The psychological side effects of acebutolol and atenolol

M. J. LEWIS¹, D. M. JONES², A. M. DART^{*3} & A. H. HENDERSON³

¹Department of Pharmacology and Therapeutics, Welsh National School of Medicine,

²Department of Applied Psychology, University of Wales Institute of Science and Technology

and ³Department of Cardiology, Welsh National School of Medicine, Heath Park, Cardiff CF4 4XN

We have measured the psychological effects of acebutolol and atenolol in sixteen patients with essential hypertension. The drugs were administered in a randomized, placebo-controlled, double-blind manner, in single daily doses of 100 mg atenolol, 400 mg acebutolol or placebo for periods of 6 weeks, each drug period being separated by a placebo period. At each 2 weekly clinic visit, a questionnaire designed for assessment of state anxiety and state arousal was administered for self-completion. Arousal was significantly reduced by atenolol over the whole 6 weeks of administration. It was not affected by acebutolol. Anxiety was significantly reduced by acebutolol but only at the first of the three 2 weekly assessments on treatment. It was not affected by atenolol. Differences in the psychological effects of these two β -adrenoceptor blockers are discussed in terms of their lipid solubility and haemodynamic effects.

Keywords acebutolol atenolol psychological effects

Introduction

Even minor drug side-effects are important during the long-term administration of drugs to symptom-free patients, such as during treatment with β -adrenoceptor blockers for hypertension or secondary prevention of myocardial infarction. In such indications, lack of side effects may be a most important consideration.

Central nervous system (CNS) effects of β -adrenoceptor blockers in particular are not uncommon. They include what may become intolerable tiredness, or vivid dreams (Kayed & Godtliebsen, 1977). Conversely β -adrenoceptor blockers may relieve anxiety (Krishnan, 1976) and have a special role during certain forms of acute stress (James *et al.*, 1977). The severity of CNS side-effects of different β -adrenoceptor blockers is generally thought to be related to their lipid solubility which determines their penetration into the CNS. The precise relationship of lipid solubility to CNS effects however is poorly understood, there has been little attempt to distinguish between different CNS effects, and little attention has been paid to minor effects which are not severe enough to cause the patient

to complain but may nonetheless colour what should otherwise be a normal life.

In the present study a questionnaire was used to compare the psychological effects of acebutolol and atenolol, two commonly used 'cardio-selective' β -adrenoceptor blockers which nevertheless differ in their lipid solubility (Cruikshank, 1980). Two psychological dimensions in particular were assessed—arousal (which reflects a state of alertness but without the implication of an ideational state) and anxiety (which may be accompanied by physiological manifestations but whose primary element is cognitive).

Methods

Sixteen patients (nine female, age range 25–65 years, mean 47.9 years) with essential hypertension participated in the study. Patients were receiving no treatment other than a thiazide diuretic and had no other serious illness.

Subjects were randomly assigned to four 6 week treatment periods in a double-blind placebo-controlled cross-over design such that

*Present address: Department of Medicine, The Royal Infirmary, Edinburgh.

the two drug periods were separated by a placebo period. Acebutolol (400 mg), atenolol (100 mg) or similar placebo tablets were given in a similar dosage regime of a single tablet taken every morning after breakfast.

At the end of each two-weekly clinic visit (between 11.00 h and 13.00 h—3 to 5 h after tablet ingestion), the patients were given a questionnaire for self-completion. The questionnaire was designed to provide scales measuring state anxiety (Spielberger *et al.*, 1969) and state arousal (Nowlis, 1965; Thayer, 1967). Blood pressure (using a random zero sphygmomanometer and taking phase 5 as diastolic pressure) and heart rate were also measured after lying (for 3 min) and after standing (3 min).

The Wilcoxon signed rank test was used for statistical analysis. Data was regarded as significantly different when $P < 0.05$. Pooled placebo scores were employed to avoid the otherwise small number of subjects contributing to the separate comparison of pre- and post-drug measurements.

Results

The heart rate and blood pressure responses during placebo and active treatment are shown in Figure 1.

Figure 2 shows the changes in state anxiety and state arousal. Anxiety was significantly reduced by acebutolol but only at the first of the three 2 weekly assessments on treatment (compared to the pooled placebo control scores) ($P < 0.05$); it was not affected by atenolol. Arousal on the

other hand was significantly reduced by atenolol over the whole 6 weeks of administration ($P < 0.05$); it was not affected by acebutolol.

Discussion

In this study of 16 hypertensive patients, atenolol 100 mg significantly lowered arousal during a 6 week treatment period whereas acebutolol 400 mg did not, relative to comparable placebo treatment periods. Conversely, atenolol did not affect state anxiety whereas acebutolol significantly reduced anxiety though only at the start of the 6 week treatment period, suggesting that this may be a short-lived effect of acebutolol treatment.

The effect of acebutolol but not of atenolol on anxiety is in accordance with the view that CNS effects of β -adrenoceptor blockers are related to lipid solubility, since acebutolol is some forty times more lipid soluble than atenolol. The explanation for the effect of atenolol but not of acebutolol on state arousal must however lie elsewhere. It may be related to the different haemodynamic effects of these two drugs. For example, there is some evidence that cardiac output may be lowered more on long-term treatment with atenolol than with acebutolol (Man In T'Veld & Schalekamp, 1982).

It is important to note some qualifications which need to be attached to the present findings. First, there was evidence for small differences in the antihypertensive effects of the two drugs at the doses used in this study and hence the qualitative changes in mood could have been

Figure 1 Mean lying and standing heart rate (HR) (beats/min); systolic and diastolic blood pressure (BP) (mm Hg) at each 2 weekly visit during the four 6 week treatment periods, (●—●) placebo; (■—■) acebutolol; and (○—○) atenolol. * $P < 0.05$ for comparison between acebutolol and atenolol.

Figure 2 (a) Mean anxiety score at each 2 weekly visit while on placebo or active drug treatment with (○—○) acebutolol 400 mg or (●—●) atenolol 100 mg. * $P < 0.05$ compared to pooled placebo scores, (b) Mean arousal score at each 2 weekly visit while on placebo or active drug treatment with (○—○) acebutolol 400 mg or (●—●) atenolol 100 mg. * $P < 0.05$ compared to pooled placebo scores.

a consequence of differences in blood pressure. Second, the relatively small numbers of subjects did not allow for a separate assessment of pre- and post-drug effects and thus evidence of carry-over and withdrawal effects are difficult to ascertain.

In summary this study suggests that β -adreno-

ceptor blockers in conventionally used doses may cause minor side effects more commonly than has been supposed. There would seem to be a need for comparative trials of different β -adrenoceptor blockers with a more sophisticated evaluation of psychological side effects than has generally been considered necessary.

References

- Cruikshank, J. M. (1980). The clinical importance of cardioselectivity and lipophilicity in beta blockers. *Am. Heart J.*, **100**, 160–178.
- James, I. M., Pearson, R. M., Griffith, D. N. W. & Newbury, P. (1977). Effect of oxprenolol on stage-fright in musicians. *Lancet*, **ii**, 952–954.
- Kayed, K. & Godtliksen, O. B. (1977). Central effects of the beta-adrenergic blocking agent acebutolol. *Eur. J. clin. Pharmacol.*, **12**, 327–331.
- Krishnan, C. (1976). Oxprenolol in the treatment of examination stress. *Cur. Med. Res.*, **4**, 241–243.
- Man In T'Veld, A. J. & Schalekamp, M. A. D. H. (1982). How intrinsic sympathomimetic activity modulates the haemodynamic responses to β -adrenoceptor antagonists. A clue to the nature of their antihypertensive mechanism. *Br. J. clin. Pharmacol.*, **13**, 245S–257S.
- Nowlis, V. (1965). Research with the mood adjective check list. In *Affect: measurement of awareness and performance*, eds. Tomkins, S. & Izard, C., pp. 352–389. London: Springer.
- Spielberger, C. D. & Lushene, R. (1969). *The State-Trait Anxiety Inventory*. Consulting Psychologists Press, Palo Alto.
- Thayer, R. E. (1967). Measurement of activation through self-report. *Psychological Reports*, **20**, 663–678.

(Received February 21, 1983,
accepted November 14, 1983)