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Effect of sulthiame on blood and brain levels of diphenylhydantoin in the rat

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THE POSSIBILITY that a drug may interfere with the metabolic degradation or the tissue redistribution of another drug must be always considered when a combined treatment is performed.

Drugs able to decrease the metabolism of diphenylhydantoin (DPH) may exert a negative effect because high DPH plasma and tissue levels may result in nistagmus, ataxia and cerebellar syndroms or they may improve the therapeutic effect in patients able to metabolize DPH at a fast rate.[1–4] Recently Hansen *et al.* described a marked rise in serum DPH levels in epileptic patients after sulthiame, a carbonic anhydrase inhibitor, had been added to the DPH therapy.[5]

This report concerns the effect of sulthiame on plasma and brain levels of DPH in the rat.

Female Sprague–Dawley rats (body wt. 180 g) kept on a standard diet and at constant room temperature (22°) and humidity (60%) were used.

A first group of rats received DPH orally at the dose of 200 mg/kg twice a day (8.30 a.m. and 6.30 p.m.) for 4 days. A second group of rats received DPH as the previous group plus sulthiame at the doses of 600 mg/kg once a day (12.30 a.m.) for 4 days.

At the fifth day both groups received 200 mg/kg of DPH at 8.30 a.m. and were then sacrificed 4 hr later.

DPH plasma and brain levels were determined according to Wallace's[6] method with several modifications.[7]

The results are summarized in Table 1.

TABLE 1. EFFECT OF SULTHIAME ON DPH PLASMA AND BRAIN LEVELS IN RATS

Treatment	DPH level in plasma (μg/ml ± S.E.)	DPH level in brain (μg/ml ± S.E.)	Ratio plasma/brain
Diphenylhydantoin	22·9 ± 1·5 (11)	17·3 ± 2·1 (11)	1·6 ± 0·2
Diphenylhantoin + sulthiame	21·3 ± 1·7 (12)	24·9 ± 2·3* (12)	0·9 ± 0·1*

Diphenylhydantoin group received 200 mg/kg of DPH twice a day for 4 days. The other group received DPH as the control group plus 600 mg/kg of sulthiame once a day for 4 days. On day 5, 4 hr after DPH administration, both groups were sacrificed. In parentheses the number of determinations.

* $P < 0.025$.

The plasma DPH levels of the combined treatment group did not differ from the control group levels, but the DPH brain levels were significantly higher ($P < 0.025$) in the DPH–sulthiame group than in the group treated only with DPH.

These findings may explain several clinical investigations showing that sulthiame was not very active per se but it was effective in improving the therapeutic effect of other anticonvulsant drugs and in particular DPH.[8–16]

Whether the increased concentration of DPH in the brain after sulthiame association is due to a metabolic inhibition of the hydroxylation of DPH or to a modification of DPH redistribution for the tissue acidosis induced by sulthiame[17] remains to be established.

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Species differences in diazepam metabolism—I. Metabolism of diazepam metabolites*

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THE DISTRIBUTION and metabolism of *N*-demethyldiazepam and *N*-methyloxazepam have been studied in rats and in mice, after i.v. injection of these drugs (5 mg/kg). The levels of the compounds administered and their disappearance are similar in blood, brain and adipose tissue of rats and mice.

The accumulation of oxazepam coming from metabolization of both the parent compounds is observed in mice but not in rats.

Evidence is presented for the more rapid disappearance of oxazepam from rat than from mouse tissues.

Previous studies have shown that diazepam exerts a longer lasting anticonvulsant activity in mice than in rats.[1] In order to explain this species difference, the brain levels of diazepam and its metabolites were investigated.[2] These *in vivo* studies have shown that the level of diazepam is similar in both species, while there is an accumulation of *N*-demethyl metabolites in mice, but not in rats.

Since the *N*-demethyl metabolites of diazepam, namely *N*-demethyldiazepam and oxazepam, exert an anticonvulsant activity comparable to that of diazepam[1–3] these biochemical findings may explain why in mice the anticonvulsant activity of diazepam is longer lasting than in rats. Further studies were carried out *in vitro* considering the diazepam is *N*-demethylated and hydroxylated in the reticulum endoplasmic system of the liver[4, 5] in order to observe possible differences between rats and mice. By using liver microsomal preparations it was found that the mouse liver microsomes metabolize

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