## Plasma levels of clomipramine and its N-desmethyl metabolite following oral administration of clomipramine in man

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Clomipramine is a tricyclic antidepressant which has been in clinical use for a number of years, however, only limited information is available on blood levels (Faigle & Dieterle, 1973). For this reason, we have determined plasma concentrations of clomipramine together with its *N*-desmethyl metabolite following oral administration of single and multiple doses of clomipramine in man. Analysis of plasma samples was carried out using a modification of the double radio-isotope derivative technique described by Riess (1974) for the quantitative estimation of maprotiline in body fluids.

Five healthy male volunteers received a single oral dose of clomipramine (50 mg) after being fasted overnight. Venous blood samples were collected before and at various times up to 48 h after dosing. Clomipramine appeared rapidly in the plasma and reached peak levels between 2.0 h ($37.1 \pm 10.4$ (s.e. mean) ng/ml) and 4.0 h ($38.1 \pm 7.8$ ng/ml). The mean value of individual peak plasma levels was 44.8 ng/ml (range 22.5–64.6 ng/ml). On the other hand, desmethylclomipramine was not detected in the plasma until 1.0 h after dosing and reached maximum concentrations between 4 and 24 h of 0.5–12.0 ng/ml (mean 5.0 ng/ml). Both parent drug and metabolite were still detectable at 48 h indicating relatively long plasma half-lives for both substances.

In a multi-dose study carried out in nine patients diagnosed clinically as endogenous depressives, clomipramine (25 mg) was administered orally three times daily for four weeks. Venous blood samples were collected immediately prior to the first dose and at 7, 14 and 28 days. Steady-state plasma levels of clomipramine were reached at day 7 and mean individual values ranged from 21.4 to 64.2 ng/ml (mean 38.6 ng/ml). In contrast, mean plasma levels of desmethylclomipramine continued to rise during the treatment period from $48.9 \pm 8.4$ ng/ml at day 7 to $68.7 \pm 17.1$ ng/ml at day 28.

Marked individual variation in the ratio between the tertiary amine and its secondary amine metabolite was noted in the patient study indicating the varying abilities of individuals to metabolize clomipramine. In the majority of patients, plasma levels of metabolite were greater than parent drug and since desmethyl-clomipramine possesses biological activity (Sigg, Soffer & Gyermek, 1963; Carlsson, Corrodi, Fuxe & Hökfelt, 1969) it may be a major contributory factor in the overall antidepressant effect of administered clomipramine.

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## Inducing dependence by a single administration of morphine in rats

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Studies on acute dependence in rodents have chiefly centred on antagonist-induced jumping in morphine treated mice, by which some workers claim to have assessed dependence following a single injection of opiate (Cheney & Goldstein, 1971; Smits, 1975). However, the validity of such a measure has been disputed (Barthelemy & Jacob, 1972; Kosersky, Harris & Harris, 1974). A conditioned aversion technique, which has been shown to permit reliable assessment of dependence in rats receiving low doses of morphine (Pilcher & Stolerman, 1975) has now been employed to investigate single dose effects.

Rats were adapted to drinking their daily fluid intake in two sessions totalling one hour. The first of