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Different Effects of Amitriptyline and Imipramine on the Pharmacokinetics and Metabolism of Perazine in Rats

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Abstract

The aim of this study was to search for possible effects of imipramine and amitriptyline on the pharmacokinetics and metabolism of perazine at steady state in rats. Perazine ($10\,mg\,kg^{-1}$, i.p.) was administered to rats twice daily for two weeks, alone or jointly with imipramine or amitriptyline ($10\,mg\,kg^{-1}$ i.p.). Concentrations of perazine and its two main metabolites (5-sulphoxide and *N*-desmethylperazine) in the plasma and brain were measured at 30 min (C_{max}), 6 h and 12 h (slow disposition phase) after the last dose of the drugs. Liver microsomes were prepared 24 h after withdrawal of the drugs.

Amitriptyline increased the plasma and brain concentrations of perazine (up to 300% of the control) and *N*-desmethylperazine, while not affecting those of 5-sulphoxide. Imipramine only tended to increase the neuroleptic concentration in the plasma and brain. Studies with control liver microsomes showed that amitriptyline and imipramine added to the incubation mixture in-vitro, competitively inhibited *N*-demethylation (K_i (inhibition constant) $= 16\,\mu M$ and $164\,\mu M$, respectively) and 5-sulphoxidation ($K_i = 57\,\mu M$ and $86\,\mu M$, respectively) of perazine, amitriptyline being a more potent inhibitor of perazine metabolism, especially with respect to *N*-demethylation. Studies with microsomes of rats treated chronically with perazine or tricyclic antidepressants, or both, did not show significant differences in the rate of perazine metabolism between perazine- and perazine+antidepressant-treated rats. The data obtained were compared with the results of analogous experiments with promazine and thioridazine.

It was concluded that elevations of perazine concentration were caused by direct inhibition of the neuroleptic metabolism by the antidepressants. Similar interactions, possibly leading to exacerbation of the pharmacological action of perazine, may be expected in man. Since the interactions between phenothiazines and tricyclic antidepressants may proceed in two directions, reduced doses of both the neuroleptic and the antidepressant are recommended when the drugs are administered jointly.

Because of its psychotropic profile and spectrum of side-effects, perazine is a neuroleptic suitable for combination with antidepressants in the therapy of psychotic and drug-resistant depression, depression in schizophrenia and schizo-affective disorders (Nelson 1993; Keck et al 1994; Naftolowitz et al 1995). However, a possible substantial influence of tricyclic antidepressants on the pharmacokinetics of perazine may be of clinical importance in light of recent views on the relationship between therapeutic efficacy of neuroleptic drugs and their plasma concentrations (Baldessarini et al 1988; Vergese et al 1991; Midha et al 1994). Moreover, certain side-effects of the drug combination (e.g. drowsiness, extrapyramidal symptoms, cardiovascular effects) are concentration dependent. In both man and rats, perazine is metabolized by 5-sulphoxidation in the thiazine ring and by *N*-demethylation in the piperazine side-chain (Figure 1), as well as by aromatic hydroxylation in position 3 and by *N*-oxidation and degradation of the piperazine ring (Breyer 1969, 1972; Kanig & Breyer 1969). It has not yet been determined which enzymes catalyse these particular metabolic pathways. Clinical studies with another phenothiazine neuroleptic of the piperazine-type, perphenazine, have shown that its pharmacokinetics includes polymorphic hydroxylation of debrisoquine, which indicates that

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CYP2D6 is involved in its metabolism (Dahl-Puustinen et al 1989). Murine CYP2D1 is a counterpart of human CYP2D6, sharing 97% of the amino-acid sequence and showing a comparable catalytic activity (Gonzalez 1990; Kobayashi et al 1989; Laurenzana et al 1995). Our unpublished results indicate that *N*-demethylation of perazine in the rat is catalysed by CYP2D1, CYP2B and CYP1A2, while its sulphoxidation is catalysed by CYP2D1 and CYP2B. CYP2C and CYP3A do not seem to be engaged in these metabolic pathways. Aromatic hydroxylation of phenothiazines has not been ascribed to any specific isoenzymes so far, but it is possible that, like in the case of tricyclic antidepressants, isoenzyme 2D6 may be responsible for aromatic hydroxylation of phenothiazines (Spina et al 1987; Steiner et al 1988; Brøsen et al 1991).

It has been shown that phenothiazine neuroleptics inhibit the metabolism of tricyclic antidepressants and increase their plasma concentration in man (Gram et al 1974a; Vandel et al 1979; Nelson & Jatlow 1980; Bock et al 1983; Brøsen et al 1986) and plasma and brain concentrations in the rat (Gram et al 1974b; Daniel & Melzacka 1986; Daniel 1991). However, little is known about the possible mutual effect of tricyclic antidepressants on the metabolism of neuroleptics. The available data refer to too small a number of patients, some of those receiving two neuroleptics simultaneously. Also only one time-interval after drug administration was investigated and the data relate only to plasma concentration of the parent compound. Nevertheless, they suggest that amitriptyline can increase concentrations of phenothiazines (Jus et al 1978), and that nortriptyline increases the plasma concentration of chlorpromazine in schizophrenic patients (Loga et al 1981). Our recent studies carried out in rats showed that amitriptyline increased (up to 300% of the control) the plasma and brain

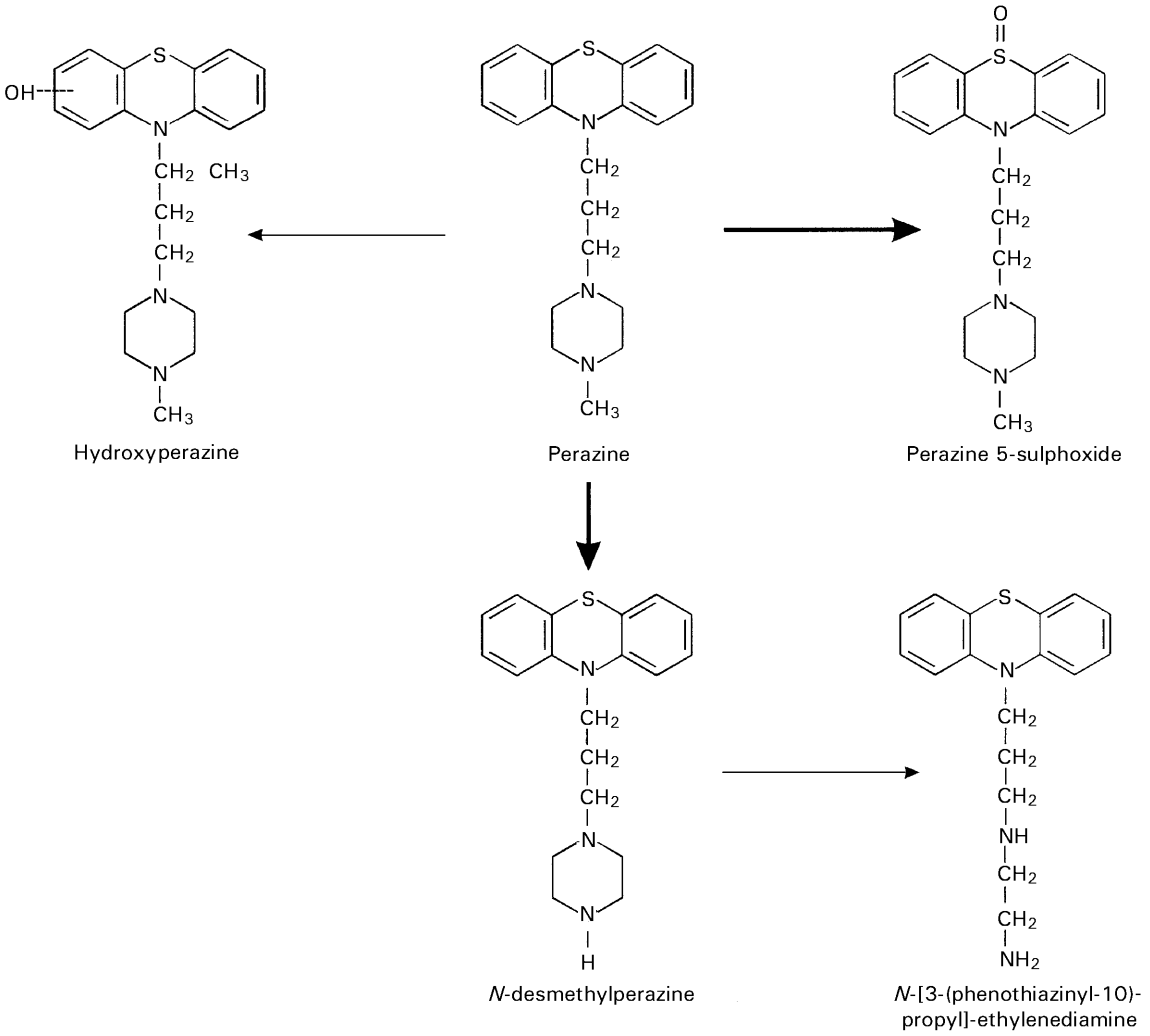

Figure 1. Metabolic pathways of perazine.

concentrations of promazine, a phenothiazine neuroleptic with the simplest chemical structure (Syrek et al 1997). Imipramine did not produce any distinct changes in promazine pharmacokinetics. Pharmacokinetic interactions were much stronger in the case of thioridazine (Daniel et al 2000). Imipramine and amitriptyline elevated 30 and 20 fold, respectively, the plasma concentration of thioridazine. Parallel determination of concentrations of the neuroleptic metabolites in-vivo and metabolic studies in-vitro indicated that the investigated antidepressants inhibited main metabolic pathways of promazine and thioridazine. It seems, therefore, that the results of drug interactions involving the simplest phenothiazine neuroleptic promazine cannot be referred to phenothiazine neuroleptics with a more complex chemical structure which determines both their affinity for different cytochrome P-450 isoenzymes and their metabolism.

The aim of this study was to search for possible effects of imipramine and amitriptyline on the pharmacokinetics and metabolism of perazine at steady state in rats. It seemed interesting to determine whether the piperazine-type phenothiazine neuroleptic perazine behaved pharmacokinetically like promazine (aliphatic type), or rather like thioridazine (piperidine type) when it was given jointly with tricyclic antidepressants.

Materials and Methods

Drugs and chemicals

Imipramine was provided by Polfa (Jelenia Góra, Poland) and amitriptyline was obtained from H. Lundbeck A/S (Copenhagen, Denmark). Perazine (dimaleate) was obtained from Labor (Wrocław, Poland). Perazine 5-sulphoxide and *N*-desmethylperazine were synthesized in our laboratory as described previously (Daniel et al 1998). NADP, glucose-6-phosphate and glucose-6-phosphate dehydrogenase were purchased from Sigma (St Louis, MO). All the organic solvents of HPLC purity were supplied by Merck (Darmstadt, Germany).

In-vivo experimental procedure

Male Wistar rats, 240–270 g, kept under standard laboratory conditions, were used in the experiment. To avoid possible drug interaction at the level of absorption from the gastrointestinal tract, and to achieve better correlation between concentrations of the drugs and the rate of their metabolism, the investigated psychotropics were administered intraperitoneally. Perazine ($10\,mg\,kg^{-1}$ i.p.) was administered to rats twice daily for two weeks, alone or jointly with imipramine or amitriptyline ($10\,mg\,kg^{-1}$ i.p.). The doses used were of pharmacological magnitude which produced a therapeutic plasma concentration of the drugs (Daniel et al 1981, 1998; Breyer-Pfaff et al 1983, 1988; Coudore et al 1996).

After decapitation the rats' trunk blood was collected in tubes moistened with a 30% solution of sodium citrate, and their brains were rapidly removed and stored frozen in solid CO_2. Blood samples were centrifuged at $2000\,g$ for 30 min. Concentrations of perazine and its two main metabolites (5-sulphoxide and *N*-desmethylperazine) in the plasma and brain were measured at 30 min (C_{max}), 6 h and 12 h (slow disposition phase) after the last dose of the drugs.

Liver microsomes were prepared by differential centrifugation in 20 mM Tris-KCl buffer (pH = 7·4), and by washing with 0·15 M KCl at 24 h after withdrawal of the drugs according to a conventional method (Legrum et al 1979). This procedure deprives microsomes of the presence of drugs administered in-vivo.

HPLC measurement of perazine and its metabolites

Concentrations of perazine and its two main metabolites (5-sulphoxide and *N*-desmethylperazine) were assessed in the blood plasma, brain homogenate and in a microsomal suspension by the HPLC method previously developed in our laboratory (Daniel et al 1998). After alkalization (pH 12; 3 M NaOH), perazine and its metabolites were extracted with dichloromethane and hexane (1 : 1, v/v). The residue obtained after evaporation of the plasma or brain extracts was dissolved in 100 μL of the mobile phase described below. A 20-μL sample was injected into the HPLC system LaChrom (Merck-Hitachi) which was equipped with a UV detector, an L-7100 pump and a D-7000 System Manager. The analytical column (Econosphere C18 5 μm, 4·6 × 250 mm) was purchased from Alltech (Carnforth, England). The mobile phase consisted of an acetate buffer (pH 3·4, containing triethylamine $1\,mL\,L^{-1}$) and acetonitrile in the proportion 30 : 70. Elution proceeded at an ambient temperature at flow rates of $0{\cdot}6\,mL\,min^{-1}$. (1–10 min), $1–2\,mL\,min^{-1}$ (10·1–18 min) and $1{\cdot}8\,mL\,min^{-1}$ (18·1–24 min). Absorbance was measured at a wavelength of 254 nm. The sensitivity of the method allowed for quantification of levels as low as 0·04 nmol perazine, 0·013 nmol *N*-desmethylperazine and 0·043 nmol

perazine sulphoxide in 1 mL of plasma or microsomal suspension. The detection threshold in the brain allowed for quantification of levels as low as 0·058 nmol perazine, 0·06 nmol *N*-desmethylperazine and 0·009 nmol perazine sulphoxide in 1 g of the brain tissue. The intra- and inter-assay coefficients of variance were similar and amounted to 3% for perazine and 5% for *N*-desmethylperazine and perazine sulphoxide in all the investigated tissues.

In-vitro studies of perazine metabolism

Perazine metabolism was studied in liver microsomes under conditions of linear dependence of the product formation on time and on protein and substrate concentrations (Daniel et al 1998). To distinguish between a direct effect of antidepressants on the metabolism of perazine and changes produced by their chronic co-administration, two experimental models were used.

Model I consisted of pooled liver microsomes from three control rats. The rate of *N*-demethylation and sulphoxidation of perazine (perazine concentration: 10–50 nmol mL^{-1}) was assessed in the absence and presence of one of the antidepressants added in-vitro (50 nmol mL^{-1}). The concentrations of perazine and antidepressants used in-vitro were in the range presumed to be present in the liver after administration of pharmacological doses of the drugs (Daniel et al 1981, 1998; Coudore et al 1996; Daniel & Wójcikowski 1999). All the samples were prepared in duplicate. Model II consisted of liver microsomes from perazine- or antidepressant-treated rats (or both). Perazine (50 nmol mL^{-1}) was added to the incubation mixture in-vitro. Perazine metabolism was studied in the absence of antidepressants.

Incubations (Models I and II) were carried out in a system containing liver microsomes (0·5 mg of protein in 1 mL), a Tris-KCl buffer (20 mM, pH 7·4), $MgCl_2$ (2·5 mM), NADP (0·1 mM), glucose 6-phosphate (1·2 mM) and glucose-6-phosphate-dehydrogenase (0·3 IU mL^{-1}). The final incubation volume was 1 mL. After a 2-min pre-incubation, the reaction was initiated by introducing perazine. After incubation for 10 min, the reaction was stopped by adding 200 μL of methanol and cooling to 0°C. The metabolites yielded during incubation were determined by the HPLC procedure described above.

Assessment of cytochrome P-450 and cytochrome b-5

Concentrations of cytochromes P-450 and b-5 in liver microsomes were determined by the methods of Omura & Sato (1964) and Omura & Takesue (1970), respectively, using a Beckman DU-65 Spectrophotometer. The protein content was assayed according to Lowry et al (1951), using bovine serum albumin as a standard.

Statistics

Statistical significance was estimated using an analysis of variance followed by Dunnett's test.

Results

In-vivo studies

Table 1 presents absolute concentration values of perazine and its metabolites in a steady state. After 30 min (C_{max}) and 6 h, concentrations of the parent compound in the plasma were about 3 times higher than those of its metabolites. At a longer time interval (i.e. after 12 h), differences between plasma concentrations of the parent compound and its metabolites were not so distinct. In the brain, concentrations of the measured compounds were much higher than in the plasma. The brain concentrations of the parent compound (at 30 min) and *N*-desmethylperazine (at 6 and 12 h) were 10 times

Table 1. Steady-state concentrations of perazine and its metabolites in the plasma and brain of rats at 30 min, 6 h and 12 h after perazine withdrawal.

Time	Perazine	*N*-desmethylperazine	Perazine 5-sulphoxide
Plasma concn (nmol ml^{-1})			
30 min	1·009 ± 0·140	0·325 ± 0·090	0·372 ± 0·051
6 h	0·614 ± 0·106	0·215 ± 0·047	0·270 ± 0·063
12 h	0·116 ± 0·012	0·085 ± 0·023	0·207 ± 0·041
Brain concn (nmol g^{-1})			
30 min	10·717 ± 2·516	1·284 ± 0·356	0·915 ± 0·203
6h	1·923 ± 0·204	2·154 ± 0·187	0·435 ± 0·126
12 h	0·249 ± 0·051	0·937 ± 0·109	0·291 ± 0·051

Perazine (10 mg kg^{-1} i.p.) was administered twice daily for 2 weeks. Values are means ± s.e.m., n = 5–6.

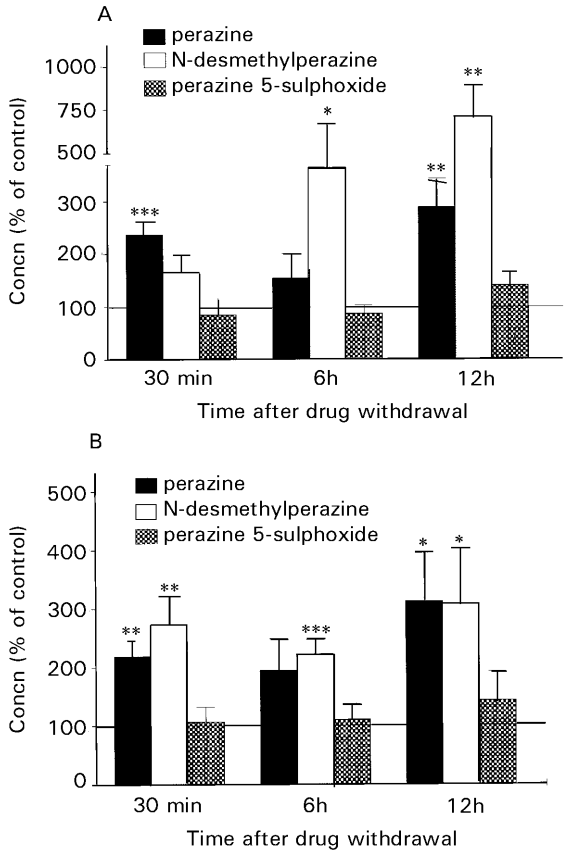

Figure 2. The influence of amitriptyline (10 mg kg^{-1} i.p., twice daily) on the pharmacokinetics of perazine (10 mg kg^{-1} i.p., twice daily) in the rat after 2-week treatment with a combination of the drugs. Plasma (A) and brain (B) levels of perazine and its metabolites, *N*-desmethylperazine and perazine 5-sulphoxide, at 30 min, 6 h and 12 h after withdrawal of the drugs. Values are means ± s.e.m., n = 5–7; $*P < 0.05$, $**P < 0.01$, $***P < 0.001$ vs control (Dunnet's test).

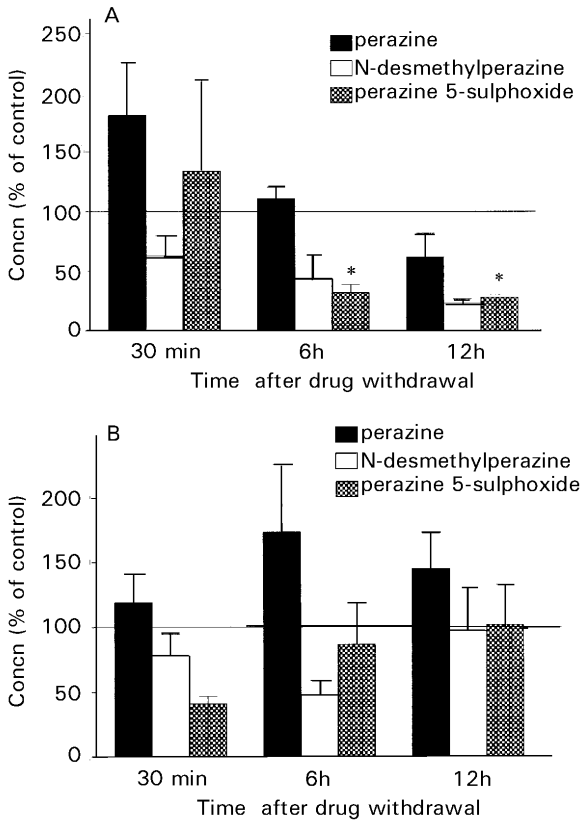

Figure 3. The influence of imipramine (10 mg kg^{-1} i.p., twice daily) on the pharmacokinetics of perazine (10 mg kg^{-1} i.p., twice daily) in the rat after 2-week treatment with a combination of the drugs. Plasma (A) and brain (B) levels of perazine and its metabolites, *N*-desmethylperazine and perazine 5-sulphoxide, at 30 min, 6 h and 12 h after withdrawal of the drugs. Values are means ± s.e.m., n = 5–7; $*P < 0.05$ vs control (Dunnett's test). Absolute control values (animals treated with perazine alone) are presented in Table 1.

higher, and that of 5-sulphoxide (at 30 min) was 2·5 times higher than the respective plasma levels.

Amitriptyline increased the plasma and brain concentrations of perazine and *N*-desmethylperazine, but did not affect those of 5-sulphoxide (Figure 2). The concentrations of perazine and its *N*-demethylated metabolite were increased by amitriptyline up to 300% and 700% of the control (control = perazine-treated rats) after 12 h, respectively. Consequently, an increase in the sum of perazine + metabolite concentration and a significant elevation in the perazine/5-sulphoxide concentration ratio in the plasma ($P < 0.01$) and brain ($P < 0.05$) were observed. The perazine/*N*-desmethylperazine concentration ratio rose after 30 min ($P < 0.05$), and fell after longer time-intervals in the plasma ($P < 0.01$), no significant changes being observed in the brain.

Imipramine did not significantly affect the pharmacokinetics of perazine, but a tendency to increase the neuroleptic concentrations in the plasma (30 min) and brain was noted (Figure 3). Concentrations of perazine metabolites fell in the plasma (at 6 and 12 h) and showed a similar tendency in the brain at 30 min (5-sulphoxide) and 6 h (*N*-desmethylperazine)). The perazine/metabolite concentration ratio significantly rose in both the plasma and brain. The biggest increase in the perazine/*N*-desmethylperazine concentration ratio was observed after 30 min and 6 h in the plasma ($P < 0.05$) and after 6 h in the brain ($P < 0.01$). The most pronounced rise in the perazine/5-sulphoxide ratio was found after 6 h in the plasma ($P < 0.001$) and after 30 min in the brain ($P < 0.01$).

In-vitro studies

Model I. Studies with control rat liver microsomes showed that imipramine and amitriptyline, added to the incubation mixture in-vitro, competitively inhibited *N*-demethylation and 5-sulphoxidation of

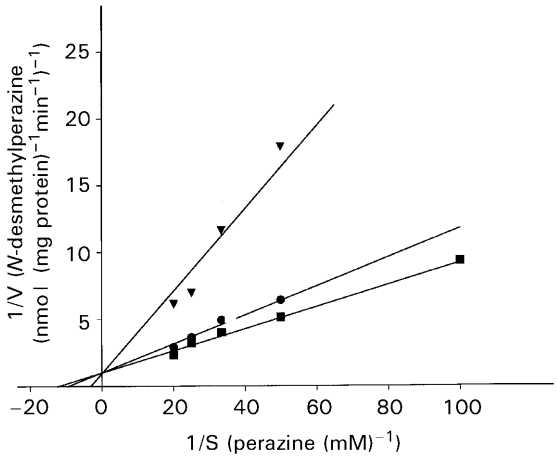

Figure 4. The kinetics of inhibition of perazine *N*-demethylation by imipramine (●; $K_i = 164\,\mu M$) or amitriptyline (▼; $K_i = 16\,\mu M$) in-vitro using pooled liver microsomes from 3 rats. Control (■; $K_m = 82\,\mu M$), perazine only. V = velocity of the reaction; S = concentration of the substrate. The concentration of each inhibitor was 50 nmol mL^{-1}.

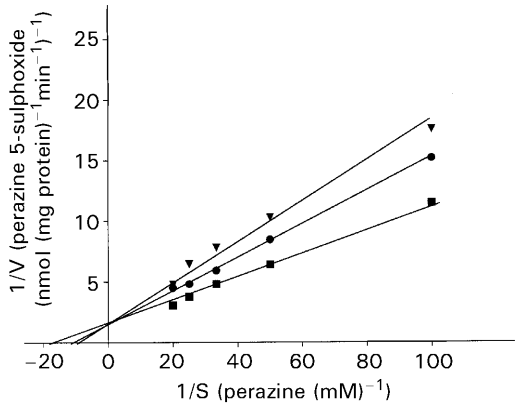

Figure 5. The kinetics of inhibition of perazine 5-sulphoxidation by imipramine (●; $K_i = 86\,\mu M$) or amitriptyline (▼; $K_i = 57\,\mu M$) in-vitro using pooled liver microsomes from 3 rats. Control (■; $K_m = 57\,\mu M$), perazine only. V = velocity of the reaction; S = concentration of the substrate. The concentration of each inhibitor was 50 nmol mL^{-1}.

perazine (Figures 4 and 5). As shown by Lineweaver-Burk plots and K_i (inhibition constant) values, amitriptyline was a more potent inhibitor of perazine metabolism than imipramine, especially with respect to *N*-demethylation.

Model II. Studies with microsomes of rats treated chronically with perazine or imipramine (the drugs administered in-vivo were washed out from the microsomes) indicated that neither joint nor separate administration changed the concentration of cytochrome P-450 or b-5 in the liver (Figure 6). Amitriptyline decreased the level of cytochrome P-450 compared with the control, although when

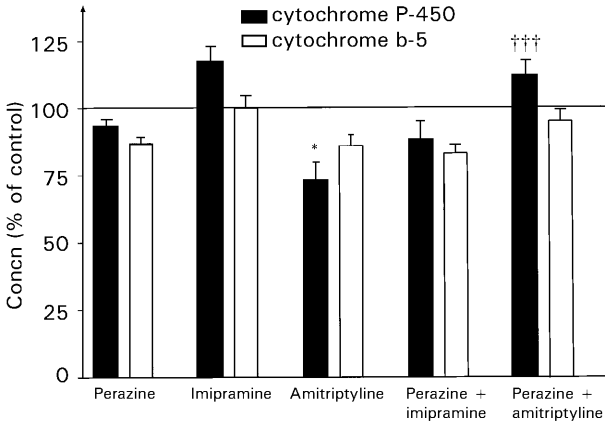

Figure 6. Concentrations of cytochrome P-450 and cytochrome b-5 in rat liver microsomes after treatment with perazine (10 mg kg^{-1} i.p., twice daily) with or without tricyclic antidepressants (10 mg kg^{-1} i.p., twice daily) for 2 weeks. Microsomes were prepared 24 h after withdrawal of drugs. Control: cytochrome P-450 = 0·85 nmol (mg protein)$^{-1}$, cytochrome b-5 = 0·63 nmol (mg protein)$^{-1}$. Values are means ± s.e.m., n = 5–6; $*P < 0{\cdot}05$ vs control, $^{\dagger\dagger\dagger}P < 0{\cdot}001$ vs perazine-treated rats (Dunnett's test).

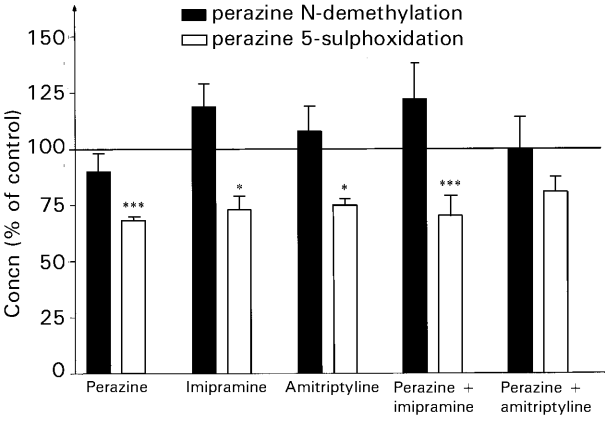

Figure 7. The rate of perazine *N*-demethylation and 5-sulphoxidation in rat liver microsomes after treatment with perazine (10 mg kg^{-1} i.p., twice daily) with or without tricyclic antidepressants (10 mg kg^{-1} i.p., twice daily) for 2 weeks. Microsomes were prepared 24 h after withdrawal of drugs. Control: 0.59 nmol *N*-desmethylperazine (mg protein)$^{-1}$ min^{-1} or 0.78 nmol perazine 5-sulphoxide (mg protein)$^{-1}$ min^{-1}, respectively. Values are means ± s.e.m., n = 5–6; $*P < 0{\cdot}05$, $***P < 0{\cdot}001$ vs control (Dunnet's test).

administered jointly with perazine, it elevated the concentration of the cytochrome compared with the perazine-treated group. Like imipramine, amitriptyline did not affect the level of cytochrome b-5. Perazine and tricyclic antidepressants administered chronically, separately or jointly, significantly decreased the activity of cytochrome P-450 towards perazine 5-sulphoxidation in liver microsomes compared with the control (Figure 7), although in the case of perazine combined with amitriptyline the decrease was not statistically significant. No significant differences were found in the rate of

perazine sulphoxidation between perazine- and perazine + antidepressant-treated rats. The rate of perazine *N*-demethylation was not affected by treatment with the investigated drugs.

Discussion

The results show different effects of amitriptyline and imipramine on the pharmacokinetics and metabolism of perazine. Amitriptyline substantially elevated plasma and brain concentrations of the neuroleptic (up to 300% of the control), whereas imipramine showed only a tendency to do so. The observed increases in the concentration of *N*-desmethylperazine after co-administration of perazine and amitriptyline may also be of pharmacological significance, since the metabolite retains 50% of the parent compound's activity (Rao 1989).

The observed rises in perazine concentration seem to be connected with direct inhibition of the neuroleptic's metabolism by antidepressants. Lineweaver-Burk analysis (Model I) showed that both amitriptyline and imipramine competitively inhibited perazine *N*-demethylation and 5-sulphoxidation in-vitro. However, the effect of amitriptyline on the metabolism of perazine was stronger than that of imipramine, especially in the case of *N*-demethylation. The reaction was inhibited by amitriptyline at $K_i = 16\,\mu M$, and by imipramine at $K_i = 164\,\mu M$. Thus the intensity of inhibitory effects on perazine metabolism in-vitro correlated positively with the in-vivo ability of the antidepressants to increase the concentration of the neuroleptic in the plasma and brain. Moreover, the observed direct inhibition of perazine metabolism by the antidepressants corresponded well with imipramine-produced increases in the perazine/metabolite concentration ratio and with the amitriptyline-evoked elevation of perazine/perazine 5-sulphoxide concentration ratio (and perazine/*N*-desmethylperazine ratio after 30 min).

The elevation of *N*-desmethylperazine concentration and decrease in the perazine/*N*-desmethylperazine concentration ratio after 6 and 12 h in-vivo evoked by amitriptyline are at variance with the amitriptyline-induced competitive inhibition of perazine *N*-demethylation observed in-vitro (Model I). Chronic joint treatment with perazine and amitriptyline did not, however, significantly affect the activity of cytochrome P-450 towards perazine *N*-demethylation when compared with the perazine-treated group (Model II). Therefore it is conceivable that amitriptyline may inhibit the subsequent metabolism of *N*-desmethylperazine.

Our unpublished data show that, in the rat, *N*-demethylation of perazine is catalysed by CYP2D1, CYP2B and CYP1A2, and 5-sulphoxidation by CYP2D1 and CYP2B. Thus competitive inhibition of one or more these enzymes by the investigated antidepressants is a pivotal mechanism of their influence on perazine pharmacokinetics. Moreover, the observed in-vivo increase in the sum of concentrations of perazine + metabolites measured suggests simultaneous inhibition by amitriptyline of another metabolic pathway of perazine (e.g. aromatic hydroxylation), not yet investigated by us. Taking into account similar metabolic pathways, amino-acid sequences and catalytic activities of cytochrome P-450 isoenzymes (especially CYP2D) involved in perazine metabolism in rat and man, as well as K_i values obtained for amitriptyline (reflecting both the order of magnitude of the respective K_m values and the presumed concentrations of the antidepressants in the liver) (Breyer-Pfaff et al 1983, 1988; Daniel & Wójcikowski 1999), it is feasible that the interactions found in the rat may also occur in man.

Our earlier and present results show that the investigated tricyclic antidepressants differently affect the pharmacokinetics of phenothiazines with diverse chemical structures (e.g. promazine (Syrek et al 1997), thioridazine (Daniel et al 2000) and the presently investigated perazine). The effects of tricyclic antidepressants on the pharmacokinetics of perazine seem to resemble those involving promazine rather than thioridazine. Both amitriptyline and imipramine dramatically increase the concentration of thioridazine (by 20 and 30 times, respectively), but only amitriptyline significantly affects the pharmacokinetics of promazine and perazine, this effect being less potent than in the case of thioridazine (3-fold increases). Thus amitriptyline may be regarded as a more effective inhibitor than imipramine of the metabolism of phenothiazine neuroleptics. It is therefore assumed that the effects of the investigated antidepressants on the metabolism of phenothiazine neuroleptics depend mainly on differences in the affinity of the combined drugs for active centres of cytochrome P-450 isoenzymes which contribute substantially to the metabolism of a particular phenothiazine.

In conclusion, amitriptyline co-administered with perazine to rats substantially increases the concentration of the neuroleptic via competitive inhibition of its metabolism, whereas imipramine shows only a tendency to act likewise. Similar interactions, possibly leading to exacerbation of the pharmacological action of perazine, may be expected in man. Since the interactions between phenothiazine neuroleptics and tricyclic anti-

depressants may be mutual (i.e. may proceed in two directions), reduced doses of both neuroleptic and antidepressant are recommended when these drugs are administered jointly.

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