

EFFECT OF DEUTERATION OF IMPRAMINE ON ITS PHARMACOKINETIC PROPERTIES IN THE RAT

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Abstract—Imipramine was specifically deuterated in either both aromatic rings or in the *N*-methyl group, or in both positions, and the pharmacokinetic properties of the products were determined in the rat and compared with those of the non-deuterated analogue. Deuteration of imipramine resulted in a small but significant isotope effect on *N*-demethylation while aromatic hydroxylation was unaffected. This isotope effect led to a slower rate of systemic clearance, a longer half-life and, when orally administered, enhanced bioavailability. Urinary excretion of didesmethylimipramine-*d*₄, following oral administration of imipramine-*d*₇, was significantly lower than the excretion of didesmethylimipramine following administration of unlabelled imipramine, indicating inhibited demethylation. Similarly, the urinary excretion of desmethylimipramine-*d*₄, didesmethylimipramine-*d*₄ and 2-hydroxydesmethylimipramine-*d*₄ were lower than for the corresponding unlabelled or *d*₇-analogues, indicating the stability of the *N*-CD₃ group. Deuteration had no effect on the pharmacological properties of imipramine as determined in this study.

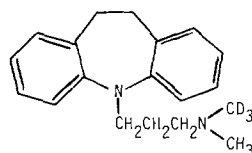
The duration and nature of the pharmacological effect(s) of a drug may be affected by the rate(s) and pathways of its metabolism [1]. The rate of metabolism of a drug may be decreased by substitution of the isotope deuterium for hydrogen atoms [2-5]. The maximum theoretical isotope effect (K_H/K_D) is 18, and in biological systems values as high as 2-13 have been reported [3, 6, 7].

The tricyclic antidepressant, imipramine, is widely used in the management of endogenous depression, its antidepressant effect being mediated by the major metabolite, desmethylimipramine, formed by *N*-demethylation [8-10]. Imipramine itself has tranquillizing properties [8, 11] which are not overtly manifested in human subjects because of its rapid metabolism to desmethylimipramine and other products. It is conceivable that deuteration of imipramine would retard this metabolism giving rise to a prolongation of the antidepressant effects of the drug tempered by an initial tranquillising activity, which would enhance its value.

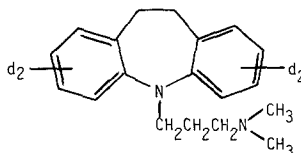
To examine this possibility, deuterated analogues of imipramine were synthesized and their pharmacokinetic and pharmacological properties compared with those of unlabelled imipramine. The rat was chosen as the animal model as this species exhibits a similar metabolic profile and pharmacokinetics of the drug to man; *N*-demethylation and aromatic hydroxylation being the major metabolic pathways.

(>99.8% D) (Nuclear Magnetic Resonance Ltd, High Wycombe, U.K.), ketodase (William R. Warner & Co. Ltd, Eastleigh, U.K.), LiAlD₄ (>99% D) and all other reagents (Analar grade) (BDH Ltd, Poole, U.K.) were purchased. Protriptyline hydrochloride (Merck Sharp & Dohme Research Laboratories, Hoddesdon, U.K.), imipramine and desmethylimipramine hydrochlorides (Biorex Laboratories Ltd, London, U.K.) and metabolites of imipramine (Dr V. A. John, Ciba-Geigy Ltd, Macclesfield, U.K.) were generous gifts.

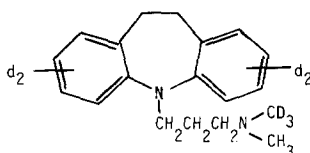
Deuteration of imipramine. Imipramine was specifically deuterated in either the aromatic rings (*d*₄, four deuterons) or in the *N*-methyl group (*d*₃, three deuterons) or in both positions (*d*₇, seven deuterons) (see Scheme).



Imipramine-*d*₃



Imipramine-*d*₄



Imipramine-*d*₇

MATERIALS AND METHODS

Chromatography solvents of HPLC grade (Rathburn Chemicals Ltd, Walkerburn, U.K.), D₂O

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Imipramine- d_3 was synthesized by the method of Shaw and Markey [12]. Ethylchloroformate (1.8 g, 16.5 mmoles) was added to a solution of desmethylimipramine hydrochloride (2.5 g, 8.2 mmoles) in pyridine (50 ml) and the mixture was stirred for 20 hr at room temp. Water was added (50 ml) and the mixture extracted with ethyl acetate (100 ml); the organic layer was washed in turn with 2 M HCl (5 \times 50 ml), 2 M NaOH (2 \times 50 ml) and water (3 \times 50 ml) and then dried (anhydrous Na_2SO_4) before removing the solvent by evaporation. The carbamate residue was redissolved in anhydrous tetrahydrofuran (20 ml), then added dropwise with stirring to a suspension of $LiAlD_4$ (700 mg) in tetrahydrofuran (40 ml) and the mixture refluxed for 8 hr. The excess $LiAlD_4$ was decomposed by dropwise addition of water and the mixture filtered. The lithium salts were rinsed with tetrahydrofuran (2 \times 10 ml) and the combined tetrahydrofuran extracts concentrated (10 ml) and diluted with chloroform (50 ml). This solution was washed with 2 M HCl (2 \times 10 ml), water (3 \times 20 ml), dried (anhydrous Na_2SO_4) and evaporated to dryness to leave a residue of imipramine- d_3 .

Imipramine- d_4 was synthesised by deuterium exchange, essentially as described by Heck *et al.* [13]. Imipramine hydrochloride (1 g, 31 mmoles) was added to a mixture of heptafluorobutyric acid (1 ml) and D_2O (5 g, 250 mmoles) and refluxed for 48 hr. Following addition of water (10 ml) the mixture was made alkaline with 5 M NaOH and extracted with diethyl ether (2 \times 10 ml). The combined extracts were dried (anhydrous Na_2SO_4) and the ether evaporated to leave a residue of imipramine- d_4 . Imipramine- d_7 was synthesised by aromatic deuteration (deuterium exchange) of imipramine- d_3 .

The hydrochloride salt of each deuterated analogue of imipramine was prepared by dissolving the compound in acetone and adding a slight excess of

a solution of HCl in acetone (3 mmoles/ml). The hydrochlorides crystallised within 24 hr of standing at 4° and were recrystallised from acetone. M.ps of all analogues were 174–176°. Purities were >99% by TLC on silica gel in three different solvent systems (chloroform:*n*-propanol:25% ammonia, 100:100:2 by vol.; chloroform:toluene:acetone, 50:40:5; and petroleum ether:ether:acetone, 8:1:1). The yields were 46, 56 and 34% for imipramine- d_3 , imipramine- d_4 and imipramine- d_7 respectively. The products were characterised by i.r. spectrometry using a Pye-Unicam SP 1000 spectrometer and their deuterium content determined by NMR using a 60 MHz Varian EM-360 spectrometer with a 10 ppm sweep width and using $CDCl_3$ as solvent. The identity of each product was confirmed by mass spectrometry using an A.E.I. MS 12 instrument operating at ionisation potentials of 10 or 70 eV and source and inlet temperatures of 200 and 40° respectively. The relative abundance of the various isotope species in each product is shown in Table 1.

Determination of imipramine and its metabolites.

This was carried out by HPLC as described by Sutfin and Jusko [14] using a Waters Associates 440 liquid chromatograph to which a Perkin-Elmer 3000 spectrofluorimeter was connected. A stainless steel column (25 \times 0.46 cm) packed with Lichrosorb Si 60-5 (Chromapak U.K., London, U.K.) was operated at room temp using a flow rate of 3.5 ml/min with a solvent system of acetonitrile-methanol-ammonia solution (sp. g. 0.88) (200:40:1 by vol.) and a detector set at an excitation wavelength of 240 nm and an emission wavelength of 370 nm.

Imipramine and its metabolites were extracted as follows: samples (250 μ l) of plasma or urine were mixed with water (250 μ l), 1 M acetate buffer (pH 5.0) (1.0 ml), the protriptyline hydrochloride internal standard (50 μ g), 10 M ammonia solution (50 μ l) and extracted with 1.0 ml of a mixture of *n*-

Table 1. Relative abundance of isotopic species

	Percentage present as following species					
	d_2	d_3	d_4	d_5	d_6	d_7
Imipramine- d_3	2.2	97.8	0	0	0	0
Imipramine- d_4	5.8	27.7	66.5	—	—	—
Imipramine- d_7	0	0	1.8	11.3	38	48.8

Table 2. Retention times and extraction recoveries of imipramine and its metabolism

Compound	Retention time (min)	Recovery (%)
Imipramine	3.6	79 \pm 3*
2-Hydroxyimipramine	4.4	83 \pm 7
Imipramine <i>N</i> -oxide	17.5	64 \pm 7
Desmethylimipramine	11.5	74 \pm 5
2-Hydroxydesmethylimipramine	14.0	80 \pm 4
Didesmethylimipramine	5.3	70 \pm 4
Protriptyline	16.0	80 \pm 3

* Results presented as means \pm S.D. for at least four determinations.

butanol-hexane (1:4 v/v) in a 3.5 ml screw-capped septum vial (Phase Separations Ltd, Queensferry, U.K.). The phases were separated by centrifugation and the organic phase evaporated to dryness under N_2 . The residue was redissolved in methanol and 90 μ l was injected into the chromatograph. Hydrolysis of conjugates was achieved by replacing half the volume (500 μ l) of buffer with ketodase and incubating for 24 hr at 37° before extraction. Recoveries and retention times of each compound are shown in Table 2.

Pharmacokinetic studies. Male Wistar albino rats (240–320 g) (Animal Breeding Unit, University of Surrey, Guildford, U.K.) were anaesthetised with an intraperitoneal injection of chloral hydrate (300 mg/kg) and an intraperitoneal dose of urethane (800 mg/kg) given 1 hr after the chloral hydrate. Imipramine and its deuterated analogues (as hydrochlorides) were infused through a femoral vein (10 or 20 mg/kg) over a period of 5 min; blood samples (600 μ l) were removed at regular intervals by heart puncture. For studies by the oral route the animals were fasted for 12 hr prior to administration of the compounds (50 mg/kg) by gastric intubation; blood samples (600 μ l) were obtained by tail bleeding. Absorption kinetics and elimination kinetics were studied in separate experiments.

Pharmacokinetic parameters were calculated as follows. For the intravenous bolus studies the half-life ($t_{1/2}$) was determined from semi-logarithmic plots of plasma concn vs time. The initial plasma concn (C_0) was estimated from the same graph following extrapolation of the curve to zero time. The elimination rate constant (K_{el}), total area under the curve (AUC), volume of distribution (V_D) and clearance (Cl) were determined from the following equations:

$$K_{el} = \frac{0.693}{t_{1/2}}, AUC = \frac{C_0}{K_{el}}, V_D = \frac{\text{dose}}{C_0}, Cl = V_D K_{el}.$$

For the oral studies the absorption rate constant (K_a) was determined by the method of residuals. The AUC was determined from the equation:

$$AUC = I \left(\frac{1}{K_{el}} - \frac{1}{K_a} \right)$$

where I is the intercept at zero time. The fraction of the oral dose entering the body (F) is calculated from the equation:

$$F(\%) = \frac{AUC_{\text{oral}}}{AUC_{\text{iv}}} \times \frac{\text{dose}_{\text{iv}}}{\text{dose}_{\text{oral}}} \times 100.$$

The V_D , time of peak plasma concn (t_p) and the maximum plasma concn (C_{max}) were calculated from

the following equations:

$$V_D = \frac{K_a F(\text{dose})}{I(K_a - K_{el})}, t_p = \frac{2.303}{(K_a - K_{el})} \log \frac{K_a}{K_{el}},$$

$$C_{\text{max}} = \frac{F(\text{dose})}{V_D} e^{-K_{el} t_p}.$$

Pharmacological studies. The charcoal meal test was carried out as described by Sacra and McColl [15], but using rats (90–110 g) instead of mice. The animals received single oral doses of imipramine, its deuterated analogues, or desmethylinipramine (all at 30 mg/kg), or atropine sulphate (600 μ g/kg) 1 hr prior to oral administration of a charcoal suspension (1 g of charcoal, 5–6 μ , suspended in 10 ml water containing 0.5 g of gum acacia). The animals were killed by cervical dislocation and the small intestines, from the pyloric sphincter to the appendix, were removed. The passage of charcoal was calculated as a percentage of the charcoal movement seen in saline-treated animals.

For the *in vivo* studies on the isolated rabbit jejunum preparation [16] a female rabbit (3.5 kg) was killed by a blow to the head and exsanguination. The jejunum was dissected out, placed into Tyrodes solution and cut into strips (2–3 cm long) which were then attached to a fixed pin in an organ bath at one end and at the other end to a tension transducer and recorder. The jejunum preparation was bathed in Tyrode's solution at 37° and gassed with O_2/CO_2 (95:5 v/v). The effect of imipramine and its deuterated analogues, and the ability of these to potentiate the noradrenaline-induced response, were investigated. The jejunum preparation was washed thoroughly with Tyrode's solution after each experiment.

RESULTS

The elimination of imipramine obeys first-order kinetics for a single compartment open model. Saturation kinetics are not evident at the dose levels employed in the present study in rats, and the drug is eliminated with a $t_{1/2}$ of around 3 hr, a K_{el} of 0.0045 min^{-1} , a total systemic Cl of 85 $\text{ml min}^{-1} \text{ kg}^{-1}$, and has a V_D of approximately 20 l kg^{-1} (Tables 3 and 4). Following oral administration to rats, imipramine exhibits poor bioavailability ($F = 4\%$) (Table 4).

Pharmacokinetic comparison of imipramine with its deuterated analogues demonstrates an isotope effect of 1.33 on *N*-demethylation (imipramine- d_3 , calculated from K_{el} , $t_{1/2}$ or Cl), but no isotope effect on aromatic hydroxylation (imipramine- d_4) (Table 4). Following oral administration of imipramine- d_3 ,

Table 3. Effect of deuteration on the pharmacokinetics of imipramine administered intravenously to rats

Drug	Dose (mg/kg)	$t_{1/2}$ (min)	K_{el} (min^{-1})	Cl ($\text{ml min}^{-1} \text{ kg}^{-1}$)	C_0 (ng ml^{-1})	V_D (l kg^{-1})	AUC ($\mu\text{g min ml}^{-1}$)
Imipramine	20	183 \pm 26	0.0039 \pm 0.0006	92 \pm 16	788 \pm 24	23 \pm 1	197 \pm 32
Imipramine- d_3	10	155 \pm 24	0.0046 \pm 0.0006	85 \pm 20	533 \pm 194	18 \pm 5	109 \pm 28
Imipramine- d_7	10	205 \pm 31	0.0035 \pm 0.0006	59 \pm 17	564 \pm 94	16 \pm 2	158 \pm 44

Results are expressed as the mean values \pm S.D. for four animals.

Table 4. Effect of deuteration on the pharmacokinetics of imipramine administered orally to rats

Drug	t_i (min)	K_{el} (min^{-1})	K_a (min^{-1})	V_D (l kg^{-1})	AUC ($\mu\text{g min ml}^{-1}$)	F (%)	I (min)	t_p (ng ml^{-1})	C_{max} (ng ml^{-1})
<u>Absorption study</u>									
Imipramine	139 \pm 25	0.0051 \pm 0.0009	0.066 \pm 0.062	20 \pm 5	11.2 \pm 8.4	2.3 \pm 1.7	59 \pm 33	54 \pm 22	37 \pm 22
Imipramine- d_7	150 \pm 58	0.0053 \pm 0.0026	0.042 \pm 0.020	20 \pm 8	12.3 \pm 3.8	2.5 \pm 0.8	69 \pm 23	64 \pm 26	41 \pm 12
<u>Elimination study</u>									
Imipramine	159 \pm 27	0.0045 \pm 0.0007	—	19 \pm 5	21 \pm 7	4.3 \pm 1.4	115 \pm 55	51 \pm 3	90 \pm 51
Imipramine- d_4	168 \pm 26	0.0042 \pm 0.0006	—	21 \pm 5	24 \pm 6	4.8 \pm 1.1	115 \pm 7	51 \pm 2	83 \pm 5
Imipramine- d_3	211 \pm 42	0.0034 \pm 0.0007	—	26 \pm 7	36 \pm 8	7.3 \pm 1.7	147 \pm 82	55 \pm 3	112 \pm 56

Results are expressed as the mean values \pm S.D. for at least four animals. The compounds were administered orally (50 mg/kg).

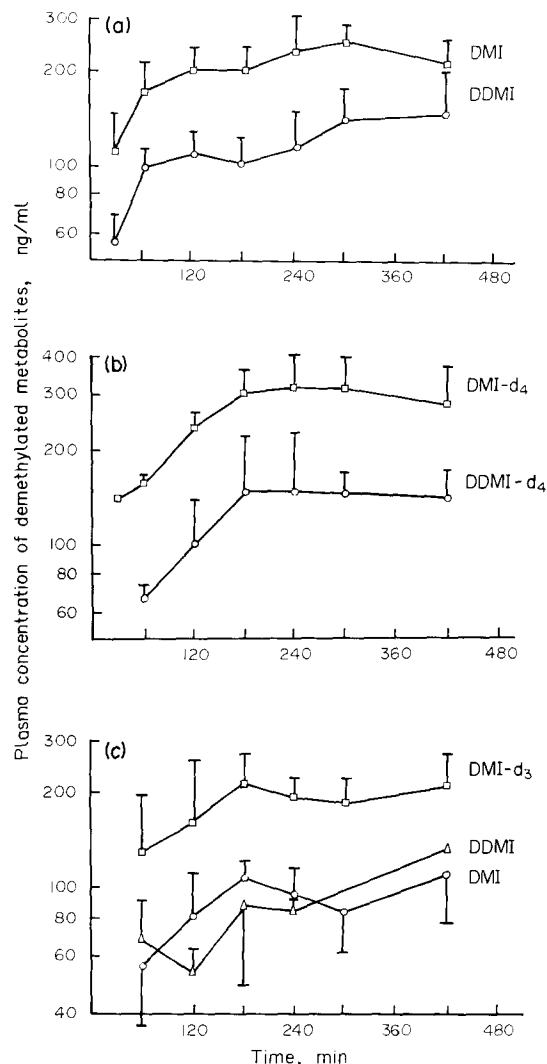


Fig. 1. Plasma levels of demethylated metabolites of imipramine following oral administration of the drug. Each point represents the mean \pm S.D. for at least four determinations. Animals received a single oral administration of: (A) imipramine, (B) imipramine- d_4 or (C) imipramine- d_3 (50 mg/kg). DMI = desmethylinipramine; DDMI = didesmethylinipramine.

a longer plasma t_i , a larger V_D and AUC, as well as greater bioavailability, than for the non-deuterated analogue were observed, while none of these parameters was affected for the aromatically deuterated imipramine- d_4 (Table 4). The absorption kinetics of the imipramine- d_7 analogue were the same as for imipramine itself (Table 4). However, the elimination kinetics of the d_7 -analogue administered intravenously differed from those of imipramine (Table 3); the plasma t_i and AUC were increased while the K_{el} and systemic Cl were decreased. Further evidence of the isotope effect on *N*-demethylation is obtained from the plasma levels of demethylated products following imipramine- d_3 administration, when the desmethylinipramine- d_3 levels were almost twice those of desmethylinipramine (Fig. 1C).

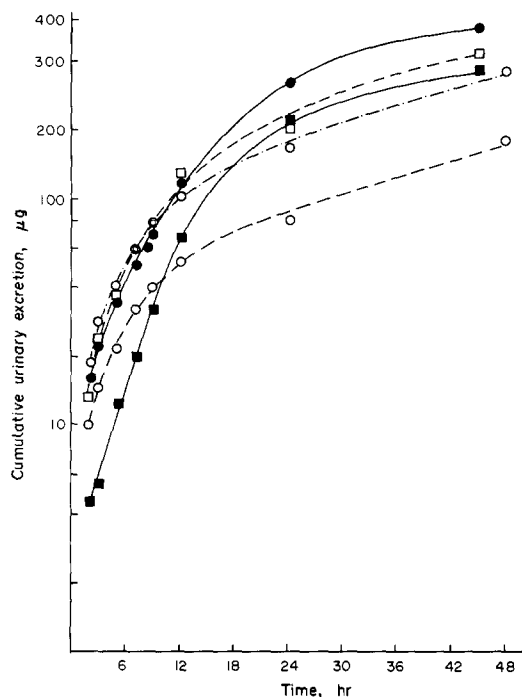


Fig. 2. Effect of deuteration on the urinary excretion of hydroxylated metabolites of imipramine following oral administration. Animals received a single oral administration of either imipramine or imipramine- d_7 and urine samples from five animals were pooled together and analysed. Values represent total metabolite, i.e. including the glucuronic acid conjugates. (●—●), 2-Hydroxydesmethylimipramine; (□—□), 2-hydroxyimipramine- d_7 ; (■—■), 2-hydroxyimipramine; (○—○), 2-hydroxydesmethylimipramine- d_7 ; (○—○), 2-hydroxydesmethylimipramine- d_4 .

Table 5. Effect of deuteration on the pharmacological properties of imipramine; the charcoal meal test

Treatment	Mean % travelled	Inhibition (%)
Control	66 ± 6 (9)	—
Imipramine	51 ± 9 (8)	23
Imipramine- d_7	49 ± 11 (9)	25
Desmethylimipramine	44 ± 10 (9)	33
Atropine sulphate	29 ± 8 (10)	56

Results are presented as means ± S.D. for the number of determinations shown in parentheses.

$P < 0.001$ for all groups when compared with controls

Urinary analysis following administration of imipramine and the d_7 -analogue shows that the amount of 2-hydroxyimipramine excreted is not affected by deuteration (Fig. 2). In contrast, the urinary excretion of 2-hydroxydesmethylimipramine- d_4 was lower than the excretion of 2-hydroxydesmethylimipramine or its d_7 -analogue, reflecting the stability of the N -CD $_3$ group. Furthermore, the urinary excretion of didesmethylimipramine- d_4 and desmethylimipramine- d_4 were lower than those of their non-deuterated analogues (Fig. 3). Finally, the urinary excretion of unchanged deuterated imipramine is

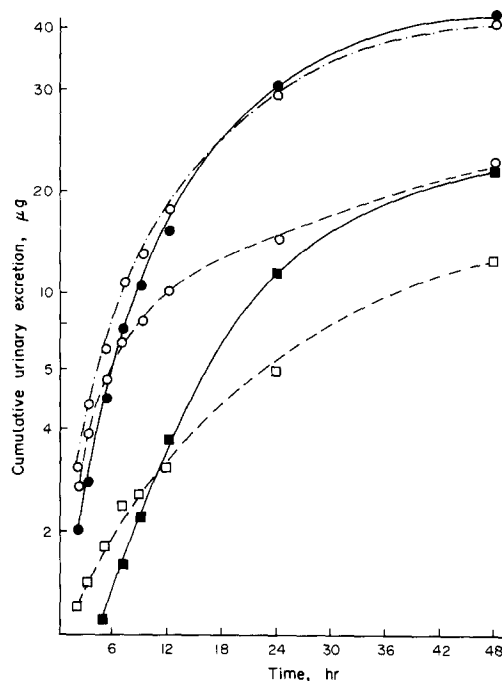


Fig. 3. Effect of deuteration on the urinary excretion of demethylated metabolites of imipramine following oral administration. Animal pretreatment and urinary analysis were carried out as in Fig. 2. (●—●), Desmethylimipramine; (□—□), desmethylimipramine- d_7 ; (○—○), desmethylimipramine- d_4 ; (■—■), didesmethylimipramine; (□—□), didesmethylimipramine- d_4 .

Table 6. Effect of deuteration on the pharmacological properties of imipramine; direct effects on the isolated rabbit jejunum

Concn of test compound (10 ⁻⁶ M)	Percentage decrease in pendular movement	
	Imipramine	Deuterated imipramine*
5	22 (2)	21 ± 2 (4)
7.5	26 ± 1 (2)	25 ± 1 (4)
10	33 ± 5 (5)	35 ± 5 (11)
15	38 (1)	37 ± 1 (2)
20	43 ± 3 (2)	44 ± 3 (8)
25	57 (1)	54 ± 3 (3)
50	69 ± 1 (2)	68 ± 2 (8)

Results are expressed as the means ± S.D. for the number of determinations shown in parentheses.

* Although all three deuterated analogues were administered individually, as no difference was observed between them, these results have been pooled.

higher than that of the unlabelled drug (Fig. 4). These differences in the rate of demethylation may be quantitatively determined as the isotopic fractionation of the N -methyl-deuterated forms, which occurs during chromatography, leads to complete separation of the deuterated and non-deuterated forms.

No significant differences in the pharmacological properties of the deuterated imipramines from those of imipramine were observed (Tables 5–7).

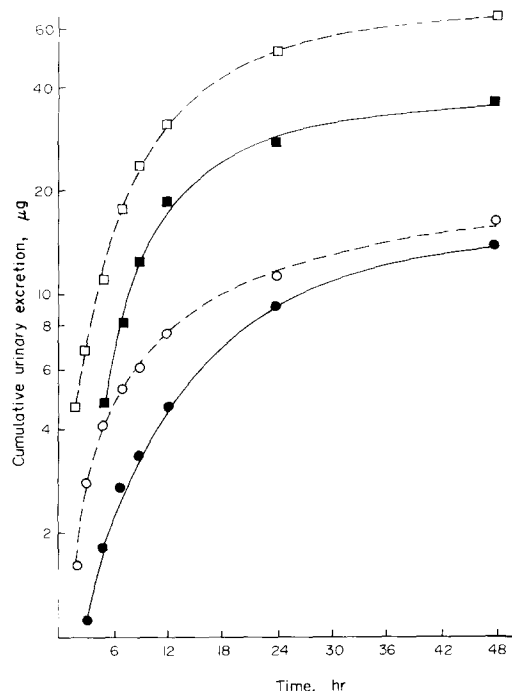


Fig. 4. Effect of deuteration of imipramine on the urinary excretion of imipramine *N*-oxide and unchanged drug. Animal pretreatment and urinary analysis were carried out as in Fig. 2. (□—□), Imipramine- d_7 *N*-oxide; (■—■), imipramine *N*-oxide; (○—○), imipramine- d_7 ; (●—●), imipramine.

DISCUSSION

Imipramine is a highly lipophilic compound and is rapidly absorbed from the gastrointestinal tract and distributed into the various tissues, the highest concns being found in lung, kidney and liver [17]. It is metabolised by the hepatic mixed-function oxidase system into some 20 hydrophilic and lipophilic metabolites [18]. In the present study imipramine was eliminated with a biological t_1 of nearly 3 hr, similar to values previously reported [8]. Saturation kinetics were not observed in the present study, contrary to a previous report [9]. Imipramine had a large V_D in the rat (201 kg^{-1}) indicating that the compound is localised in certain tissues; in humans, imipramine is extensively bound to tissue proteins [9, 10]. Imipramine is eliminated with a total systemic Cl of $85 \text{ ml min}^{-1} \text{ kg}^{-1}$ which, when compared to a hepatic blood flow of $70 \text{ ml min}^{-1} \text{ kg}^{-1}$ [19], indicates that the elimination is largely dependent on the rate of blood flow. Following oral administration, the bioavailability of imipramine was very poor (4%). As imipramine is completely absorbed through the gastrointestinal tract [20, 21] these findings indicate that imipramine undergoes very extensive first-pass metabolism. Similar findings were reported for man [20].

Deuteration of imipramine resulted in a small but significant isotope effect of 1.33 on *N*-demethylation, the magnitude of which is consistent with those reported for similar reactions. Aromatic hydroxyl-

Table 7. Effect of deuteration on the pharmacological properties of imipramine; potentiation of noradrenaline activity

Concn of test compound (10^{-5} M)	Percentage decrease in pendular movement	
	Imipramine	Deuterated imipramine*
0.63	20 ± 5 (2)	18 ± 4 (2)
1.25	20 ± 3 (4)	20 ± 3 (4)
2.50	39 ± 1 (3)	41 ± 7 (4)

Results are expressed as the means \pm S.D. of the % decrease in pendular activity due to noradrenaline ($2.5 \times 10^{-8} \text{ M}$) in the presence of test compound (added first) but corrected for the initial response to this test compound. The number of determinations is given in parentheses.

* Results for individual deuterated analogues have been combined.

ation of imipramine was unaffected by deuteration. The isotope effect led to a slower rate of systemic Cl and a longer plasma t_1 but had no effect on the V_D . When orally administered, imipramine- d_3 achieved a greater bioavailability than the non-deuterated analogue.

Imipramine is metabolised in the rat by three independent pathways, *N*-oxidation to imipramine *N*-oxide, aromatic hydroxylation to 2-hydroxyimipramine, and *N*-demethylation to desmethylinipramine [17, 22]. The latter reaction occurs very readily and desmethylinipramine appears in the blood minutes after imipramine administration [17]. Desmethylinipramine may also be hydroxylated [23], or further demethylated to the didesmethylimipramine. In man further demethylation of desmethylinipramine is a minor pathway, as in the rat, the major pathway being hydroxylation, predominantly at the 2-position with a lesser amount at the 10-position [24, 25]. The isotopic fractionation which occurred during chromatography led to complete separation of the *N*-methyl-deuterated compounds from their non-deuterated analogues and made possible the determination of the relative rates of removal of the CH_3 and CD_3 groups. This phenomenon of isotopic fractionation has been observed by other workers [13] and is presumably the result of the stronger binding of the deuterated, more basic, form to the weakly acidic hydroxyl groups of silica, leading to longer retention times. Urinary excretion of demethylated metabolites of imipramine shows that the excretion of the d_4 -metabolites is lower than those of the d_3 -analogue and the non-deuterated drug, and demonstrate once again an isotope effect with a magnitude of about 2. As only one of the methyl groups is deuterated this is in agreement with the overall isotope effect of 1.33 observed *in vivo*. As expected, no switching of metabolic pathways was evident, as this is associated with larger isotope effects.

Although isotope effects on *N*-demethylation reactions having a magnitude of <2 have given rise to modified pharmacological properties [26–28], in the present study deuteration had no effect on the activity of imipramine in the screening tests used.

Similar findings were reported with respect to chlorambucil [4]. However, imipramine exhibits multiple pharmacological effects, only one of which was studied in the present work, and the possibility that deuteration of imipramine may affect some of its other pharmacological properties cannot be excluded.

In conclusion, deuteration of an *N*-methyl group of imipramine, but not of the aromatic rings, has been shown to result in an overall isotope effect of 1.33, which decreased the rate of elimination of the drug, but had no effect on its absorption, distribution or those pharmacological properties studied.

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