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# ACCUMULATION AND ELIMINATION OF A NOVEL METABOLITE DURING CHRONIC ADMINISTRATION OF THE PHENOTHIAZINE DRUG PERAZINE TO RATS

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**Abstract**—Male rats were given perazine (methyl-piperazinyl-propyl-phenothiazine) *per os* in varying doses and for different periods of time. Liver, lung, kidney, spleen and brain tissue were analyzed for their content of perazine and three metabolites by means of extraction and thin layer chromatography followed by u.v. spectroscopy.

A metabolite resulting from piperazine ring cleavage, *N*-[γ-phenothiazinyl-(10)-propyl]-ethylenediamine (PPED), was found to accumulate in all tissues in a dose- and time-dependent fashion. After administration of 25 or 50 mg/kg perazine for 7 days or longer, it was the only or the most abundant metabolite present in tissues. With a dose of 2 × 50 mg/kg daily, high concentrations of desmethyl perazine (DMP) were attained in lung, while PPED was the major metabolite in the other organs studied. Small quantities of perazine and γ-[phenothiazinyl-(10)]-propylamine were also present.

After termination of a treatment with high perazine doses, perazine and DMP levels declined rapidly in all tissues (half-life < 5 hr). In contrast, PPED concentrations in liver decreased with a half-life of approximately 30 hr, and in extrahepatic tissues there was a transient increase followed by a decline with a half-life of more than 2 days. In these tissues PPED was still detectable 2 weeks after the last perazine dosage. These findings and the subcellular distribution in liver, characterized by a distinct concentration in mitochondria, suggest a strong binding of PPED to membrane proteins and/or lipids.

PPED formation from perazine has also been demonstrated in the rabbit and the mouse. Its biosynthesis from DMP could be shown in the rat and the mouse.

THOUGH a number of studies have been concerned with the distribution and elimination of phenothiazines and related psychoactive drugs following a single dose (e.g. cf. refs. 1–6), few investigations have been carried out on tissue levels of these drugs and their metabolites after repeated administration.[7–10] The latter kind of studies are of special concern, since in psychiatric therapy tricyclic drugs are mostly applied over a longer period of time.

In humans, metabolic studies on chlorpromazine,[11,12] perazine[13,14] and imipramine[15] have been performed by determining the metabolites excreted in urine during long-term therapy. However, Forrest *et al.*[16] stated that there is no quantitative relationship between the metabolite pattern in urine and that revealed in autopsy material.

The present study was carried out in continuation of investigations on the metabolism of perazine in various systems. Apart from the aforementioned studies on the urinary metabolite pattern,[13,14] the metabolic transformations in microsomal preparations had been investigated.[17] The pathways of perazine biotransformation, namely *N*-demethylation, *N*-oxidation, sulfoxidation and aromatic hydroxylation,

were found to be virtually the same *in vivo* and *in vitro*, but more complex products resulting from two or three metabolic reactions on the same molecule were not formed in short term incubations, though they were present in urine. In addition, oxidation of the piperazine ring skeleton could only be demonstrated *in vivo*: about 0·5 per cent of a daily perazine dose of 300–600 mg was excreted in the form of a piperazine-2,5-dione derivative in humans.[14,18]

An approach to the kinetic behaviour of perazine in tissues was now attempted by analyzing the drug metabolite pattern in rat organs during repeated administration of perazine. This study led to the detection of a novel metabolite derived from desmethyl perazine (DMP) by partial degradation of the piperazine ring to form an ethylenediamine derivative. The constitution of this metabolite, *N*-[γ-phenothiazinyl-(10)-propyl]-ethylenediamine (PPED), could be elucidated by physico-chemical methods and confirmed by chemical synthesis.[19] PPED is the major perazine metabolite in tissues under nearly all conditions of chronic treatment. Besides, a minor metabolite was identified as γ-[phenothiazinyl-(10)]-propylamine (PPA), which shows that the piperazine ring can be completely degraded, leaving only one amino group.

PPED exhibits a marked tendency to accumulate in parenchymatous tissues. Its accumulation has been studied in detail using varying dosage schedules, and the decline of tissue levels after termination of treatment has been followed. Concentrations of perazine, DMP and PPA in rat organs have also been measured.

## MATERIALS AND METHODS

### *Treatment of animals*

Male Wistar rats weighing 200–300 g were given aqueous solutions of perazine dimalonate or desmethyl perazine dimalonate (Chemische Fabrik Promonta, Hamburg, Germany) by oesophageal tube. Drug doses are always specified as amounts of free base. Treatment was usually carried out at 8 a.m. (one daily dose), or at 8 a.m. and 8 p.m. (two daily doses). A standard laboratory diet and tap water *ad lib.* were fed throughout the study.

### *Determination of metabolites in tissues*

Rats were killed by decapitation, organs were removed, chilled and either extracted immediately or stored at −20° for up to 3 weeks. The extraction procedure was varied according to the metabolite concentration expected and to the nature of the tissue.

(A) *Extraction of liver, lung, kidney and spleen tissue containing high or medium metabolite concentrations.* 0·5–2 g of tissue were suspended in the 4-fold volume of 10% NaCl solution, cut and homogenized for 20 sec with an Ultra-Turrax. In the case of high concentrations, 2 ml of the homogenate (corresponding to 0·4 g of tissue) were mixed with 0·05 ml 10% sodium deoxycholate solution (0·1 ml in the case of liver) and 0·3 ml 25% ammonia and after addition of 2 ml 1,2-dichloroethane shaken vigorously for 30 sec. Phases were separated by centrifuging twice for 10 min at 4000 rev/min. The clear organic layer was removed with a Pasteur pipette and the aqueous phase re-extracted twice with 2 ml dichloroethane. The combined organic phases were evaporated under reduced pressure in a conical centrifuge tube. When medium concentrations were expected, 4 ml of the homogenate were worked up with the double quantity of reagents, but re-extraction was again carried out twice with 2 ml of dichloroethane. Two spleens had to be pooled in these experiments.

(B) *Extraction of liver, lung and kidney tissue containing low metabolite concentrations.* Five g of liver or two pairs of lungs or kidneys were worked up with correspondingly larger quantities of reagents than used in A. The organic phases were filtered into a round-bottom flask, evaporated and the residue transferred to a conical tube with dichloroethane.

(C) *Extraction of brain tissue.* Two brains were pooled for each determination. They were homogenized with 6 ml 10% NaCl solution in an all-glass Potter–Elvehjem apparatus, which was washed twice with 3 ml 10% NaCl. The combined homogenate and washings were mixed with 0·2 ml 10% sodium deoxycholate solution and 1·2 ml 25% ammonia and extracted with successive portions of 25, 20 and 20 ml dichloroethane. The combined organic phases were taken to dryness in a round-bottom flask under reduced pressure, and the lipid residue was transferred to a centrifuge tube with three 1-ml portions of chloroform. The chloroform solution was concentrated to 0·3 ml by passing a stream of nitrogen.

*Recovery experiments* were carried out accordingly with additions of perazine or its metabolites to homogenates of drug-free tissues.

*Thin-layer chromatography.* Freshly activated plates (20 × 20 cm) coated with Kieselgel $GF_{254}$ (E. Merck) were used. Tissue extracts were dissolved in chloroform–methanol, 2:1, and quantitatively transferred to bands 3·5–8 cm wide according to the amount of tissue extracted (3·5 cm for 0·4 g; 4 cm for 0·8 g; 8 cm for 3–5 g). Brain extracts were applied as chloroform solutions in bands of 6·5 cm width. Plates containing extracts from 3–5 g of tissue were washed with benzene–acetone, 4:3, and dried for 2 min before being developed, plates with brain extracts were washed with chloroform–isopropanol, 10:1. Separation of metabolites was achieved with isopropanol–chloroform–water–25% ammonia, 40:20:2·5:2, by vol. Ultraviolet absorbing bands were marked under 254 nm light and substances isolated from the gel according to Breyer.[17]

| | | |
|---|---|---|
| $R_F$ values: | perazine | 0·79 |
| | PPA | 0·63 |
| | DMP | 0·40 |
| | PPED | 0·30. |

PPED was purified by rechromatography in acetone–isopropanol–1 N $NH_3$ 36:28:16, where it has an $R_F$ value of 0·56; only PPED from brain extracts was not rechromatographed.

*Spectrophotometry.* Isolated substances were dissolved in 4 ml 0·1 N HCl and the u.v. spectrum read between 230 and 380 nm on a Zeiss PMQ II spectrophotometer. Perazine and PPA obtained from brain extracts were contaminated with small amounts of lipids and were therefore purified by distribution between 4 ml 0·1 N $H_2SO_4$ and 1 ml dichloroethane. The spectrum of the aqueous phase was read as above. The concentration of perazine metabolites was calculated from $E_{255}$–$E_{280}$.[13] The extinction coefficient of PPED was obtained by dissolving a weighed amount of synthetically prepared material[19] in 0·1 N HCl, that of PPA was measured on the synthetic hydrochloride (Chemische Fabrik Promonta, Hamburg). $E_{255}$–$E_{280}$ in a $5.10^{-5}$ M solution was 1·17 for PPED and 1·20 for PPA, respectively (light path 1 cm). The calculated quantities of metabolites were corrected for recoveries.

*Isolation of subcellular fractions*

Rat liver was homogenized in a Potter–Elvehjem with 4 vol. of 0·25 M sucrose. After centrifugation at 1000 *g* for 10 min the sediment was again homogenized and recentrifuged. The combined supernatants were run for 10 min at 10,000 *g*. The sediment was washed three times by resuspension in sucrose solution and sedimentation at 4100 *g* for 15 min to yield the mitochondrial fraction.[20] The 10,000 *g* supernatant was separated into microsomes and 100,000 *g* supernatant by centrifugation in a Spinco model L ultracentrifuge at 40,000 rev/min for 60 min.

The fractions were analyzed for perazine metabolites by extracting aliquots according to method A.

Protein was measured by the procedure of Lowry *et al.*[21] using bovine serum albumin as a standard.

## RESULTS

*Metabolite pattern*

The four substances depicted in Fig. 1 could be identified in organs from rats treated with high doses of perazine (2 × 50 mg/kg) for at least 3 days and sacrificed 12 hr after the last dosage.

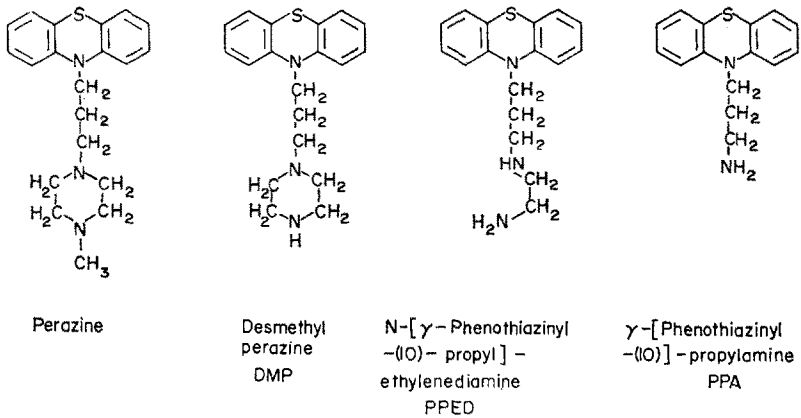


FIG. 1. Structures of perazine and its metabolites identified in rat tissues after chronic administration of perazine.

*Recovery of metabolites*

The percentage of perazine and its metabolites recovered in control experiments depended upon the quantity added. Data for perazine, DMP and PPA are contained in Table 1. No difference was found in the recoveries from liver tissue compared to those from other peripheral organs. The limit of detectability was around 0·2 μg/g using method C.

PPED proved to be very labile during work-up, and recoveries were more dependent on absolute amounts present than with the other metabolites. In Fig. 2, this dependence is illustrated for experiments using method A. When larger quantities of peripheral tissues were treated according to method B, recoveries were somewhat lower, but the limit of detectability was decreased to 2 μg/g tissue. With brain (method C) recoveries

TABLE 1. RECOVERY OF PERAZINE, DMP AND PPA FROM RAT TISSUES

| Substance | Extraction method | $n$ | Quantity added ($\mu$g/g tissue) | Recovery (%) |
|---|---|---|---|---|
| Perazine | A | 18 | 7–20 | 70–80 |
| | C | 6 | 0·5–2 | 69–95 |
| DMP | A | 22 | 7–230 | 69–87 |
| | C | 8 | 0·6–6 | 63–90 |
| PPA | A | 5 | 10–30 | 85–89 |
| | C | 4 | 0·8–1·6 | 63–71 |

Experimental procedure as in Materials and Methods.

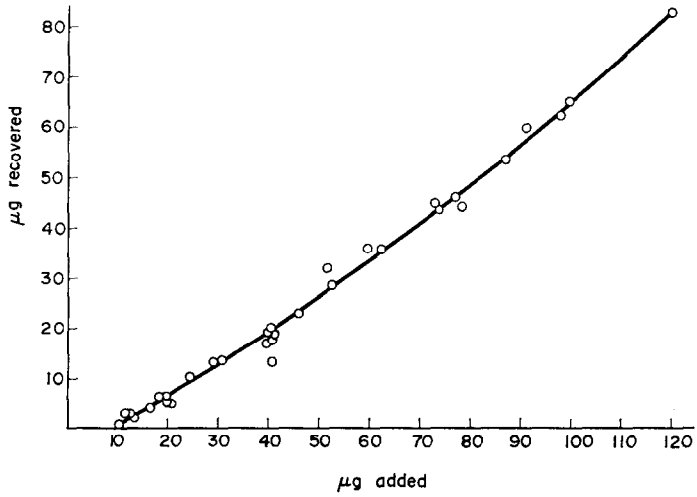


FIG. 2. Recovery of PPED from liver, lung, kidney and spleen tissue according to method A (see Materials and Methods).

were slightly higher than those depicted in Fig. 2, since the second chromatographic step was omitted, but the relationship between the amount added and the per cent recovery was virtually the same.

A considerable part of the PPED losses was due to decomposition during chromatography, since in model experiments 50–53 per cent of 8 $\mu$g PPED were lost during one chromatographic run. Extraction from ammoniacal solutions into dichloroethane, however, proved to be complete.

*Accumulation of metabolites during treatment with varying doses of perazine*

*Twenty-five mg/kg daily, sacrifice* 24 hr *after the last dosage* (Table 2). After 7 or 14 days of treatment, traces of DMP were found in lung and occasionally also in spleen. PPED could be demonstrated in all organs, and in most of them it was the only metabolite detectable. In liver it had attained a constant level after 7 days, and no increase was observed during a further week of perazine administration. The PPED concentration in brain was just above the limit of detectability.

TABLE 2. CONCENTRATIONS OF DMP AND PPED IN RAT TISSUES DURING TREATMENT WITH 25 OR 50 mg/kg PERAZINE DAILY

| Perazine dose | Tissue | Days of treatment | Metabolite concentration (μg/g) DMP | PPED |
|---|---|---|---|---|
| 25 mg/kg | Liver | 7 | — | 13 ± 1 |
| | | 14 | — | 13 ± 1 |
| | Brain | 7 | — | 1·7; 2·0 |
| | | 14 | — | 1·6; 2·0 |
| 50 mg/kg | Liver | 7 | trace | 53 ± 2 |
| | | 14 | trace | 66 ± 3 |
| | | 21 | trace | 81 ± 3 |
| | Lung | 7 | 12 ± 1 | 41 ± 1 |
| | | 14 | 16 ± 2 | 62 ± 4 |
| | | 21 | 22 ± 4 | 89 ± 7 |
| | Kidney | 7 | trace | 39 ± 2 |
| | | 14 | trace | 57 ± 4 |
| | | 21 | trace | 82 ± 4 |
| | Spleen | 7 | trace | 55; 59; 60 |
| | | 14 | trace | 84 ± 4 |
| | | 21 | trace | 85; 103; 116 |
| | Brain | 7 | 0·7; 0·75; 0·8 | 3·3; 3·6; 3·7 |
| | | 14 | 0·9 ± 0·05 | 4·3 ± 0·5 |
| | | 21 | 0·7; 0·8; 1·0 | 4·5; 5·1; 5·4 |

Sacrifice 24 hr after the last dose. $n = 4$–12 in those cases where mean values ± S.E.M. are given.

*Fifty mg/kg daily, sacrifice* 24 hr *after the last dosage* (Table 2). After treating for 7–21 days, traces of PPA and small amounts of DMP were present in all tissues. In lung the DMP level was clearly higher than in other organs, and it showed a progressive increase with time. In brain, however, the DMP concentration did not increase between days 7 and 21.

Tissue levels of PPED continued to increase during the 3 weeks of treatment. The concentrations in lung and kidney were lower than that in liver after 7 days, but equally high or higher after 21 days. In spleen, too, the increase between days 7 and 21 was greater than in liver.

*Fifty mg/kg twice daily, sacrifice* 12 hr *after the last dosage* (Table 3). Perazine and the three metabolites were consistently present in all organs; perazine and PPA levels have been determined in liver and brain only. The perazine concentration did not change significantly with time, whereas that of DMP exhibited a slight to moderate increase between days 3 and 7 and a steep increase between days 7 and 14. The accumulation of PPED proceeded steadily during the time interval investigated. Liver always contained the highest concentration, but the difference between liver and other peripheral tissues was clearly smaller on day 14 than on day 3.

Concentrations of perazine and all three metabolites in the brain were lower than those in the peripheral organs by a factor of 5 or more for all dosage schedules applied.

Low concentrations were also present in muscle. Two samples of skeletal muscle from rats pretreated for 7 days with 2 × 50 mg/kg perazine were extracted according to method A. The DMP levels were found to be 2 and 4 μg/g, respectively, and PPED

TABLE 3. CONCENTRATIONS OF PERAZINE AND ITS METABOLITES IN RAT TISSUES DURING TREATMENT WITH 2 × 50 mg/kg PERAZINE DAILY

| Tissue | Days of treatment | Metabolite concentration (μg/g) | | | |
|---|---|---|---|---|---|
| | | Perazine | DMP | PPED | PPA |
| Liver | 3 | 8·2 ± 1·0 | 30 ± 3 | 85 ± 5 | |
| | 7 | 6·9 ± 1·5 | 35 ± 3 | 182 ± 6 | 5·7 ± 0·8 |
| | 14 | 10·2 ± 1·2 | 102 ± 26 | 330 ± 27 | 10·2 ± 1·7 |
| Lung | 3 | | 94 ± 11 | 42 ± 4 | |
| | 7 | | 134 ± 13 | 124 ± 9 | |
| | 14 | | 295 ± 50 | 268 ± 22 | |
| Kidney | 3 | | 21 ± 2 | 47 ± 3 | |
| | 7 | | 23 ± 3 | 79 ± 7 | |
| | 14 | | 94 ± 21 | 226 ± 21 | |
| Spleen | 3 | | 56 ± 8 | 60 ± 5 | |
| | 7 | | 70 ± 8 | 120 ± 4 | |
| | 14 | | 178 ± 33 | 270 ± 19 | |
| Brain | 3 | 0·9; 1·1 | 4·5 ± 0·1 | 2·7 ± 0·4 | 0·4; 1·0; 1·4 |
| | 7 | 0·7 ± 0·2 | 4·8 ± 0·2 | 4·7 ± 0·2 | 1·2 ± 0·2 |
| | 14 | 1·0 ± 0·2 | 7·0 ± 1·0 | 10·2 ± 0·2 | 1·4 ± 0·2 |

Sacrifice 12 hr after the last dose. Mean values ± S.E.M., $n$ = 4–16.

was detected in a concentration of approximately 10 μg/g in both samples. Following the same treatment, the metabolite content of rat blood was shown to be still lower. DMP could just be detected (about 0·2 μg/ml), but the presence of PPED could not be demonstrated (extraction according to method B).

*Elimination of metabolites following termination of perazine treatment*

Elimination kinetics were only measured in rats that had been pretreated with 2 × 50 mg/kg perazine for 7 days. Perazine had completely disappeared 36 hr after the last dosage. PPA was detected on chromatograms at this time in quantities not much lower than 12 hr after the last dosage. The behaviour of DMP and PPED is illustrated in Fig. 3. It can be seen that DMP declined rapidly in all tissues, so that 36 hr after the last dose its concentration in lung and brain was about one fifth of that measured 24 hr previously.

In contrast, PPED persisted for a long time after termination of treatment, and distinct differences were found concerning the time course of PPED concentrations in the various organs. In liver a slight decrease was observed within the first 24-hr interval studied, and afterwards the PPED level declined with a half-life of approximately 30 hr. However, in the other tissues including brain PPED showed an increase rather than a decrease during the first day after termination of treatment, and it decreased very little during the following 2 days. Afterwards there was a decline that occurred much slower than in liver, the half-life being 2·5–4 days in lung, kidney and spleen and more than 7 days in brain. Therefore, PPED levels were still measurable in extrahepatic organs 14 days after the last perazine dose had been administered, whereas in liver they were just above the limit of detectability after 7 days.

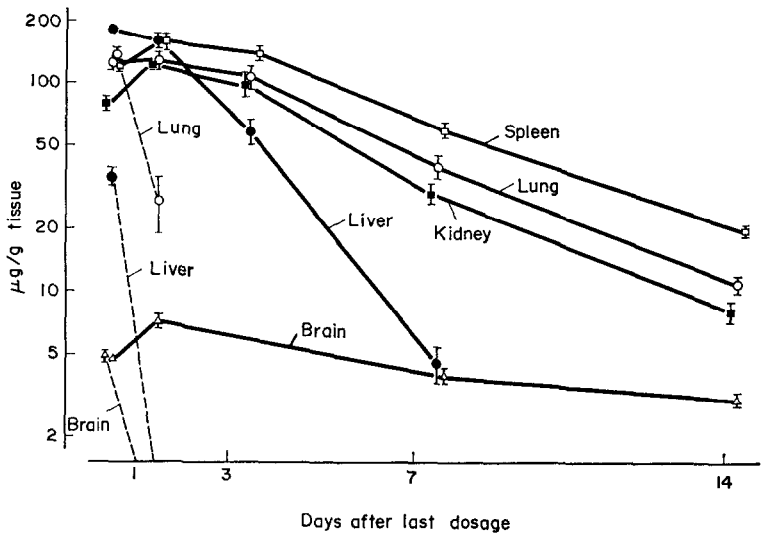


FIG. 3. Time course of concentrations of DMP (- - - -) and PPED (———) in rat organs following termination of perazine treatment (2 × 50 mg/kg for 7 days). Vertical bars represent standard errors.

*Subcellular distribution of DMP and PPED*

This was studied on livers of two rats that had received a high-dose treatment with perazine and were killed 12 hr after the last dosage. The results are given in Table 4. They show that the 1000 *g* sediment did not differ from the total homogenate in its content of DMP and PPED, whereas mitochondria possess a higher affinity for DMP and especially for PPED than other cell fractions. In contrast, microsomes contained a far smaller amount of PPED per milligram of protein than the homogenate, and in the soluble fraction the metabolites were not detectable.

TABLE 4. CONCENTRATIONS OF DMP AND PPED IN HOMOGENATE AND SUB-CELLULAR FRACTIONS OF TWO RAT LIVERS FOLLOWING TREATMENT WITH 2 × 50 mg/kg PERAZINE FOR 7 DAYS

| Fraction | Experiment 1 | | Experiment 2 | |
|---|---|---|---|---|
| | DMP (µg/mg protein) | PPED | DMP (µg/mg protein) | PPED |
| Homogenate | 0·14 | 0·79 | 0·09 | 0·84 |
| 1000 *g* sediment | 0·15 | 0·81 | 0·11 | 0·86 |
| Mitochondria | 0·39 | 3·2 | 0·17 | 3·4 |
| Microsomes | 0·19 | 0·53 | 0·10 | 0·40 |
| 100,000 *g* supernatant | <0·1 | <0·3 | <0·1 | <0·3 |

*PPED formation from single perazine doses*

Two hr after a single oral dose of perazine (50 mg/kg) PPED could be detected in the livers of male rats in a concentration of 6·0 ± 0·4 µg/g ($n = 6$), but it was absent from extrahepatic tissues.

*Accumulation of metabolites in mouse and rabbit organs*

The liver of a male mouse treated with 2 × 50 mg/kg perazine for 7 days contained 150 μg/g PPED. This metabolite was also present in lung and kidney along with DMP.

Treatment of a male rabbit for 10 days with perazine doses increasing from 25 to 40 mg/kg led to the formation of PPED stores in liver (19 μg/g), lung (5 μg/g) and kidney (4 μg/g).

*Formation of PPED during treatment with DMP*

One male rat and two male mice received 2 × 50 mg/kg DMP for 7 days. Twelve hr after the last dosage the rat liver contained 360 μg/g PPED, the rat lung 140 μg/g. The PPED concentrations in the mouse livers were 130 and 164 μg/g.

## DISCUSSION

The extraction procedure described above using additions of sodium chloride and sodium deoxycholate was found to result in a far better separation of phases than when alkalinized homogenates were extracted without additions or with addition of either of the substances. Nevertheless, recoveries of the ethylenediamine derivative PPED were poor when small quantities were present, probably due to decomposition of the compound during the work-up procedure. This lack of stability of PPED can be regarded as the main cause for the limited sensitivity of the method designed for its determination. It necessitated the extraction of large amounts of tissue. Removal of the bulk of lipids from extracts could be achieved by washing the chromatographic plates with unpolar solvents before development. This procedure allows for applying large quantities of tissue extracts in relatively narrow bands on the chromatogram, thus minimizing losses of PPED.

The results of the tissue analyses show that PPED is the most prominent or even the only perazine metabolite present at the time when the next perazine dose would have been applied in chronic treatment of rats with medium or low doses. Also during a high-dose regimen its concentration exceeded that of DMP in most tissues. Other metabolites and perazine were contained in far smaller amounts, and polar biotransformation products, such as perazine sulfoxide, were not present at all. However, PPED was neither detected in human urine[13] nor can it be demonstrated in rat urine, as preliminary investigations have shown, nor is it formed in liver microsomes upon incubation with perazine.[17] This discrepancy stresses the importance of studies on tissues, especially under the condition of repeated administration of a drug.

The lowest perazine dose studied in rats, viz. 25 mg/kg, is comparable with drug doses used in human therapy. These are 250–600 mg/day which means 3–10 mg/kg daily.

Since PPED does not contain a methyl group, it is likely to be produced from perazine via its desmethyl derivative. This assumption is supported by the finding that upon treatment with DMP for 7 days PPED accumulates to at least as high tissue levels as during administration of perazine. Though DMP is probably an intermediate in the biosynthesis of PPED, the tissue concentrations of these two metabolites attained upon different treatment schedules do not correlate (Tables 2 and 3). This fact and the results of the elimination studies prove that the accumulation of PPED is not secondary

to an accumulation of DMP, but is rather due to the pharmacokinetic properties of the ethylenediamine metabolite itself.

The site of PPED formation is most probably the liver, since in acute experiments it is the only organ to contain this metabolite already 2 hr after an oral perazine administration. From the fact that the PPED elimination proceeds fastest in the liver (Fig. 3), it can be concluded that this organ is also the main site for disposition of PPED, either by biliary excretion or by metabolic degradation.

The accumulation of PPED in liver is clearly dose-dependent and follows the laws common to other cumulation processes. Upon repeated administration of a low dose (25 mg/kg), a state of equilibrium is reached within 7 days, in which the disposition of PPED equals its formation and thus the tissue concentration does no longer increase. With 50 or 2 × 50 mg/kg this equilibrium has not yet been achieved after 21 or 14 days of treatment, respectively.

The distribution of perazine, DMP and PPED among the different organs roughly equals that of other phenothiazine and related tricyclic drugs.[1–6] The highest concentrations are found in the peripheral parenchymatous organs, whereas low levels are observed in brain, skeletal muscle and blood. However, a peculiar facet in the kinetic behaviour of PPED is the delayed rise of its concentration in extrahepatic tissues (Tables 2 and 3). This phenomenon might be explained from the results of the subfractionation studies (Table 4) which demonstrated a strong binding to cell particles, especially to mitochondria. This is probably due to a tight attachment to membrane proteins and/or lipids. In contrast, the PPED content of the supernatant fraction was not measurable. It can be assumed that the affinity of plasma proteins for PPED is similarly low as that of the soluble liver proteins, so that in equilibrium the plasma contains extremely small concentrations of PPED. This is consistent with the failure to demonstrate PPED in blood. Thus the transport of the metabolite in blood occurs at a low rate and apparently cannot keep up with its synthesis. On the other hand, the decline of PPED in lung, kidney, spleen and brain is far slower than that in the liver, because the former tissues are not able to degrade foreign compounds at an appreciable rate and the redistribution to the liver is again delayed by the limited transport capacity of the blood.

After perazine administration has been stopped, PPED formation is likely to continue as long as DMP is available. The rate of this conversion however, is not adequate to maintain the PPED concentration in liver between the 12th and 36th hr after the last perazine dosage. Nevertheless, there is a transient rise in the PPED concentrations in kidney, spleen and brain during this time interval which must be attributed to the slow equilibration process between liver and extrahepatic organs.

The metabolic degradation of PPED has not been studied in detail, but indications have been obtained that PPA is a metabolite of PPED.

Accumulation of a metabolite during repeated administration of a drug is not unusual, but has been observed upon treatment with mephobarbital,[22] tricyclic antidepressants,[8,23] chlorcyclizine[24] and trimethadione.[25] In these examples, the metabolite results from a demethylation of the parent drug and constitutes a major biotransformation product. In perazine treatment the accumulation of PPED is a peculiar feature insofar as it requires a series of metabolic reactions for its formation and it proves to be a minor metabolite in acute experiments. In addition, its long half-life in tissues is remarkable in view of its chemical instability.

Excretion of metabolites for periods of months[26] or even more than 1 year[27] after termination of chlorpromazine administration has been claimed in psychiatric patients. From chlorpromazine, an ethylenediamine derivative cannot be formed by metabolic degradation, but nonetheless it seems worthwhile to search for metabolites with a long half-life also in this series, since they might contribute to the therapeutic or side-effects of a drug.

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