HAEMODYNAMIC EFFECTS OF BM 10.188, A NEW ORALLY ACTIVE INOTROPIC AGENT, IN HEALTHY VOLUNTEERS

BRIAN WHITING, ANDREW W. KELMAN, DAVID J. SUMNER, W. STEWART HILLIS & HELLMUTH LEDERMANN

Department of Materia Medica, University of Glasgow, Stobhill General Hospital, Glasgow G21 3UW and Department of Clinical Physics and Bio-Engineering, West of Scotland Health Boards, 11 West Graham Street, Glasgow G4 9LF

1 BM 10.188 (Doxaminol, Boehringer Mannheim, GmbH) is a recently developed β -sympathomimetic agent which has shown promising positive inotropic activity in experimental animal models. It is a dibenzoxepine derivative.

2 The effects of 20 mg oral BM 10.188 on systolic time intervals and standard echocardiographic parameters have been studied in six normal healthy male volunteers.

3 When assessed by repeated measures analysis of variance, QS_2 and LVET shortened significantly ($P < 0.005$) in the 8 h period following BM 10.188. Mean maximum shortening values were: QS_2 , 25.7 ± 25.6 (s.d.) ms at 155 min and LVET, 10.7 ± 9.5 (s.d.) ms at 155 min. There was a corresponding small but significant increase of 4.2 ± 3.9 (s.d.) ml in stroke volume at 6 h ($P < 0.025$).

4 These results indicate that in normal volunteers, BM 10.188 exhibits effects on noninvasive cardiological indices similar to those observed after cardiac glycosides.

Introduction

BM 10.188 (Doxaminol, Boehringer Mannheim, GmbH), a dibenzoxepine derivative, is a new orally active β -sympathomimetic agent which has shown promise as a positive inotropic agent in experimental animal models and in limited trials in healthy volunteers (personal communication, Boehringer Mannheim GmbH). These preliminary studies have indicated that BM 10.188 has positive inotropic activity without obvious effect on heart rate or blood pressure, and is pharmacologically active after oral administration.

This study was designed to determine the effect of oral BM 10.188 on systolic time intervals (STI) and echocardiographic parameters when given to normal healthy volunteers.

Methods

Subjects

Six normal male healthy volunteers, aged between 18 and 40 years were studied. Each volunteer was fully informed as to the purpose of the study and was included only after giving informed consent. The study was also approved by the Hospital Research and Ethical Committee. Each subject had a normal resting supine blood pressure (range 100/60 to 140/90

mmHg) and heart rate (range 45 to 90 beats/min). Exclusion criteria included the presence of any clinically significant disease or abnormality of pre-study laboratory data, a history of asthma, eczema or allergic disease or medication of any kind in the 2 weeks prior to the study.

All subjects underwent full clinical examination, including ECG before the study. Blood (10 ml) and a urine specimen were obtained for full haematological and biochemical screening.

Experimental protocol

Systolic time intervals Systolic time intervals (STI) were measured at rest in the supine position by simultaneously recording electrocardiographic, phonocardiographic and differentiated carotid artery pulse pressure signals onto magnetic tape using a Racal (Store 4D) instrumentation recorder. Subsequent data analysis, based on a signal averaging technique, was performed on a Varian V71 Series digital computer (Kelman *et al.*, 1981). The intervals measured were the total electromechanical systole (QS_2), the left ventricular ejection time (LVET) and, by subtracting the LVET from the QS_2 , the pre-ejection period (PEP). Since the duration of the QS_2 and LVET are influenced by changes in heart rate (HR)

alone, the STI/HR regression relationship for each subject was determined by measuring the STI over a HR range of approximately 50–100 beats/min achieved by small bolus doses of atropine administered intravenously at 3 min intervals to a maximum of 1.4 mg (Kelman *et al.*, 1978, 1980 and 1981).

Echocardiography Left ventricular end-diastolic and end-systolic diameters were measured echocardiographically with a Smith Kline Ekoline 20A ultrasoundoscope and attached strip chart recorder running at a paper speed of 50mm/s. A continuous ECG rhythm strip was recorded simultaneously. The same interspace and distance from the mid-sternum were used for sequential echo recordings. The probe was held at right angles to the chest wall to visualise and record the characteristic motion of the anterior mitral valve. It was then directed inferolaterally to traverse the septum, parts of the mitral valve (including the chordae tendineae) and the posterior wall. In this position measurement of systolic and diastolic dimensions were made. The mean of the measurements from five cardiac cycles was used for each of the indices.

Systolic and diastolic volumes were determined using standard calculations (Teichholz *et al.*, 1976). Stroke volume, cardiac output, left ventricular ejection fraction, circumferential left ventricular shortening and mean rate of circumferential shortening were derived from these data.

Drug study BM 10.188 (20 mg) or identical placebo tablets were administered orally in the fasting state according to a double-blind randomised sequence with at least 1 week between studies. Each study day proceeded as follows:

(a) Baseline measurements were made after the subjects had rested quietly in the supine position for 10 min and consisted of blood pressure, echocardiographic and STI recordings. These observations were repeated twice again at 10 min intervals in the control period.

(b) Drug or placebo was administered orally with 25–50 ml water: subjects were then studied for 8 h in the supine position. STI were recorded at 5 min intervals throughout the first 3 h, then at 15 min intervals for the next 3 h and finally at 30 min intervals for a further 2 h. Blood pressure measurements and echocardiography were performed 15, 30, 45, 60, 75, 90, 120, 150, 180, 240, 360 and 480 min after drug or placebo administration. A light lunch (without caffeine) was provided after 4 h. On completion of all parts of the study, 10 ml blood and a urine specimen were again collected for full biochemical and haematological screening.

Statistical analysis All STI data and data collected at the 13 time points corresponding to echo-

cardiographic measurements were analysed by repeated measures analysis of variance on a Varian V71 Series digital computer. Average baseline readings were subtracted from each observation on the appropriate days so that the analysis compared changes in relation to the baseline after drug or placebo.

Results

The acquisition of STI data on magnetic tape and subsequent computer analysis yielded 54 STI observations over the 8 h period of the study. An example of the changes in QS_2 and LVET, corrected for both heart rate and placebo, are shown in Figure 1. In five of the six subjects, the QS_2 and LVET shortened, with a maximum change in the 1 to 4 h period after drug administration. The mean maximum QS_2 shortening was 25.7 ± 25.6 (s.d.) ms (at 155 min). The mean maximum LVET shortening was 10.7 ± 9.5 (s.d.) ms (at 155 min) and PEP, 16.4 ± 16.2 (s.d.) ms (at 135 min). The large standard deviations reflected a considerable degree of inter-

Figure 1 Changes in (a) QS_2 and (b) LVET (both corrected for heart rate), observed in an individual subject over the 8 h period following administration of 20 mg BM 10.188 orally.

Figure 2 Changes in stroke volume observed in all subjects over the 8 h period following administration of 20 mg BM 10.188 orally. Error bars represent 1 s.d.

subject variability. The analysis of variance showed, however, that there was a significant difference between BM 10.188 and placebo with respect to changes in LVET and QS_2 ($P < 0.005$), but the trend of shortening in the duration of PEP just failed to reach significance, as did the PEP/LVET ratio.

There were no significant changes in end-systolic diameters, but end-diastolic diameters were significantly larger after the active drug ($P < 0.05$) and were associated with apparently significant changes in stroke volume ($P < 0.025$) with a small mean maximum increase of 4.2 ± 3.9 (s.d.) ml, at 6 h. This effect profile was somewhat flat and erratic with large standard deviations at each time point, again reflecting a marked degree of inter-subject variability (Figure 2). There were no significant changes in the magnitude of the other echocardiographic parameters, although differences did occur in the shape of the effect-time profiles when placebo and active drug days were compared.

Neither systolic nor diastolic blood pressures were influenced by BM 10.188, and no significant changes occurred in heart rate. No adverse effects were recorded either clinically or biochemically.

Discussion

Both the measurement of systolic time intervals and the assessment of cardiac dimensions and performance by echocardiography have been utilised in the study of drugs which have an action, either directly or indirectly, on the heart. These non-invasive techniques—as they relate to drug studies—have been usefully reviewed by Gibson (1978, 1979).

Shortening of the LVET and PEP has been demon-

strated following administration of the β -adrenoceptor agonist isoprenaline (Harris *et al.*, 1966; Lewis *et al.*, 1972) and similar changes have been shown with the β_1 -adrenoceptor agonist prenalterol (Hutton *et al.*, 1980). Other compounds with inotropic activity but with different modes of action, for example the phosphodiesterase inhibitors, also exhibit changes in LVET and PEP (Hutton *et al.*, 1977). The present study was designed to determine whether or not a new β -sympathomimetic agent had any detectable effect on these non-invasive indices. It was clear that within 1 to 5 h of drug administration, both the QS_2 , and to a lesser degree, the LVET shortened to an extent similar to that found after digoxin and β -methyl digoxin (Kelman *et al.*, 1980). Similar results were obtained by Das *et al.* (1977), although the method for correcting STI for variations in heart rate was not comparable. The degree of shortening of these intervals varied from individual to individual but the analysis of variance confirmed that these effects were statistically significant when compared to placebo. It can be concluded, therefore, that BM 10.188 exerts an effect on STIs similar to that previously demonstrated for cardiac glycosides and other compounds with positive inotropic activity.

Other studies have shown that changes in the PEP after digitalis glycosides are less impressive than changes in QS_2 or LVET and that shortening of the QS_2 has the greatest significance (Weissler *et al.*, 1965; Lewis *et al.*, 1974; Das *et al.*, 1977). While the PEP in the present study certainly tended to shorten with a profile similar to that observed for the QS_2 and LVET the analysis of variance failed to show that this represented a significant change over the placebo. This may reflect the small dose used but also stresses the sensitivity of the other measurements performed.

The offset of pharmacological effect followed the pattern shown in Figure 1, i.e., after the peak effect at 1.5–2 h the STI tended towards pre-treatment values over the next 6 h. In the absence of multiple dosing studies or plasma concentration data, however, no further useful comment can be made about the single dose or projected multiple dose pharmacological effect profiles.

Although the methods used in this study do not necessarily separate any potential vasodilator activity from specific inotropic activity the lack of significant change in the left ventricular end diastolic diameter (a reflection of preload) and the absence of any change in blood pressure (a reflection of afterload) both suggest that the observed effects were probably based on positive inotropic activity. The only echocardiographic evidence of such activity was a small increase in stroke volume. The intersubject variability in this value (Figure 2) was, however, quite marked and this probably reflects one of the cautionary notes made by Gibson (1979): the derivation of stroke volume from end-systolic and end-diastolic diameters involves the

process of cubing and this may introduce considerable mathematical errors.

In summary, the STI changes in this study were consistent with inotropic activity similar to that shown in normal subjects given cardiac glycosides and in the absence of any detectable changes in pre-

load and afterload, the small, albeit variable increases in stroke volume, lend support to this. The presence of this activity without associated increase in heart rate suggests that this compound might have potential clinical use and suggests that further longer term studies with larger doses would be worthwhile.

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