Plasma concentrations of nortriptyline and its 10-hydroxy metabolite in depressed patients—relationship to the debrisoquine hydroxylation metabolic ratio

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In 20 depressed patients treated with nortriptyline (NT) there was a significant relationship between the plasma concentration of NT and the debrisoquine metabolic ratio ($r_s = 0.77$; $P < 0.01$). (The debrisoquine test was performed after stopping NT treatment). This is in agreement with the hypothesis that the hydroxylations of NT and debrisoquine are mediated by similar enzymatic mechanisms. In contrast there was no significant relationship between the debrisoquine metabolic ratio and the plasma concentrations of the active metabolite 10-hydroxy-nortriptyline. In 11 of the patients the debrisoquine metabolic ratio was significantly higher during than after NT treatment. This may be due to an inhibition of the debrisoquine hydroxylation by NT.

Keywords debrisoquine nortriptyline hydroxylation depression

Introduction

Plasma concentrations of tricyclic antidepressants vary extensively between patients treated with similar doses. This is explained by inter-individual differences in the rate of metabolism. For some antidepressants, e.g. nortriptyline (NT), clinical effects are related to the plasma concentrations achieved (Potter et al., 1981).

Studies in healthy volunteers have shown that E-10-hydroxylation, the major metabolic pathway of NT, is regulated in a similar manner to the polymorphic 4-hydroxylation of debrisoquine (Mellström et al., 1981; Woolhouse et al., 1984). It has also been found that the debrisoquine hydroxylation phenotype ratio predicts the steady state plasma concentration of desipramine obtained in patients on a fixed dosage schedule (Bertilsson & Åberg-Wistedt, 1983).

The purpose of the present study was to investigate whether the debrisoquine hydroxylation test (Mahgoub et al., 1977) may be used to predict steady-state plasma concentrations of NT and its 10-hydroxy metabolite (10-OH-NT) during treatment with NT. The interest to predict and to measure plasma concentrations of 10-OH-NT stems from the finding that this metabolite is almost as potent as the parent drug in inhibiting the neuronal uptake of noradrenaline (Bertilsson et al., 1979). In addition, in vitro receptor binding studies indicate that 10-OH-NT might have much less anticholinergic side effects than NT (Wagner et al., 1984). We are therefore in the process of evaluating the clinical pharmacology of this metabolite.

Preliminary data have been presented at the Third International Meeting on Clinical Pharmacology in Psychiatry in Odense, Denmark, 1982 (Bertilsson et al., 1983) and at the 13th CINP Congress in Jerusalem, Israel, 1982 (Nordin et al., 1983).

Methods

Twenty patients were treated with NT (Sensaval®, Pharmacia) (17 obtained a dose of 50 mg three times daily; the other three were treated...
with doses of 50 mg twice daily, 25 + 50 mg/day and 125 mg twice daily) for depression during at least 3 weeks. The kinetics of NT have been shown to be dose independent (Alexanderson, 1983) and plasma drug concentrations in this study were expressed per dose unit. All patients were phenotyped with respect to debrisoquine hydroxylation after stopping the NT-treatment. In 11 of the patients the debrisoquine test was also performed during NT treatment.

After oral administration of 5 or 10 mg debrisoquine (Declinax®, Roche) in the morning, urine was collected for 6 h and the ratio between debrisoquine and its metabolite, 4-OH-debrisoquine, was measured (Mellström et al., 1981). When the doses of 5 and 10 mg of debrisoquine were given to 11 healthy subjects the metabolic ratios obtained were not significantly different (unpublished observation) which confirms the results of Sloan et al. (1983).

Blood samples were drawn in heparinized Venoject tubes before the morning dose of NT was given. From each patient three samples were drawn during steady state of NT. Concentrations reported are the means.

Plasma concentrations of NT, unconjugated 10-OH-NT and the total [unconjugated + conjugated measured after acid hydrolysis (Borg à & Garle, 1972)] 10-OH-NT were determined by mass fragmentography (Borg à et al., 1972). Trideuterium labelled species of both NT and 10-

OH-NT served as internal standards for the measurements.

The study was approved by the Ethics Committee of the Huddinge Hospital. Patients and healthy subjects gave their informed consent.

Results

There was a pronounced variation between the 20 patients in the plasma concentrations of NT (186–960 nmol/l), unconjugated 10-OH-NT (313–1072 nmol/l) and total 10-OH-NT (1158–3319 nmol/l).

The steady-state plasma concentration of NT (per dose unit) was significantly related to the debrisoquine metabolic ratio ($r_s = 0.77; n = 20; P < 0.01$) (Figure 1). In contrast there was no significant relationship between either the unconjugated 10-OH-NT in plasma ($r_s = -0.03; n = 20; NS$) or total 10-OH-NT in plasma ($r_s = -0.31; n = 16; NS$) and the debrisoquine metabolic ratio (Figure 1).

The debrisoquine metabolic ratio was significantly higher during than after NT treatment [the Wilcoxon matched-pairs signed-ranks test (Siegel, 1956); $n = 11; P < 0.005$, Figure 2]. The recovery of the debrisoquine dose (as debrisoquine and its 4-hydroxymetabolite) was significantly higher during (43.3 ± 14.2%) than after NT treatment (31.0 ± 8.3%) [the Wilcoxon

![](Figure 1) Mean steady-state plasma concentrations of NT, unconjugated 10-OH-NT and total 10-OH-NT and the debrisoquine metabolic ratio in 20 patients. The debrisoquine test was performed after stopping the NT treatment.
The metabolic ratio


The lack of correlation between the debrisoquine metabolic ratio and the plasma concentrations of 10-OH-NT (Figure 1) indicates that the 10-OH-NT concentrations are not only determined by the rate of hydroxylation but also by further elimination (metabolism and excretion). Very little of the formed 10-OH-NT seems to be further oxidized but a major portion is conjugated (Alexanderson & Borgå, 1973). The renal excretion of conjugated but not the unconjugated 10-OH-NT is dependent on normal kidney function (Dawling et al., 1982). Thus the debrisoquine test cannot be used to predict plasma concentrations of 10-OH-NT.

A higher debrisoquine metabolic ratio was obtained when the test was performed during compared to after NT-treatment (Figure 2). This shows that concomitant NT treatment inhibits the hydroxylation of debrisoquine. The two drugs probably compete for a common metabolizing enzyme. In analogy to this the hydroxylation of debrisoquine in human liver microsomes is inhibited by NT (von Bahr et al., unpublished observation). Previously it has also been shown that desipramine inhibits the metabolism of debrisoquine in rat liver microsomes (Mitchell et al., 1970).

Interestingly we found a higher recovery of the debrisoquine dose during than after NT treatment. Debrisoquine is taken up by the presynaptic noradrenaline pump and stored in granules (Simpson, 1980). This intraneuronal storage of debrisoquine thus represents a deep compartment for the drug. During NT-treatment the uptake of debrisoquine might be inhibited and more of the drug or metabolite excreted in urine. In healthy subjects given a single dose of amitriptyline the accumulation of debrisoquine by platelets was inhibited (Silas et al., 1980).

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Figure 2 The debrisoquine metabolic ratio determined during and at least one month after stopping NT treatment. The metabolic ratio was significantly higher during than after NT treatment. (The Wilcoxon matched-pairs signed-ranks test *n* = 11; *P* < 0.005).

matched-pairs signed-ranks test (Siegel, 1976); *n* = 11; *P* < 0.025.

Discussion

These results suggest that the debrisoquine hydroxylation test might be used to predict steady-state plasma concentrations of the parent drug during NT treatment. This confirms previous studies showing that the rate of hydroxylation determines plasma NT concentrations (Alexanderson & Borgå, 1973). The hydroxylations of NT and debrisoquine were thus closely related in our patients. Indications that the hydroxylations of these two drugs are mediated by the same subunit of the cytochrome P-450 system have previously been obtained from studies in healthy volunteers (Mellström et al., 1981) and in human liver microsomes (von Bahr et al., 1983).


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