J. Pharm. Pharmacol. 1982, 34: 45–46
Communicated June 4, 1981

0022–3573/82/010045–02 $02.50/0

A study on the metabolism of dipropylacetamide to dipropylacetic acid in rats

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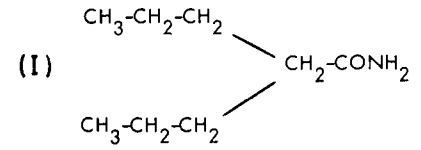
Dipropylacetamide (DPM) is commonly used in clinical practice as an antiepileptic and psychotropic drug. It is a white crystalline powder, slightly alkaline, scarcely soluble in water, with a molecular weight of 143·2, of structure I.



(I)

It is the primary amide of the more widely known dipropylacetic acid (DPA), which, in the form of sodium salt, is largely employed for different forms of epilepsy and as the drug of first choice against 'petit mal' seizures (Simon & Penry 1975; Pinder et al 1977).

After oral administration, dipropylacetamide is subject to degradation to the corresponding acid before reaching the systemic circulation and only traces of unmodified amide have been observed in patients on chronic therapy (Pisani et al 1981). The present experiment was undertaken to investigate if dipropylacetamide degradation in rats occurs in the gastrointestinal tract or systemically.

Materials and methods

Male albino Wistar rats, 300–350 g, were allowed free access to water and a normal laboratory diet. A group of 20 rats were given a single i.m. dose of 20 mg dipropylacetamide (Depamide, Sigma-Tau, Italy), dissolved in 30% ethanol (0·5 ml). Each rat of two other groups of 20 rats received a single oral dose of 40 mg DPM suspended in water. To avoid or decrease the eventual action of the intestinal microflora, one of these groups was pre-treated with neomycin sulphate, dissolved in water, of 15 mg orally every 12 h for 3 days, the last dose being given on the fourth day, 1 h before DPM administration. Five drug-free rats and another five pre-treated with neomycin were used as controls. Rats were decapitated in groups of 5, 15, 30, 45, 60 min after DPM administration. Blood samples were collected and plasma was kept frozen at − 20 °C until analysed. DPM and DPA in plasma were determined by standard gas-liquid chromatographic methods, according to Pisani et al (1979) and Kupferberg (1978), respectively.

Student's *t*-test was used for statistical analysis.

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Results and discussion

No interfering peaks with DPM or DPA and relative internal standards were found in the gas-chromatogram of the control rats. In rats that received DPM, only unmodified amide was found at each time (Table 1). Both DPM and DPA were found in the plasma of rats that had received DPM orally (Fig. 1), DPM being a significantly higher percentage in the group of rats pre-treated with neomycin (Fig. 2). The DPA : DPM ratio increased with time (Fig. 2).

Our results indicate that DPM is metabolized to the corresponding acid in the gastrointestinal tract. No rat that received the drug i.m. had traces of the metabolite in the plasma throughout the duration of the experiment (Table 1). The gastrointestinal tract may play role in the degradation of several drugs by virtue of physicochemical factors, such as acid or enzymatic hydrolysis, or by the action of the bacterial microflora.

The bacterial flora is able to determine a wide variety of metabolic processes, either in rats or in man, including the

Table 1. Dipropylacetamide (DPM) plasma concentrations in rats at different times after i.m. administration of the drug (20 mg).

Time (min)	15	30	45	60
DPM (μg ml^{-1})	75·5 ± 5·4	97·3 ± 7·9	113·2 ± 7·0	165·5 ± 11·4

Values are expressed as the group mean ± s.e.m. In each group (n = 5).

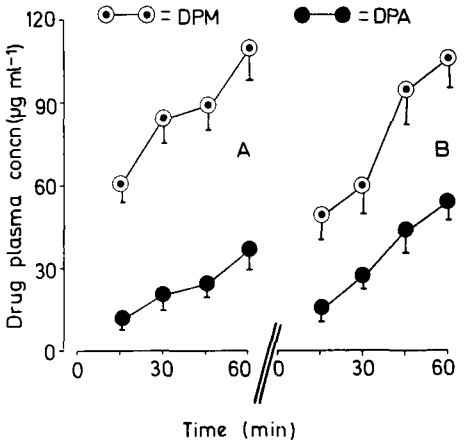

FIG. 1. Dipropylacetamide (DPM) and dipropylacetic acid (DPA) plasma concentrations at different times after a single oral dose of DPM to groups of rats (n = 5) pre-treated (B) or not (A) with neomycin. Values are expressed as means ± s.e.m.

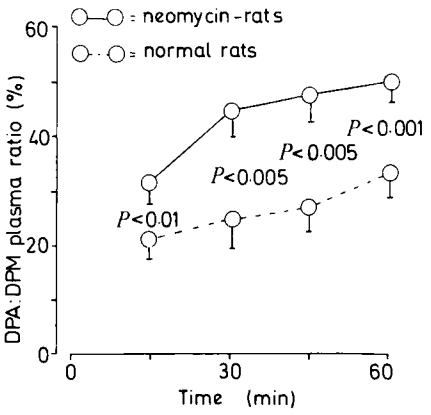

FIG. 2. Dipropylacetic acid (DPA): Dipropylacetamide (DPM) plasma ratios observed at different times after a single oral dose of DPM in groups of rats (n = 5) pre-treated or not with neomycin. Values are expressed as means ± s.e.m.

hydrolysis at the amide linkage of several drugs (for extensive review see Scheline 1968). The degradation of chloramphenicol (Holt 1967), *p*-aminohippuric acid and *p*-acetylaminohippuric acid (Hülsmann & Statius van Eps 1967), methotrexate (Zuherko et al 1969), L-dopa (Sandler et al 1969) and nicotinamide (Tanigawa et al 1970) represent some clear examples of such a type of reaction. In most of the cited studies the suppression of the flora by neomycin resulted, as expected, in a decreased formation of the metabolites. In view of this, our data appear difficult to explain. The acid:amide plasma ratio was higher in rats pre-treated with neomycin than in normal rats (Figs 1 and 2). One hypothesis that might be advanced is that the modifications of the intestinal microflora by neomycin under our experimental conditions have resulted in an increase of resistant bacteria which have been more effective in metabolizing DPM. Although neomycin possesses a broad antibiotic spectrum, several intestinal microorganisms are markedly resistant and others may become so by processes of adaption (Waksman 1953).

It is conceivable also that physicochemical factors, other than bacterial metabolism, may need to be taken into account. Neomycin, for instance, has been shown to alter the intestinal absorption of several substances (Jacobson & Faloon 1961) and could have a similar effect on DPM. Furthermore, it is known that pH plays a considerable role in modifying the solubility of drugs. In the case of DPM, which is a very weak base, the dissolution rate should be optimal in gastric fluids (Gibaldi 1977). Being a basic substance, neomycin increases the pH of the stomach so the dissolution of DPM could be decreased. Both factors could be involved in our experiment, resulting in a prolonged stay of the drug in the gastrointestinal lumen with a consequent greater formation of DPA. The observation that the acid:amide plasma ratio increased with time (Fig. 2) may be easily explained by the fact that the absorption of DPA is slower and the peak concentration is reached later than DPM, because of the time required for the DPM-DPA degradation. In man, DPA concentrations following single doses of amide have been seen to peak later in comparison with the sodium salt (Loiseau et al 1975; Meijer & Kalff 1975; Pisani & Di Perri 1980).

Our data do not allow definitive conclusions to be made on the factors involved in the metabolism of DPM and our hypotheses are conjectural. However, the drug would appear to be metabolized to the active metabolite in the gastrointestinal tract, at least in rats. To our knowledge, this aspect has not been investigated in man, but the clinical observation that patients on DPM therapy experience the same gastrointestinal symptoms experienced during DPA therapy, i.e. nausea, vomiting, changes in appetite (Musolino et al 1980), support the view that DPM degradation also occurs in the gastrointestinal tract in man. The traces of unmodified amide observed in patients (Pisani et al 1981) could represent drug escaping intestinal metabolism.

We wish to thank Dr J. A. Davies for kindly reviewing the manuscript.

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