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N-METHYLATION OF MAPROTILINE IN DEBRISOQUINE/MEPHENITOIN-PHENOTYPED DEPRESSIVE PATIENTS

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Enzymatic N- and O-methylation of amines or phenols are considered to be detoxificating processes. However, the presence of the antidepressants imipramine (1) and amitriptyline (2) has been reported in some patients, after medication with desipramine and nortriptyline, respectively. On the other hand, there is strong evidence for a deficient hydroxylation of these tricyclics in poor metabolizers of debrisoquine.

A study was designed to test the hypothesis whether N-methyl-action of secondary amines occurs preferentially in subjects unable to eliminate the drug by hydroxylation (PM). To avoid artefacts by non-compliance of the patients, Mp was chosen for the treatment, as the corresponding tertiary amine is not commercially available, in contrast to the above-mentioned drugs.

PATIENTS, MATERIAL AND METHODS

51 and 31 depressive patients hospitalized in Zurich or Lausanne, respectively, were submitted to the debrisoquine/mephenytoin-test (3,4) after a brief wash-out period and then treated with 150 mg maprotiline (Mp) daily for ten days. During this period, investigations were carried out to compare clinical and bio-chemical parameters (Bosshart et al., in preparation). After one and ten days of treatment, blood was collected for the analysis by GC-NPD and GC-EI-MS of the tertiary amine N-methyl-Mp, Mp and desmethyl Mp in plasma. The metabolites were separated by capillary GC in the splitless mode, on a 25 m fused silica SE-54 column and analysed quantitatively by MS, by a method described for amitriptyline (5,6). Calibration curves were established for N-methyl-Mp in the range 2 - 10 ng/ml, whereby the following m/z were monitored: 58.2, 291.2.

RESULTS AND DISCUSSION

The results of the mephenytoin/debrisoquine test were obtained from 50 patients in Zurich and 30 patients in Lausanne. Three of the first group were P.M. of debrisoquine and one of mephenytoin, while the corresponding values were two and one for the second group. After a ten days treatment, the levels of Mp in the 82 depressives were 116 ± 47 ng/ml (mean±s.d.). There was no difference between the groups. These preliminary results show that poor metabolism of debrisoquine is not associated with high levels of Mp. Moreover, N-methyl-Mp was absent (i.e. < 2 ng/ml) in the plasma of all patients, as well in P.M. as in E.M.

Thus, the results of this study performed with Mp in two carefully selected groups of patients and using selective and sensitive methods do not confirm previous reports with other antidepressants. Besides the already mentioned possible reasons for these differences, it is important to note that N-methylation is species but also substrate-dependent (7).

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REFERENCES
1. N. Narasimhachari, J.J. Saady, A.Joseph, P.Ettigi and R.O. Friedel, J. Clin. Pharmac. 2, 413 (1982).
2. M. V. Rudorfer and E. Robins, Am. J. Psychiat. 138, 982 (1981).
3. B. Dick, A. Küpfer, J. Molnar, S. Braunschweig and R. Preisig, Schweiz. med. Wschr. 112, 1061, (1982).
4. A. Küpfer, P. Desmond, S. Schenker and R. Branch, Pharmacologist 21, 173, (1979).
5. P. Baumann, B. Dick, L. Koeb, M. Perey, J. Schöpf and D. Tinguely, in Forschungen zur biologischen Psychiatrie (Eds. A. Hopf and H. Beckmann), p. 298, Springer, Berlin (1984).
6. P. Baumann, J.-M. Gaillard, M. Jonzier-Perey, C. Gerber and C. Bouras, Psychopharmac. (in press)
7. U. K. Walle, M. J. Wilson and T. Walle, Biomed. Mass Spectrometry 8, 78, (1981).