Preliminary pharmacological study of N,2-dimethyl,2-(p-aminophenyl) succinimide

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Aminoglutethimide is the p-aminophenyl derivative of the hypnotic drug glutethimide. It was available as an anti-epileptic compound until 1966, when it was withdrawn because of adverse drug reactions including several endocrine effects. These latter effects were associated largely with an inhibition by the drug of adrenal steroid biosynthesis. Because of this activity, aminoglutethimide is being evaluated in patients with excessive cortisol and aldosterone production (Hughes & Burley, 1970). We have synthesized p-aminophenyl derivatives of a number of substituted glutarimides and succinimides with a view to determine their pharmacological activity and potential therapeutic value. The present report describes some pharmacological properties of one of these compounds, N,2-dimethyl,2-(p-aminophenyl) succinimide, (aminomethsuximide).

The compound was synthesized by the nitration and subsequent reduction of N,2-dimethyl, 2-phenylsuccinimide, (methsuximide). Chemical structure and purity were confirmed by elemental analysis, i.r., u.v. and n.m.r. analysis and mass spectrometry.

Anticonvulsant activity of aminomethsuximide and methsuximide (both at 50 mg/kg i.p.) was determined in male mice and rats. Both compounds exhibited anti-leptazol activity. The response of mice, in groups of six, to leptazol (100 mg/kg s.c.) was expressed as a seizure severity score and the area under the response/time (to 6 h) curve was taken to represent the overall effect. On this basis, aminomethsuximide and methsuximide reduced seizure activity by 25.9 and 35.4% respectively and the times of maximum effect were at 1 and 4 h respectively for these compounds. In rats (groups of ten) leptazol was infused i.v. at a constant rate to determine the minimum dose inducing clonic convulsion (Orloff, Williams & Pfeiffer, 1949). Anticonvulsant activity, expressed as percentage increase in threshold dose of leptazol over controls, was 20% and 73% respectively, 1 h after administration of aminomethsuximide and methsuximide. At the above doses, these succinimides did not protect mice against maximal electroshock. The intermediate compound, N,2-dimethyl,2-(p-nitrophenyl) succinimide (50 mg/kg i.p.) was inactive in all of these tests.

In male rats (160 g; six per group) receiving three daily doses of aminomethsuximide (50 mg/kg i.p.) there was a significant ($P < 0.001$) increase in adrenal weight (mg of adrenal pairs: 21.3 ± 2.05 treated, 16.8 ± 1.83 control) and a significant ($P < 0.001$) decrease in adrenal corticosterone concentration (μg/50 mg adrenal: 3.57 ± 1.09 treated, 7.16 ± 0.71 control). Thin-layer chromatography of adrenal extracts indicated that there was a higher concentration of cholesterol in glands from aminomethsuximide-treated rats than controls. Histological examination of the adrenals from the treated animals showed the presence of extensive fatty vacuolation of the zona fasciculata. On the same dose schedule, methsuximide did not produce any of these effects in rats. However, aminoglutethimide (150 mg/kg i.p.) given to rats for three days caused a fall in corticosterone content of a similar order to that following administration of aminomethsuximide and produced similar changes in adrenal histology. It is concluded that aminomethsuximide has an inhibitory action on adrenal steroidogenesis and that further investigation of the endocrine effects of the compound would be worthwhile.

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References

HUGHES, S.W.M. & BURLEY, D.M. (1970). Aminoglutethimide: a 'side-effect' turned to therapeutic advantage. *Postgrad. med. J.*, **46**, 409-416.

ORLOFF, M.J., WILLIAMS, H.L. & PFEIFFER, C.C. (1949). Timed intravenous infusion of metrazol and strychnine for testing anticonvulsant drugs. *Proc. Soc. exp. Biol. Med.*, **70**, 254-257.