Suppression of plasma cortisol after oral administration of oxazepam in man

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In seven healthy male subjects plasma cortisol was measured at 20 min intervals from 07.00 to 13.00 h, during a drug free control test and after oral administration of 30 and 60 mg oxazepam. A significant suppression of the plasma cortisol levels for about 2 h after 30 mg oxazepam, and for about 3 h after 60 mg oxazepam was observed. The suppression wore off before the oxazepam plasma concentration started to decline significantly.

Keywords oxazepam cortisol

Introduction

The presence of hypersecretion of cortisol in depressed patients has been a matter of considerable research interest during the last decade. Clinically the major interest has concentrated on the use of the dexamethasone suppression test for differentiation between depressed and non-depressed patients, and between endogenously depressed and non-endogenously depressed patients (Carroll, 1978). A problem of these tests has been the relatively high percentage of false negative (normal) suppression tests in the depressed patients (Carroll, 1978). Recently we have shown that high plasma cortisol levels in the afternoon seem to be related as much to the severity as to the type of depression (Christensen *et al.*, 1983).

Depressed patients will frequently be treated with benzodiazepines both for sleep disturbances and anxiety in particular during the first weeks of antidepressant treatment, and sometimes quite high doses will be required. In two of our depressed patients suppression of the plasma cortisol level was suspected after relatively large doses of oxazepam (plasma concentration 2.5–3.0 $\mu\text{mol/l}$). Therefore a systematic study on this variable has been carried out in healthy subjects.

Methods

The effect of oxazepam ingestion on cortisol secretion was studied in seven healthy male volunteers age 21–35 years. The subjects met at

the laboratory in the morning at 06.45 h. Indwelling vein-catheters were inserted, and blood was sampled at 20 min intervals from 07.00 h to 13.00 h. Three tests were carried out; a control test with no drug intake ($n = 7$) and tests with ingestion at 08.00 h of oxazepam 30 mg (two tablets, $n = 7$) and 60 mg (four tablets, $n = 6$). Several days elapsed after an oxazepam test before a new test was carried out.

Cortisol in plasma was measured by competitive protein binding radio-assay according to Murphy (1967). All samples were assayed in duplicate and samples deviating more than 10 per cent were reanalysed.

Oxazepam in plasma was assayed by quantitative thin layer chromatography with measurements of UV-remission using a Zeiss Chromatogram Spectrophotometer according to principles described for the measurement of antidepressants (Pedersen *et al.*, 1982). All measurements were made in duplicate, and the reproducibility of the method was $\pm 8\%$ (coefficient of variation).

Statistical analyses were carried out with non-parametric tests (Wilcoxon signed rank test) and group variance of measurements are illustrated by indication of s.e. mean.

The subjects consented to participate on the basis of verbal and written information.

Results

Individual plasma cortisol curves from the volunteer study are shown in Figure 1. In the control

Figure 1 Plasma cortisol in seven healthy male subjects in drug free period ($\circ$ -), after ingestion of oxazepam 30 mg ($\blacktriangle$ -) and 60 mg ($\blacksquare$ -) at 08.00 h ($\uparrow$).

test all subjects had more pronounced secretory phases in particular during the first 3 h (08.00–11.00 h) than after oxazepam ingestion. As shown in Figure 2 there were significantly lower cortisol levels for about 2 h after 30 mg oxazepam and for about 3 h after 60 mg oxazepam. The suppression of the cortisol secretion was significantly more pronounced after 60 mg than after 30 mg oxazepam. The onset of suppression conformed well with the rise in oxazepam concentration, but interestingly, the suppression appeared to wear off after 3–4 h, although the oxazepam levels remained high for a longer period (Figure 2).

Only a few subjects noticed mild-moderate sedation mainly after the 60 mg dose, and no other side effects were observed.

Discussion

The present study demonstrates that ingestion of oxazepam acutely suppresses the cortisol secretion, and thus may confound interpretation of both spontaneous and post dexamethasone cortisol concentration measurements in patients.

Figure 2 Plasma oxazepam and cortisol concentration (group mean $\pm$ s.e. mean) in drug free control test ($\circ$ -, $n = 7$) and after ingestion of 30 mg ($\blacktriangle$ - $n = 7$) and 60 mg ($\blacksquare$ -, $n = 6$) oxazepam. The cortisol levels were corrected for inter-test differences in average cortisol levels before oxazepam administration (07.00–08.00 h).

Significance test (Wilcoxon, $P < 0.05$):

a: oxazepam 30 mg < control

b: oxazepam 60 mg < control

c: oxazepam 60 mg < oxazepam 30 mg

The effect is probably general for all benzodiazepines since they are pharmacologically very similar (Braestrup & Nielsen, 1982) and diazepam has been shown to exert a similar effect in man (Tormey & Darragh, 1979).

The mechanism of action underlying the benzodiazepine effect on the cortisol secretion is not clear. *In vivo* animal studies on benzodiazepine effects on cortisol excretion have shown both stimulation, suppression and development of tolerance (Chabot *et al.*, 1982). A central site of action is compatible with the presence of GABA receptors in hypothalamic regions linked to an inhibitory action of GABA on corticotropin releasing factor and ACTH secretion (Racagni *et al.*, 1982).

It is also of interest that a benzodiazepine

antagonist (3-carboethoxy- β -carboline) has been shown to cause signs of anxiety and concurrent increase in cortisol plasma levels in monkeys (Paul *et al.*, 1983). The benzodiazepine receptors have been named 'the biochemical substrate of anxiety' (Paul *et al.*, 1982), and the demonstrated association with cortisol secretion may suggest that the raised cortisol level in depressed patients mainly is a result of mental stress and anxiety.

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References

- Braestrup, C. & Nielsen, M. (1982). Benzodiazepine receptors. In *Biochemical studies on CNS receptors, Handbook of Psychopharmacology* vol. 17, eds Iversen, L. L., Iversen, S. D. & Snyder, S. H. pp 285–384. New York: Plenum Press.
- Carroll, B. J. (1978). Neuroendocrine procedures for the diagnosis of depression. In *Depressive disorders*, Symposium Rome 1977, ed Garattini, S. pp 231–236. Stuttgart, New York: Schattauer Verlag.
- Chabot, G., Brisette, Y. & Gascon, A. L. (1982). Relationship between plasma corticosterone and adrenal epinephrine after diazepam treatment in rats. *Can. J. Physiol. Pharmacol.*, **60**, 589–596.
- Christensen, L., Kristensen, C. B., Gram, L. F., Christensen, P., Pedersen, O. L. & Kragh-Sorensen, P. (1983). Afternoon plasma cortisol in depressed patients: A measure of diagnosis or severity? *Life Sci.*, **32**, 617–623.
- Murphy, B. E. P. (1967). Some studies of the protein binding of steroids and their application to the routine micro and ultramicro measurement of various steroids in body fluids by competitive protein-binding radio-assay. *J. clin. Endocrinol.*, **27**, 973–990.
- Paul, S. M., Marangos, P. J., Skolnick, P. & Goodwin, F. K. (1982). Biological substrates of anxiety: benzodiazepine receptors and endogenous ligands. *L'Encephalé*, **8**, 131–144.
- Paul, S. M., Ninan, P., Insel, T. & Skolnick, P. (1983). Benzodiazepine receptor-mediated 'anxiety' in rhesus monkey after infusion of 3-carboethoxy- β -carboline (-CCE). In *Clinical pharmacology in psychiatry: bridging the experimental therapeutic gap*, ed Gram, L. F., pp 395–401. London: Macmillan Press Ltd.
- Pedersen, O. L., Gram, L. F., Kristensen, C. B., Moller, M., Thayssen, P., Bjerre, M., Kragh-Sorensen, P., Klitgaard, N. A., Sindrup, E., Hole, P. & Brinklov, M. (1982). Overdosage of antidepressants: clinical and pharmacokinetic aspects. *Eur. J. clin. Pharmacol.*, **23**, 513–521.
- Racagni, C., Apud, J. A., Cocchi, D., Locatelli, V. & Muller, E. E. (1982). GABAergic control of anterior pituitary hormone secretion. *Life Sci.*, **31**, 823–838.
- Tormey, W. P. & Darragh, A. S. (1979). The effect of diazepam on sleep, and on the nocturnal release of growth hormone prolactin, ACTH and cortisol. *Br. J. clin. Pharmacol.*, **8**, 90–92.

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