{\cdot}6 \pm 1{\cdot}4$ against $6{\cdot}8 \pm 0{\cdot}6\ \mu g\,mL^{-1}\,min$; $p < 0{\cdot}05$). Similar degree of changes were observed between sodium bicarbonate and control groups, but no changes were detected in the pH 2 group when compared with the control. No differences in AUC were observed between omeprazole and sodium bicarbonate groups (Table 4).

In the same way, methadone plasma concentration at 120 min (log C_{120}) showed a correlation ($p < 0{\cdot}001$) with intragastric pH values at this time (Figure 6).

A significant correlation was also observed between the area under the effect–time curve and the area under the concentration–time curve ($p < 0{\cdot}01$; Figure 7) in the four groups. Similar results were observed when p_{O_2} and p_{CO_2} were considered.

Table 4. A summary of methadone pharmacokinetic data (mean ± SEM)

	C_{max} ($ng\,mL^{-1}$)	t_{max} (h)	AUC_{0-180} ($\mu g\,mL^{-1}\,min$)
Control	$51 \pm 5{\cdot}8$	1	$6{\cdot}8 \pm 0{\cdot}6$
Omeprazole	$156 \pm 6{\cdot}5$*	1	$18{\cdot}6 \pm 1{\cdot}4$*
pH 2	$33 \pm 5{\cdot}0$	1·5	$3{\cdot}6 \pm 0{\cdot}9$
$NaHCO_3$	$167 \pm 13{\cdot}0$*	1	$23{\cdot}0 \pm 2{\cdot}5$*

*$p < 0{\cdot}05$ (statistical significance of differences from control group, methadone in aqueous solution).

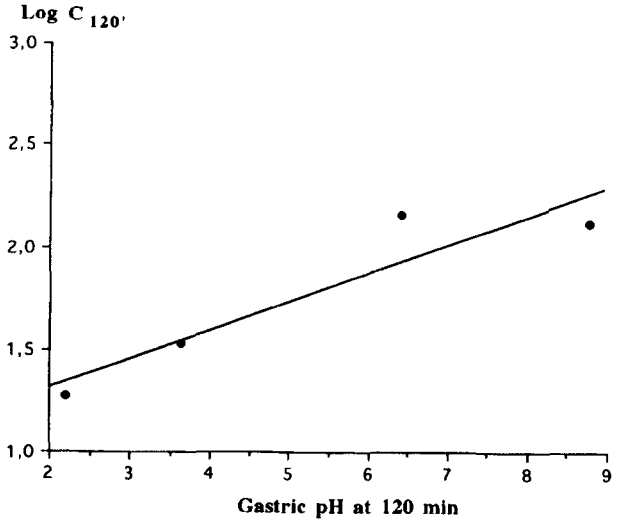

Figure 6. The correlation between methadone plasma concentration log C_{120} and intragastric pH at 120 min in all groups ($r = 0{\cdot}92$; $p < 0{\cdot}001$)

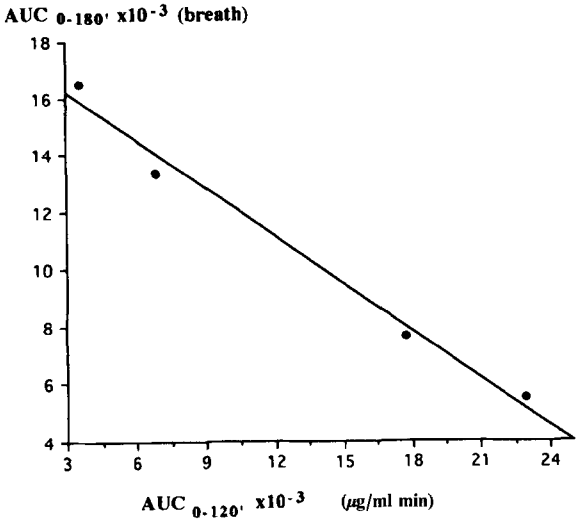

Figure 7. The correlation between the area under the effect– (respiratory frequency–) time ($AUC_{0\text{-}120}$ breaths) and the area under the concentration–time curve ($AUC_{0\text{-}180}$ μg mL^{-1} min) ($r = 0{\cdot}90$; $p < 0{\cdot}01$)

DISCUSSION

It is a common feature for patients in methadone maintenance programmes to complain that their dosage seems inadequate. However, it is difficult

constructively to answer requests for increasing doses, because there are no objective criteria by which to judge the adequacy of an individual dose. Evidences indicate that there is a threshold serum level below which an opioid-dependent individual experiences withdrawal. Some methadone pharmacokinetic changes can be responsible for low serum levels after standard doses.[7] So, for a small number of people with rapid metabolism, serum levels may fall below this threshold even with moderate or high doses of methadone. Similarly, in patients who were concomitantly using enzyme-inducing drugs, i.e. phenytoin or rifampicin, low serum levels were detected.[8,9]

To summarize, studies of the pharmacokinetics of methadone in patients maintained on the drug have suggested that there is a wide range of interindividual (and intraindividual) variability in characteristics such as the elimination half-life and clearance.[10] However, there are very few studies of methadone drug absorption, a parameter that should be of importance in achieving therapeutic threshold levels. The oral bioavailability of methadone tablets and solutions has been estimated, in cancer patients, to be about 80%, but with interindividual differences ranging from 41% to 99%.[1] First-pass intestinal metabolism has not been observed.[11] Several factors can influence oral absorption of drugs, including the physicochemical properties of the molecule, gastric motility, gut perfusion, and pH.

In accordance with the prediction of the pH partition hypothesis, weak bases could be absorbed more rapidly from the small intestine (pH 5–7) because more drug is in nonionized form.[12] Therefore, changes of the gastric content leading to an alkaline environment could favour the absorption of a basic drug. In this way it could influence its plasma concentration, and therefore contribute to interindividual differences. The results of our experimental study strongly support this hypothesis.

Previous investigations have reported a similar respiratory depressant action with methadone administration, both in man and animals. In a clinical study conducted on former heroin addicts, Marks and Goldring[13] found arterial hypercapnia and an increase in the threshold of the ventilator responsive to CO_2. Santiago *et al.*[14] confirmed these results in patients treated with methadone for less than 2 months. In animal models hypoxemia, hypercapnia, and/or acidosis were frequently found after acute methadone administration ($5\,mg\,kg^{-1}$ i.p.).[15] Our data in control rats are in agreement with these results in acute experiments.

In our study methadone-induced respiratory depression was significantly more pronounced after omeprazole than in the control group. In addition, serum levels of methadone were significantly increased. These changes cannot be attributed to a possible effect of omeprazole on methadone metabolism, because no changes in enzyme functions are likely to occur after single-dose administration. The most extensive studies of drug interaction with omeprazole show inhibition of metabolism but the effect has been always observed after high (i.e. $40\,mg\,d^{-1}$) and chronic treatment (for 14 d).[16]

Furthermore, data from published literature indicate that the isoenzymes involved in omeprazole and methadone metabolism are different.[17,18] When pH is experimentally modified (to values of similar magnitude as induced by omeprazole administration) the observed changes confirm that the differences in pharmacokinetic and pharmacodynamic behaviour of methadone after omeprazole could be explained as a consequence of the changes in gastric pH induced by the administration of this drug. Also, the time profiles of serum methadone levels and effects are very similar in omeprazole and sodium bicarbonate groups, the differences in AUC being without statistical significance.

Omeprazole is very effective in raising intragastric pH in humans (by both the parenteral and the oral routes). Values of pH close to 6 can be reached and maintained during prolonged periods of time.[19] Therefore continuous infusion of histamine H_2 antagonists can lead to a similar modification of intragastric pH. It is likely that pH-dependent absorption of drugs could be affected as has been postulated for omeprazole. In human pharmacokinetic studies short treatment with omeprazole produced a 26% increase in AUC of nifedipine, probably because of increased absorption; other pharmacokinetic parameters (i.e. $t_{1/2}$) did not change.[20] In another study, a 14 d treatment with omeprazole ($20\ mg\ d^{-1}$) caused an increase in AUC of carbamazepine in seven patients with duodenal ulcer.[21] Similarly, a significant although small increase in digoxin AUC_{0-90} has been reported. The authors proposed a double mechanism to explain this interaction: an increase in absorption and a decrease in metabolism. However, it is not possible to identify the role of the inhibition of metabolism (due to chronic omeprazole treatment because metabolites were not measured).[22] Recently an increase in the absorption of bismuth from tripotassium dicitrato bismuthate after omeprazole has been described.[23]

The correlation between gastric pH and the extent of methadone absorption and effects suggests that pharmacologically induced changes in gastric pH may play an important role in the observed variability in methadone levels and effects, and that these could be of clinical importance. However, one must not forget that other factors such as gastrointestinal motility, food, and metabolic capacity of the liver may also be involved. Excessive levels of methadone were recently associated with deaths in 10 subjects starting on methadone programmes, the main cause being unknown.[24] Further investigation could be necessary in humans to establish a correct posological design when methadone and gastrointestinal drugs such as antacid, histamine H_2 receptor blocking drugs, oral omeprazole, or sucralphate must be coadministered, the role of these drugs in methadone toxicity being uncertain.

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