CSF and plasma levels of nortriptyline and its 10-hydroxy metabolite

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After 3 weeks' nortriptyline (NT) treatment the mean plasma concentration of its 10-hydroxy metabolite (10-OH-NT) (599 ± 207 nmol l⁻¹) was higher than that of the parent drug (433 ± 199 nmol l⁻¹) in 25 depressed patients. Also in the cerebrospinal fluid (CSF) the mean level of 10-OH-NT (67 ± 20 nmol l⁻¹) was higher than that of NT (39 ± 23 nmol l⁻¹). There was a strong correlation ($P < 0.001$) between the CSF and plasma concentration of both NT ($r = 0.92$) and 10-OH-NT ($r = 0.77$). The interindividual variation in the CSF/plasma ratio of both compounds was small, compared to the variation in plasma levels. These results show that 10-OH-NT passes the blood-brain barrier as it is present in concentrations higher than those of NT in the CSF. 10-OH-NT has previously been shown to be a potent blocker of noradrenaline uptake and to have much less affinity for muscarinic receptors than NT itself. This active metabolite might therefore be a potential antidepressant with less disturbing anticholinergic side-effects.

Keywords nortriptyline hydroxy metabolite depression protein binding

Introduction

Plasma levels of tricyclic antidepressants vary among individuals given fixed dosages of the drug (cf. Sjöqvist *et al.*, 1980). For some tricyclics a relationship between total plasma level and therapeutic effect has been established (Sjöqvist *et al.*, 1980). In order to demonstrate such a relationship a number of prerequisites has to be fulfilled e.g. (a) the degree of protein binding has to be fairly constant both within and between individuals and (b) if the drug has active metabolites they have to be accounted for.

For nortriptyline (NT), a curvilinear relationship between plasma level and therapeutic outcome has been described (Åsberg *et al.*, 1971; Kragh-Sørensen *et al.*, 1976). High plasma levels of NT have also been shown to be associated with side effects (Åsberg *et al.*, 1970). Plasma levels of NT are determined by the rate of 10-hydroxylation in the liver (Alexanderson & Borgå 1973; Mellström *et al.*, 1981). The major

metabolite, 10-hydroxy-nortriptyline (10-OH-NT) has been shown to be about 50% as potent as the parent drug to inhibit the uptake of noradrenaline in rat brain slices (Bertilsson *et al.*, 1979). A preliminary study showed that 10-OH-NT was present in high concentrations both in plasma and cerebrospinal fluid (CSF) (Bertilsson *et al.*, 1979). We have now measured and compared plasma and CSF levels of NT and its metabolite 10-OH-NT in 25 depressed patients. This is to have a firm basis for evaluating the importance of 10-OH-NT for biochemical and clinical effects during NT treatment. This information is also important for studies on 10-OH-NT when given *per se*. Such studies are now in progress.

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.*, 1984).

Methods

Twenty-five depressed patients included according to Feighner's criteria of primary depression (Feighner *et al.*, 1972) were treated with NT (50 mg Sensaval three times daily in 23 patients, 50 mg twice daily in a 58-year-old patient with history of side-effects from tricyclics and 25 mg twice daily in a 75-year-old patient). Before active NT treatment was started placebo was given during 3–7 days. Oxazepam (Sobril) or nitrazepam (Mogadon) were given as occasional doses if needed. At the end of the placebo period and after 3 weeks of NT treatment lumbar punctures were performed by a standardized technique. CSF was collected in the early morning before the patient had risen and after at least 8 h of bedrest and fasting. The lumbar puncture was performed before the morning dose of the drug. The primary aim of the lumbar punctures was to measure amine metabolites in CSF in a study exploring the role of 10-OH-NT for biochemical and clinical effects of NT treatment. This will be reported separately.

The CSF samples were immediately centrifuged and frozen in silanized glass tubes and stored at -20°C until analysis. At the same time as the lumbar punctures blood samples were drawn.

NT and 10-OH-NT were determined in plasma and CSF by mass fragmentography (Borgå *et al.*, 1972). The trideuterium labelled species of both NT and 10-OH-NT served as internal standards for the quantifications. This method measures unconjugated 10-OH-NT (sum of the E- and Z-isomers). The study was approved by the Ethics Committee at the Huddinge University Hospital.

Results

In the 25 patients the mean plasma concentration of NT was $433 \pm \text{s.d. } 199 \text{ nmol l}^{-1}$ (range 102–850 nmol l^{-1}). For 10-OH-NT the corresponding value was $599 \pm \text{s.d. } 207 \text{ nmol l}^{-1}$ (range 280–1045 nmol l^{-1}). The mean CSF concentration of NT was $39 \pm \text{s.d. } 23 \text{ nmol l}^{-1}$ (range 13–98 nmol l^{-1}) and of 10-OH-NT $67 \pm \text{s.d. } 20 \text{ nmol l}^{-1}$ (range 24–131 nmol l^{-1}).

A strong correlation was found between the CSF and plasma levels for both NT ($r = 0.92$; $P < 0.001$; linear regression analysis: $y = 0.11 \times -5.8$) and 10-OH-NT ($r = 0.77$; $P < 0.001$; $y = 0.073 \times +23$) (Figure 1). The ratio between the CSF and plasma concentrations was of a similar

Figure 1 Relationship between CSF and plasma levels of NT (●) and 10-OH-NT (○). NT $r = 0.92$, $P < 0.001$; 10-OH-NT unconjugated $r = 0.77$, $P < 0.001$.

order of magnitude for NT ($9.1 \pm 2.5\%$) (range 4.9–13.6) and for 10-OH-NT ($11.7 \pm 2.6\%$) (range 7.1–17.7), but were significantly different ($P < 0.001$, paired *t*-test). There was no significant correlation between the CSF/plasma ratios of 10-OH-NT and NT ($r = 0.14$). No correlation was found between either the CSF 10-OH-NT and NT levels ($r = 0.30$, NS) or the plasma 10-OH-NT and NT levels ($r = 0.10$, NS).

Discussion

The strong correlation between the CSF and plasma levels of NT ($r = 0.92$) and the small variation in the CSF/plasma ratio (4.9–13.6%) shows that the interindividual variation in protein binding of NT is relatively small. This confirms the study by Kragh-Sørensen *et al.* (1976) who measured the CSF/plasma ratio in 13 patients and found a similar mean ($7.0 \pm 1.8\%$) and range (4.7–11.5%).

The mean plasma level of 10-OH-NT ($599 \pm 207 \text{ nmol l}^{-1}$) was higher than that of the parent drug ($433 \pm 199 \text{ nmol l}^{-1}$). Thus the mean ratio between 10-OH-NT and NT was 1.4 which is identical with that previously reported in an uncontrolled study on 87 patients treated with NT or amitriptyline (Bertilsson *et al.*, 1979).

The levels of 10-OH-NT in CSF were strongly correlated with the plasma levels ($r = 0.77$). The mean CSF/plasma ratio for 10-OH-NT was higher ($11.7 \pm 2.6\%$) than that of NT ($9.1 \pm$

2.5%). The lower degree of protein binding of 10-OH-NT is probably related to its lower degree of lipophilicity. In a preliminary study we found a lower CSF/plasma ratio of 10-OH-NT (range 5.1–5.8%) in three patients with an obsessive-compulsive disorder (Bertilsson *et al.*, 1979). The absence of a correlation between the CSF plasma ratios of the parent drug and the metabolite might indicate that they vary independently, i.e. are at least partly bound to different plasma proteins. The antidepressant imipramine has been shown to be bound to α_1 -acid glycoprotein (orosomucoid) (Piafsky & Borgå, 1977).

In this study we have shown that there is only a small variation in the plasma protein binding of NT and 10-OH-NT. The active metabolite 10-

OH-NT (Bertilsson *et al.*, 1979) is present in high concentrations in both plasma and CSF. It thus passes the blood-brain barrier. If uptake blockade in noradrenergic neurons is a mechanism of action for antidepressant effect the clinical effect of 10-OH-NT ought to be tested. This is especially interesting in the light of its low binding to muscarinic receptors, i.e. it might have very little anticholinergic side effects (Wagner *et al.*, 1984).

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