PHARMACOLOGICAL STUDIES ON N-DESMETHYLCLOMIPRAMINE

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Following oral administration of the tricyclic antidepressant clomipramine, extensive metabolism by hepatic microsomal enzymes yields a number of breakdown products, perhaps the most important of which is N-desmethylclomipramine. This metabolite has been detected in the plasma of volunteers who have received a single oral dose of clomipramine (Jones & Luscombe, 1976) and in multidose pharmacokinetic studies has been found to reach plateaux levels which are almost without exception greater than those of the parent compound by a factor of between two and three (Jones & Luscombe, 1977). The question was therefore asked as to whether N-desmethylclomipramine possesses pharmacological activity in its own right and thus contributes to the clinical efficacy of clomipramine therapy.

Attempts have now been made to determine whether N-desmethylclomipramine possesses antidepressant activity using animal models such as reversal or prevention of reserpine-induced hypothermia, prevention of oxotremorine-induced hypothermia - suggested as predictive in animals of an antidepressant effect in man, and the immobility-swim test (Porsolt et al., 1977). Groups of 10 male albino mice (18-22g) were treated intraperitoneally with reserpine (2.5mg/kg) three hours before administration of N-desmethylclomipramine (10mg/kg) or saline (control) in the case of reversal experiments and one hour after its administration in the case of preventative tests. In both instances, N-desmethylclomipramine was found to be not only active but was more potent than the parent compound and other tricyclic antidepressants. For example, comparative ED_{50} values of drugs in reversing reserpine-induced hypothermia were desmethylclomipramine 4mg/kg, clomipramine 13mg/kg, desmethylimipramine 9mg/kg and imipramine 11mg/kg. Similar results were obtained in prevention of reserpine-induced hypothermia tests.

In the oxotremorine test, antidepressant drugs (10mg/kg) or saline was injected subcutaneously into groups of 10 mice, one hour before oxotremorine (0.5mg/kg i.p) and oesophageal temperature measured every 0.25 h for up to 3 h. Again, desmethylclomipramine was found to be very potent in preventing oxotremorine-induced hypothermia. Percentage reversal of body temperature was 81% for desmethylclomipramine, 53% clomipramine, 80% desmethylimipramine and 49% imipramine.

The immobility-swim test provides a useful screening method which is not a pharmacological interaction and which identifies many atypical antidepressants which hitherto have not reacted on any of the traditional animal models available for antidepressant screening. Groups of 10 male albino mice (20-25g) were injected intraperitoneally with the antidepressant (10mg/kg) under investigation one hour prior to being placed in a tank of water for six minutes. The movement time was recorded for the latter 4 minutes and compared with saline controls, which show greatest immobility - suggested as being analogous to stress or depression. Results show desmethylclomipramine is a potent antagonist of immobility (change from control 54.2%) compared with other antidepressants (clomipramine 43.5%; desmethylimipramine 28.3%; imipramine 30.9%).

The present studies indicate that desmethylclomipramine possesses strong antidepressant activity in a number of tests used in screening for antidepressant activity.

Jones, R.B. & Luscombe, D.K. (1976) Br. J. Pharmac. 57: 430P
Jones, R.B. & Luscombe, D.K. (1977) Postgrad. Med. J. 53 (Suppl. 4): 63-76
Porsolt, R.D. et al. (1977) Arch. Int. Pharmacodyn. 229: 327-336