THE EFFECT OF MIANSERIN ON URINARY CATECHOLAMINE EXCRETION IN PSYCHIATRIC PATIENTS

Despite the established interactions between anti-depressant drugs and the central and peripheral effects of catecholamines, few systematic studies are to be found in the literature concerning quantitative aspects of catecholamine metabolism in patients during treatment. Imipramine and amitriptyline cause significant reductions in 3-methoxy 4-hydroxyphenylethylene glycol (MHPG) and vanillylmandelic acid (VMA) excretion in depressed patients whilst reductions in the output of homovanillic acid and dihydroxyphenyl acetic acid as well as VMA may occur during treatment with viloxazine (Prange, Wilson, Knox, McClane, Breeze, Martin, Alltop & Lipton, 1972; Schildkraut, Draskoczy, Gershon, Reich & Grob, 1972; Goodwin, Johnson, Ruthven & Sandler, 1975). The effects of antidepressants on other urinary catecholamine metabolites may be indirect. Thus elevations in normetanephrine excretion during treatment with imipramine and amitriptyline seems to relate best to symptom response. Noradrenaline excretion, however, seems little affected by antidepressant therapy (Maas, Fawcett & Dekirmenjian, 1972; Schildkraut *et al.*, 1972).

Mianserin is an antidepressant with a different pharmacological profile compared with tricyclic drugs (Fleischhauer & Van Reizen, 1974). It increases noradrenaline turnover in the brain following acute or chronic administration without affecting amine transport mechanisms (Leonard, 1974). In contrast, imipramine and amitriptyline cause noradrenaline turnover to decrease. Any sustained increase in catecholamine turnover during drug treatment should be reflected in the output of urinary metabolites. The aim of this study was to measure the effect of mianserin on urinary catecholamine metabolites in patients undergoing treatment to ascertain the direction and degree of any changes.

Nine female in-patients diagnosed as suffering

from manic-depressive psychosis-depressed (ICD 296.2) were admitted to the Metabolic Research Unit for a period of 17 days and placed on a fixed diet which excluded exogenous sources of indoles and catechols (fluids 1750 ml, calories 1740–50, protein 60 g, carbohydrate 197 g, fat 79 g, sodium 109 mmol, potassium 60 mmol).

Throughout the study patients received nitrazepam 5 mg four times daily. After 3 days on a diet, patients were randomly allocated to mianserin 10 mg three times daily or placebo which was maintained for the remainder of the investigation. Urine collections (24 h) were made during the first 6 days on the diet and during the final 3 days and were stored frozen pending analysis. Duplicate samples were analysed for adrenaline and noradrenaline (Anton & Sayre, 1962) total metanephrine (TMN) (Gupta, Price and Keane, 1973), VMA (Pisano, Crout & Abraham, 1962) and creatinine (Bonsnes & Tausk, 1945). Patients were assessed weekly using the Beck Self Rating Inventory and twice daily by the nursing staff on a seven point rating scale (Smith, Naylor & Moody, 1978).

Means and standard errors for the average 24 h excretion of catecholamines and major metabolite groups are given in Table 1. There were no statistically significant differences between the mianserin and placebo groups in the daily output of catecholamines and their metabolites (Mann-Witney U-Test). Within the mianserin group the excretion of TMN and VMA was greater at the end of the study compared with pretreatment values but these differences did not reach statistical significance (two-tailed Wilcoxon matched pairs signed rank test). Within the placebo group the excretion of TMN and VMA was significantly elevated during the first 3 days of treatment compared with pre-treatment and terminal values ($P < 0.05$).

The patients were also arbitrarily grouped

Table 1 24 h excretion of adrenaline, noradrenaline, total metanephrine and VMA in depressed patients treated with mianserin (mean $\pm$ s.e. mean)

	Mianserin group (n = 4)			Placebo group (n = 5)		
	Pre	Days 1–2	Days 12–14	Pre	Days 1–3	Days 12–14
Adrenaline (μ g)	19 $\pm$ 2	23 $\pm$ 3	27 $\pm$ 4	21 $\pm$ 2	29 $\pm$ 5	28 $\pm$ 4
Noradrenaline (μ g)	31 $\pm$ 7	25 $\pm$ 6	32 $\pm$ 4	32 $\pm$ 8	31 $\pm$ 8	42 $\pm$ 7
Total metanephrine (μ g)	950 $\pm$ 115	1110 $\pm$ 155	1310 $\pm$ 80	890 $\pm$ 54	1230 $\pm$ 89	980 $\pm$ 103
VMA (μ g)	3520 $\pm$ 285	4420 $\pm$ 665	4830 $\pm$ 655	3370 $\pm$ 187	4070 $\pm$ 182	3750 $\pm$ 94

Table 2 24 h excretion of adrenaline, noradrenaline, total metanephrine and VMA in responder and non-responder groups* (mean $\pm$ s.e. mean)

	Responder group (n = 5)			Non-responder group (n = 4)		
	Pre	Days 1-3	Days 12-14	Pre	Days 1-3	Days 12-14
Adrenaline (μ g)	19 $\pm$ 2	23 $\pm$ 3	24 $\pm$ 4	20 $\pm$ 2	29 $\pm$ 6	31 $\pm$ 4
Noradrenaline (μ g)	32 $\pm$ 6	29 $\pm$ 6	36 $\pm$ 2	31 $\pm$ 10	28 $\pm$ 9	38 $\pm$ 10
Total metanephrine (μ g)	980 $\pm$ 103	1240 $\pm$ 138	1240 $\pm$ 103	840 $\pm$ 60	1100 $\pm$ 125	980 $\pm$ 145
VMA (μ g)	3610 $\pm$ 200	4660 $\pm$ 478	4750 $\pm$ 554	3230 $\pm$ 310	3690 $\pm$ 305	3580 $\pm$ 190

* Responder group, classified as having a change of at least 25% on the nurse rating scales.

according to whether they improved during the period of investigation (GT 25% fall in nurse rating scores) or whether they showed no improvement. The results for the mean 24 h excretion of catecholamines and their major metabolites are given in Table 2. TMN and VMA excretion were slightly higher in the responder group compared with the non-responder group but the differences did not reach statistical significance.

Within the non-responder group there was little change in the excretion of catecholamines and their major metabolite groups between the three periods of study. Within the responder group VMA excretion was elevated in both treatment onset ($P < 0.05$) and terminal periods ($P < 0.05$) compared with the baseline values but similar elevations in TMN excretion did not reach statistical significance.

The main difficulty with studies of catecholamine excretion during treatment with psychoactive drugs lies in the discrimination between clinical and pharmacological effects. As only small changes occurred in total metanephrine excretion throughout the period of investigation for both the drug and placebo groups, no firm conclusions can be drawn concerning these changes. The overall trends in total metanephrine excretion were in the direction which would be compatible with the expected consequences of clinical improvement or a modest drug effect. The mean output of VMA also seemed to increase over baseline values especially for the mianserin group which would be compatible with the observation of

Perry, Fitzsimmons, Shapiro & Irwin (1978) of a modest increase in MHPG excretion following mianserin therapy. Grouping patients into responders and non-responders seems to accentuate some of the differences. Positive responders were associated with increased VMA excretion as early as the first 3 days of treatment. Since VMA output showed little change throughout the period of study for the non-responder group it would appear that non-pharmacological elements are largely responsible.

All things considered there seems to be little evidence to suggest that mianserin increases catecholamine turnover in psychiatric patients to a degree detectable by these studies. Any increase must be comparatively modest. Conversely there is no evidence to suggest that mianserin reduces catecholamine turnover in patients on therapeutic doses which is in contrast to the effects with imipramine and amitriptyline which reduce MHPG and VMA excretion under similar circumstances. (Prange *et al.*, 1972; Schildkraut *et al.*, 1972). This study can only emphasise the differences between mianserin and the other tricyclic antidepressants in their separate effects.

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HEPATITIS ASSOCIATED WITH CAPTOPRIL TREATMENT

We wish to report a patient who developed hepatocellular jaundice while being treated with captopril. Captopril (SQ 14225) is a converting enzyme inhibitor which has been shown to be useful in the treatment of essential hypertension. Unwanted effects reported so far have included skin rashes, proteinuria and loss of taste (Atkinson & Robertson, 1979).

A 64-year-old man with essential hypertension was started on captopril 25 mg three times daily in June 1979. At this time liver function tests were normal, including total and direct bilirubin, aspartate aminotransferase (AST), lactate dehydrogenase (LDH), alkaline phosphate and gammaglutamyl transpeptidase (γ GT). Despite the dose of captopril being increased to 150 mg three times daily, control of his blood pressure was not achieved and propranolol was added to his hypotensive medication in July. Liver function tests, which were measured monthly, remained within normal range.

In December, 1979, he complained of feeling unwell for a week, acid reflux, tiredness and low backache. He observed that his stools had become pale and his urine had turned dark orange. There was no history of alcohol excess, he had not been abroad nor in contact with infective hepatitis, nor had he had any blood transfusions or injections. On examination he was jaundiced and his blood pressure was 180/90 mmHg. The liver edge was smooth and palpable 3 cm below the right costal margin, but the gall bladder was not palpable. Rectal examination revealed light-coloured faeces, urine testing showed a large amount of bilirubin but no excess of urobilinogen. Total bilirubin was $143 \mu\text{mol l}^{-1}$ (normal up to 17), direct bilirubin $114 \mu\text{mol l}^{-1}$ (normal up to 3), LDH 615 i.u.l⁻¹ (normal 100–270), AST 780 i.u.l⁻¹ (normal 7–40), alkaline phosphate 338 i.u.l⁻¹ (normal 30–85) and γ GT 64 i.u.l⁻¹ (normal up to 28). Total white blood count was 7.8 nl^{-1} with a normal differential, there being no mononuclear cells present.

Captopril therapy was discontinued and there was

a gradual improvement in liver function tests. He remained afebrile throughout his illness. Radioimmunoassays of serum for hepatitis B surface antigen (HBsAg) and for antibody to hepatitis B core (anti HBc) and hepatitis A (anti HAV) were negative. Complement fixing antibody titres to cytomegalovirus were below 1/32, 7 and 19 days after the patient had been jaundiced and the Monospot test for infective mononucleosis was negative. Ultrasound examination of liver, gall bladder and pancreas was normal.

Discussion

This patient's liver disorder was primarily hepatocellular with secondary cholestatic elements. A liver biopsy was not performed as he had clinically improved on cessation of captopril treatment. The absence of HBsAg and anti HBc and anti HAV when jaundice had appeared excludes hepatitis B and hepatitis A. The investigations do not support a diagnosis of cytomegalovirus or infective mononucleosis. Unless it was an episode of non A non B hepatitis (unfortunately, there is no way of giving an incidence of non A non B hepatitis), the jaundice seems to have been the result of captopril, probably an idiosyncratic drug reaction. Captopril therapy has been reported to produce skin reactions (Atkinson & Robertson, 1979) and drugs which produce skin rashes often cause hepatic damage with both cholestatic and hepatocellular elements (Davis & Williams, 1977) as observed in this patient. Liver function tests should be assessed regularly in patients taking captopril.

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