Br. J. clin. Pharmac. (1985), **19**, 258–260

Treatment with β-adrenoceptor blockers reduces plasma melatonin concentration

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In treated hypertensive patients plasma melatonin levels were lower in subjects receiving β-adrenoceptor blockers than those treated with diuretics. Melatonin concentrations in middle-aged and young control subjects were similar to each other and to those of the diuretic-treated patients. The results suggest that treatment with β-adrenoceptor blockers causes a persistent reduction in plasma melatonin but it is unclear if this finding has clinical implications.

Keywords β-adrenoceptor blockers diuretics melatonin

Introduction

The pineal hormone, melatonin, is the subject of much current research in psychiatry (Lewy *et al.*, 1981), endocrinology (Waldhauser *et al.*, 1984) and circadian rhythm studies (Redmond *et al.*, 1983; Arendt & Marks, 1983). The pharmacological control of melatonin secretion is therefore of potential importance and we have demonstrated in normal subjects that the midnight elevation in plasma melatonin is suppressed by a single 100 mg dose of the β_1-selective β-adrenoceptor blocker, atenolol, (Cowen *et al.*, 1983). The present study has investigated whether longer-term treatment with β-adrenoceptor blockers is similarly associated with reduced plasma melatonin concentrations, since this could have consequences for patients and might yield clues to the functional importance of melatonin in man.

A recent study of melatonin secretion in normal subjects has reported that midnight melatonin levels decline in the period from childhood to young adulthood (Waldhauser *et al.*, 1984). In the present study, therefore, we have also investigated whether a further decline occurs in later middle age.

Methods

We studied patients with moderate hypertension treated by their general practitioner with a β-adrenoceptor blocker, diuretic or both.

Patients took the following daily medication. β-adrenoceptor blocker group: atenolol, 100 mg (six subjects); atenolol, 200 mg (one subject); atenolol, 50 mg (one subject); atenolol, 100 mg + cyclopenthiazide, 0.25 mg + potassium chloride, 600 mg (two subjects); metoprolol, 100 mg (one subject); metoprolol + chlorthalidone, 12.5 mg (one subject). Diuretic group: cyclopenthiazide, 0.25 mg + potassium chloride, 600 mg (seven subjects); bendrofluazide, 5 mg (two subjects); amiloride, 5 mg + hydrochlorothiazide, 50 mg (one subject). Patients were excluded if they were over 65 years of age or taking any drugs, apart from β-adrenoceptor blockers, known to interfere with noradrenergic transmission. We also tested two normal control groups, one age and weight-matched with the β-adrenoceptor blocker patients, the other a group of young adults (Table 1).

Venous blood samples were collected from

Table 1 Characteristics of patients and control group

	β-adrenoceptor blockers	*Diuretics*	*Age-matched controls*	*Young controls*
Number	12	10	14	15
Male:Female	6:6	2:8	7:7	8:7
Mean (median) age and range (years)	58.6 (58.0) 51–63	55.9 (57.0) 46–62	56.5 (58.0) 49–65	29.7 (29) 23–36
Mean (median) weight and range (kg)	75.8 (75.5) 60–98	74.3 (76.0) 52–86	73.0 (72.5) 55–95	65.6 (67) 45–101
Mean (median) systolic BP and range (mm Hg)	146 (145) 130–160	139 (140) 130–150	–	–
Mean (median) diastolic BP and range (mm Hg)	85 (86) 70–100	84 (80) 75–100	–	–
Mean (median) duration of treatment and range (months)	23.5 (17.0) 2–72	28.0 (22.0) 11–74	–	–
Mean (median) midnight melatonin concentration and range (pg/ml)	14.3 (10)* 10–44	53.9 (50) 10–195	45.9 (33.5) 10–165	45.8 (30) 10–190
Subjects with undetectable midnight melatonin	8†	3	2	2

*Significantly less than diuretic group ($P < 0.05$), and control groups ($P < 0.01$). (Mann-Whitney test).
†Significantly greater than control groups ($P < 0.01$) (chi-square).

each subject at midnight. Subjects were awake and under dim artificial lighting which does not suppress melatonin secretion (Lewy *et al.*, 1980). A further blood sample was taken at 14.00 h the next day. Alcohol was prohibited on both sampling days.

Melatonin was measured by a previously described radio-immunoassay which correlates well with gas chromatography-mass spectrometry measurement (Fraser *et al.*, 1983a,b). Samples with a concentration of melatonin less than the detection limit of the assay (11 pg/ml) were allotted a value of 10 pg/ml. Differences in melatonin concentration between groups were analysed by the Mann-Whitney and chi-square tests. Correlations were made using Spearman's rank method. The study was completed between May and July 1983.

Results

The midnight melatonin values for the two normal control groups were similar to each other and to the diuretic-treated patients (Table 1, Figure 1). In contrast, patients treated with β-adrenoceptor blockers had a significantly lower mean melatonin concentration than the control groups, and more of them had undetectable levels of melatonin at midnight (Table 1) (Figure 1). Only two subjects (one taking a β-adrenoceptor blocker and one age-matched control) had detectable plasma melatonin at 14.00 h. In the control groups midnight melatonin did not differ between the sexes and did not correlate the age or weight ($P > 0.05$). The blood pressures of the two hypertensive groups were not significantly different ($P > 0.05$, unpaired *t*-test) (Table 1).

Discussion

The bulk of melatonin production in man occurs at night and midnight plasma melatonin correlates highly with total secretion over 24 h (Arendt *et al.*, 1982; Cowen, unpublished observations). The mean value found for midnight melatonin in young adults in the present study is very similar to that reported by Waldhauser *et al.* (1984). The values of the middle-aged subjects did not differ from those

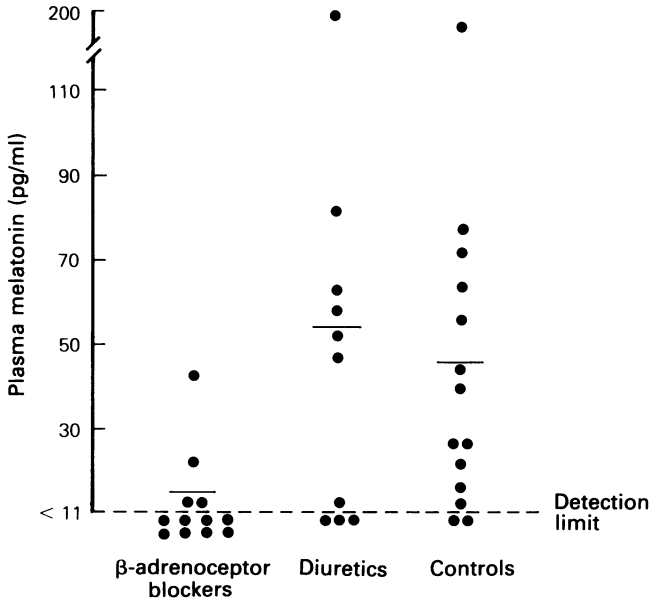

Figure 1 Midnight melatonin concentration in treated hypertensive patients and age and weight-matched controls. Each point represents the melatonin concentration of an individual subject.

of young adults, suggesting that the functional activity of the pineal gland does not decrease significantly over this period.

Our findings indicate that treatment with β-adrenoceptor blockers reduces plasma melatonin concentration and this effect persists while treatment continues. Melatonin levels in patients taking diuretics were not different from normal controls, suggesting that treatment of hypertension does not itself alter plasma melatonin concentration.

It is difficult to attribute plausibly any of the common side-effects of β-adrenoceptor blockers to reduced plasma melatonin levels. In childhood, melatonin may act to suppress gonadal activity (Waldhauser *et al.*, 1984), while in adults its role is more speculative but may involve integration of seasonal and circadian rhythms (Redmond *et al.*, 1983; Arendt & Marks, 1983). It has been argued, for example, that treatment with melatonin might alleviate jet-lag (Arendt & Marks, 1983); perhaps β-adrenoceptor blockade is associated with an exacerbation of such symptoms.

We thank Dr A. R. Green and Mrs Sheila Fraser for advice. This work was supported by the Wellcome Trust; Stuart Pharmaceuticals Limited provided additional assistance.

References

Arendt, J., Hampton, S., English, J., Kwasowski, P. & Marks, V. (1982). 24-hour profiles of melatonin, cortisol, insulin, C-peptide and GIP following a meal and subsequent fasting. *Clin. Endocrinol.*, **16**, 89–95.

Arendt, J. & Marks, V. (1983). Can melatonin alleviate jet lag? *Br. med. J.*, **287**, 426.

Cowen, P. J., Fraser, S., Sammons, R. & Green, A. R. (1983). Atenolol reduces plasma melatonin concentration. *Br. J. clin. Pharmac.*, **15**, 579–581.

Fraser, S., Cowen, P. J., Franklin, M., Arendt, J. & Franey, C. (1983a). A direct radioimmunoassay for melatonin. *Clin. Chem.*, **29**, 366–367.

Fraser, S., Cowen, P., Franklin, M. & Lewy, A. J. (1983b). Direct radioimmunoassay and gas chromatography compared for determination of melatonin in plasma. *Clin. Chem.*, **29**, 1203–1204.

Lewy, A. J., Wehr, T. A., Goodwin, F. K., Newsome, D. A. & Markey, S. P. (1980). Light suppresses melatonin secretion in humans. *Science*, **210**, 1267–1269.

Lewy, A. J., Wehr, T. A., Goodwin, F. K., Newsome, D. A. & Rosenthal, N. E. (1981). Manic-depressive patients may be supersensitive to light. *Lancet*, **i**, 383–384.

Redmond, J., Armstrong, S. & Ng, K. T. (1983). Free-running activity rhythms in the rat: entrainment by melatonin. *Science*, **219**, 1089–1091.

Waldhauser, F., Weiszenbacher, G., Frisch, H., Zeitlhuber, U., Waldhauser, M. & Wurtman, R. J. (1984). Fall in nocturnal serum melatonin during prepuberty and pubescence. *Lancet*, **i**, 362–364.

(Received June 14, 1984, accepted October 8, 1984)