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Effects of Acute Administration of Zetidoline, a New Antidopaminergic Drug, on Plasma Prolactin and Aldosterone Levels in Man

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Summary. The neuroendocrinological effects of acute oral administration of 20 mg zetidoline, a new antipsychotic drug with antidopaminergic properties, were evaluated in 8 healthy volunteers, by a double-blind, crossover comparison with placebo. Zetidoline significantly increased serum prolactin ($p < 0.01$ at 1–3 h; $p < 0.05$ at 4–6 h). No significant change was observed in blood levels of aldosterone, renin, cortisol, growth hormone and electrolytes, or in blood pressure and heart rate. The data suggest that the drug increases prolactin through blockade of dopaminergic receptors. The lack of change in the aldosterone levels may be evidence against the hypothesis of dopaminergic control of aldosterone secretion.

Key words: zetidoline, prolactin; aldosterone, dopamine, healthy volunteers, pharmacodynamic effects

Zetidoline is a new antipsychotic drug with antidopaminergic activity [1]. The compound has dopamine receptor blocking properties, as suggested by biochemical and pharmacological findings: zetidoline increases striatal levels of homovanillic acid and dihydroxyphenylacetic acid, as well as DOPA concentration following DOPA-decarboxylase inhibition [2], and it antagonizes apomorphine-induced emesis and hypermotility, and morphine-induced running fits [2]. However, unlike classical neuroleptics, such as haloperidol or chlorpromazine, zetidoline shows weak affinity for ^{3}H-spiroperidol-labelled receptors, and does not inhibit striatal dopamine-stimulated adenylate cyclase activity [2]. Since dopaminergic blockade has been reported to increase blood levels of prolactin (PRL) and aldosterone [3, 4], the effects of zetidoline on these and related hormones in normal volunteers have been studied.

Materials and Methods

Eight healthy volunteers, 4 women aged 21–28 years and 4 men aged 24–27 years, who had no history of renal, gastrointestinal, endocrine or cardiovascular disease volunteered for the study. Before entering the study, they underwent careful physical examination, as well as blood and urine tests to assess haemopoietic, hepatic and renal function. Written informed consent was obtained from each individual, and the study was carried out according to the Declaration of Helsinki. The investigation followed a cross-over experimental design, with single oral doses of zetidoline 20 mg and placebo administered under double-blind conditions, on two consecutive sessions each of 1 day, 6 days apart. The subjects were maintained on a constant diet containing 130 mEq sodium and 60 mEq potassium, 1 g protein/kg and 2000 kcal/day throughout each study day and for 5 days preceding it. On the first, third and fifth days before each session, a 24 h urine sample was collected and analyzed for sodium and potassium, to verify electrolyte balance. In each study session, after an overnight fast, the subjects laid supine in a quiet room for 120 min preceding the baseline assessments and throughout the following 6 h. Blood samples (35 ml) were collected through an indwelling catheter inserted into an antecubital vein and maintained patent with a saline infusion, at the time intervals indicated in the figures. At the same times heart rate was measured and arterial blood pressure was recorded with a mercury sphygmomanometer, diastolic pressure being assessed as the Korotkoff Phase V sound. Serum and urine sodium and potassium were measured by

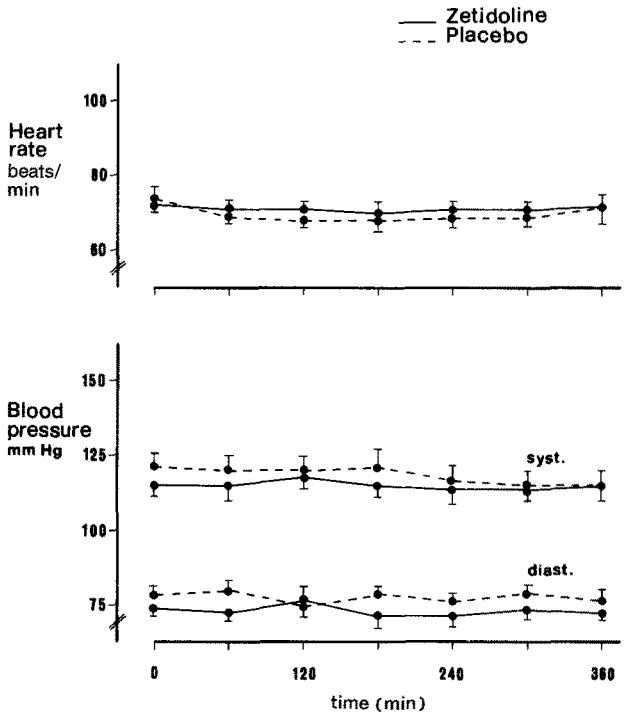

Fig. 1. Effect of zetidoline (20 mg p.o.) and placebo on heart rate and blood pressure in 8 healthy volunteers. Mean ± SEM

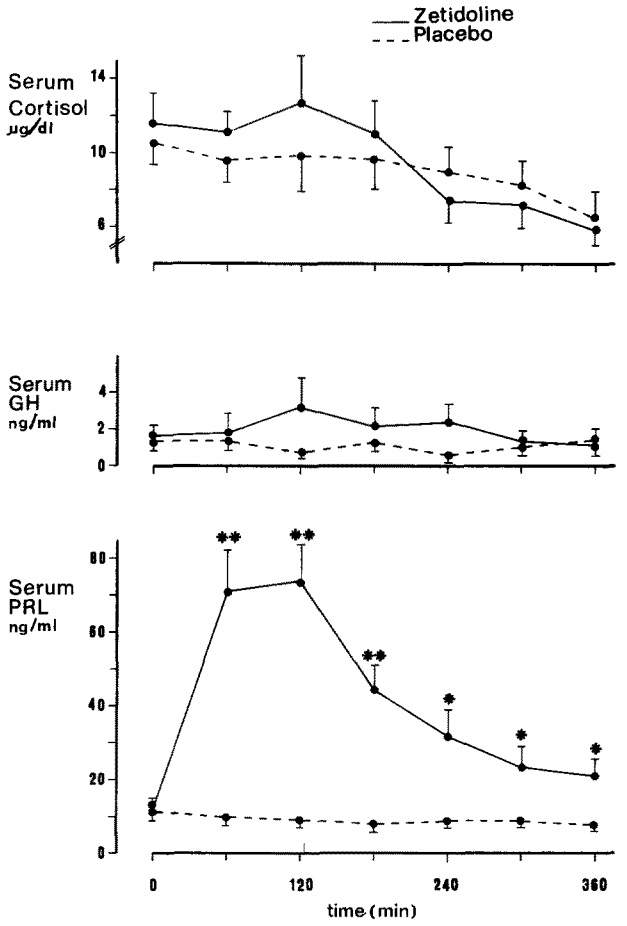

Fig. 2. Effect of zetidoline (20 mg p.o.) and placebo on serum cortisol, growth hormone (GH) and prolactin (PRL) in 8 healthy volunteers. Asterisks indicate significance of differences between zetidoline and placebo: * $p<0.05$; ** $p<0.01$; Mean ± SEM

flame photometry (Corning Model 450). All blood samples for plasma renin activity (PRA) and aldosterone were collected in chilled tubes, with EDTA as anticoagulant, and were centrifuged immediately at 4 °C. PRA, plasma aldosterone and cortisol, and serum PRL and growth hormone (GH) were determined by radioimmunoassay using commercial kits. The methods, assay sensitivity and the intra- and interassay variations have been described [5, 6].

Statistical evaluation of the results was performed by analysis of variance, using a repeated measures (split-plot) model followed by F-testing of the differences between treatments within each time interval; $p<0.05$ was considered significant. Data are shown as the means ± SEM.

Results

The subjects were in sodium and potassium balance, as indicated by the 24 h urinary electrolyte excretion, which closely matched the intake (data not shown).

No significant change in heart rate or blood pressure was observed after zetidoline (Fig. 1). A significant rise in PRL was observed after drug administration ($p<0.01$ at 1–3 h, $p<0.05$ at 4–6 h), from a basal concentration of 11.9 ± 1.9 ng/ml to a peak level of 73.9 ± 10 ng/ml at 120 min (Fig. 2). The PRL increase was greater in the female volunteers: in females PRL was raised from 15.5 ± 2.7 ng/ml to a peak level of 105.2 ± 9.1 ng/ml, while in males PRL was increased from 9.5 ± 1.9 to 74.5 ± 12.7 ng/ml. No significant changes in circulating levels of GH, PRA, aldosterone, cortisol, sodium or potassium were observed after zetidoline administration (Figs. 2, 3).

After zetidoline four subjects exhibited transient drowsiness and restlessness.

Discussion

Biochemical and pharmacological studies [2] show that zetidoline blocks the dopaminergic receptors not linked to adenylate cyclase activity, i.e. the D_2-type receptors, according to Kebabian and Calne [7]. On the basis of the well-known role of dopamine in the inhibitory control of PRL secretion [3], the PRL rise observed after zetidoline administration ap-

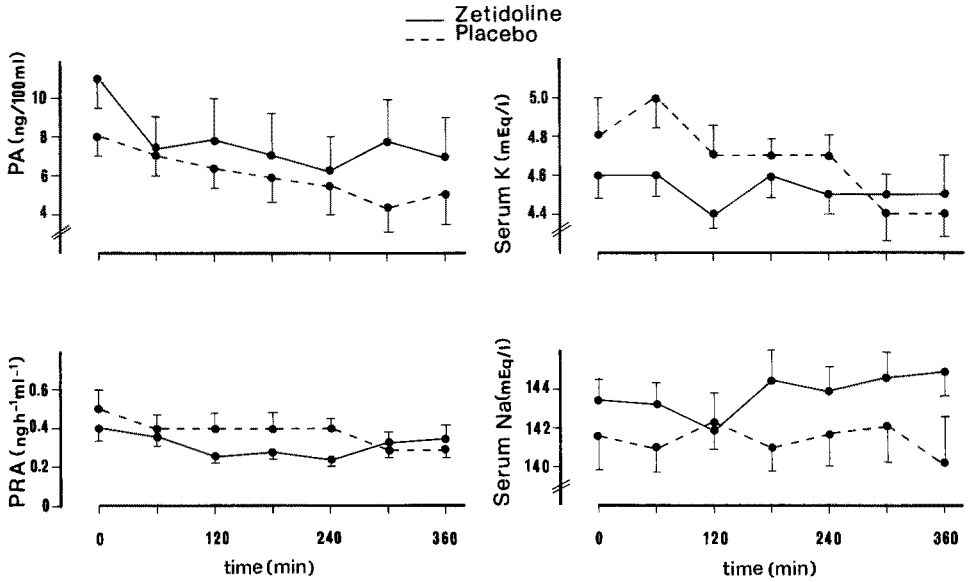

Fig. 3. Effect of zetidoline (20 mg p.o.) and placebo on plasma renin activity (PRA), plasma aldosterone (PA) and serum electrolytes. Mean ± SEM

pears to depend upon the blockade of dopaminergic receptors exerted by the compound. The increase in PRL was not due to unspecific or stress effect since only four subjects experienced drowsiness, whereas PRL was raised in all individuals and no modification of cortisol levels was apparent. The PRL response to zetidoline was greater in females than in males, probably on account of the different oestrogen level [8]. The present study does not clarify the site where zetidoline increases PRL: the compound might exert a direct effect at the lactotroph level in the pituitary or/and an action in the hypothalamus.

Interestingly, no change in plasma aldosterone levels or in its major control factors, PRA, serum electrolytes and ACTH, as mirrored by cortisol concentration, was observed after zetidoline. In recent years the existence of a dopaminergic control of aldosterone secretion has been suggested. This hypothesis is mainly based on the finding that both in the animal and in man aldosterone secretion is raised by the administration of metoclopramide, a blocker of D_2 receptors (see [4] for review). This effect is not associated with changes in PRA, cortisol or potassium levels and is generally attributed to blockade of dopaminergic receptors. The lack of change in aldosterone levels after zetidoline therefore raises interesting questions. Was the zetidoline dose too small to elevate aldosterone, or is the increase in aldosterone induced by metoclopramide not due to blockade of dopaminergic receptors? It is apparent that there is a different threshold level for the PRL and aldosterone responses to metoclopramide [4]. Thus, the administered dose of zetidoline might be not sufficient to raise the aldosterone concentration, despite a marked increase in PRL. Alternatively, the rise in aldosterone reported after metoclopramide might be due to an effect of the drug not related to blockade of dopaminergic receptors. This hypothesis is supported by the findings that in rats haloperidol does not change the plasma aldosterone level [9], and that in man chlorpromazine does not directly raise the aldosterone concentration [10].

In agreement with studies using other antidopaminergic drugs [9, 11, 12, 13] PRA was not affected following administration of zetidoline. Although the existence of a dopaminergic stimulatory influence on GH secretion is well established [3], the lack of change in GH level following dopaminergic blockade by zetidoline was to be expected, due to the low basal hormonal concentration. No change in blood pressure and heart rate was observed after zetidoline. Although there is some pharmacological evidence that the compound may exhibit a weak alpha-adrenolytic effect both in animals [2] and humans [14], the present data show that the dose of zetidoline employed was devoid of alpha-blocking properties of clinical relevance.

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