INCREASE OF α_1 -ACID GLYCOPROTEIN AFTER TREATMENT WITH AMITRIPTYLINE

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Sixteen primary depressive patients were treated for 3 weeks with amitriptyline 150 mg daily. In thirteen patients the plasma level of α_1 -acid glycoprotein (AAG) significantly increased after the treatment but the albumin levels did not change.

Introduction

Despite of its strong anticholinergic action, amitriptyline remains a favoured drug in pharmacotherapy of depression. Pharmacological research on the fate of the drug has been focused on the study of its binding to plasma proteins. Actually, tricyclics are bound to plasma albumin, lipoproteins (Bickel, 1975) and mainly to α_1 -acid glycoprotein (AAG) (Piafsky & Borga, 1977). The aim of this letter is to report the observation, that after administration of amitriptyline, there is an increase of plasma AAG but not of albumin in depressive patients.

Methods

Sixteen primary depressive patients without somatic disease were treated for 3 weeks with 150 mg amitriptyline (Laroxyl®) daily. Benzodiazepines, were given as a comedication in some cases. Weekly plasma amitriptyline and nortriptyline levels were measured in plasma. Albumin and AAG were determined twice, i.e. at the beginning and after 3 weeks of treatment. Albumin was analysed fluorimetrically (Rees *et al.*, 1954) and AAG by immunodiffusion (Behring) in plasma.

Results

Both the initial (74.7 ± 14.3 mg/100 ml) and final (91.6 ± 22.1 mg/100 ml) concentrations (mean $\pm$ s.d.) of AAG were within the normal range (50-140 mg/100 ml). However, for thirteen patients, the level of AAG increased during the pharmacological treatment (Figure 1, amitriptyline-group). This difference was statistically different for the whole group (Student's *t*-test, $t = -4.05$; $P < 0.01$). On the other hand, albumin levels were not affected ($t = 0.99$; NS).

Figure 1 α_1 -acid glycoprotein levels in sixteen control patients and sixteen depressed patients treated with amitriptyline 150 mg daily for 3 weeks. AAG levels were measured before therapy started and after 3 weeks of treatment.

Discussion

Most patients were admitted to the hospital about a week before the beginning of pharmacotherapy. It might have been possible that the result of the study is an artefact due to a modification of dietary habits of the patients. In order to test this hypothesis, sixteen newly admitted patients with varying diagnoses and receiving pharmacological treatments with neuro-

leptics or antidepressives (except amitriptyline) and some with antiparkinson agents were examined on the day of admission and 22 days later for plasma albumin and AAG. In this group (Figure 1; controls), neither AAG ($t = -0.98$; NS) nor albumin ($t = -1.22$) varied significantly during 3 weeks of hospitalisation. Thus, the nutritional status does not explain the difference for AAG in the amitriptyline.

It has recently been shown by Routledge *et al.* (1981) that epileptics treated with phenytoin and other antiepileptic compounds have higher AAG levels in plasma than healthy controls. These authors suppose that this effect is due to the enzyme-inducing properties of antiepileptic drugs, which have been shown previously to lead to an increase of sex hormone binding globulin capacity. It seemed then tempting to explain the increased AAG levels by the same mechanism. This interpretation cannot account for the effect of tricyclics. Indeed, after the administration of amitriptyline for 3 to 6 weeks, amitriptyline and nortriptyline steady-state levels remain stable in patients (Ziegler *et al.*, 1976; Volmat *et al.*, 1977; Robinson *et al.*, 1979; Baumann *et al.*, 1982). Besides, 24 h spot tests are proposed for tricyclics to predict steady state levels. Thus, the drug effect observed in

the present study awaits another explanation than enzyme induction followed by an increase of binding protein.

The clinical interest of this finding lies in the fact that the free drug level represents the therapeutically active concentration, but that in the case of a highly bound drug like amitriptyline, the bound drug reflects the total plasma concentration, which is generally measured. By an increase of the main binding protein, α_1 -acid glycoprotein, total plasma amitriptyline and nortriptyline will rise, and the free fraction but not the free levels of these drugs will decrease. As pointed out by Potter *et al.* (1981), adjusting the dose on the basis of total (instead of free) plasma concentration, one may inadvertently take a patient out of the therapeutic range if that individual has highly atypical protein binding as might occur in inflammatory conditions.

However, the slight increase of AAG observed in this study after amitriptyline will not produce a clinically important effect on the binding of amitriptyline and nortriptyline, and also on their steady-state levels.

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