Cardiac effects of sodium stibogluconate

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- 1 Sodium stibogluconate although potentially cardiotoxic is the drug of choice for Kala-azar and cutaneous leishmaniasis due to *Leishmania braziliensis*. Increasing use of this drug in the British Army has necessitated a formal evaluation of its cardiac side-effects.
- 2 Consequently a detailed study of the cardiac effects of sodium stibogluconate was undertaken in 22 male soldiers using for the first time modern non-invasive techniques.
- 3 Intravenous sodium stibogluconate 600 mg daily for 10 days did not affect blood pressure, heart rate, left ventricular contractile function or rhythm. Electrocardiography showed a reversible reduction of T wave amplitude.

Keywords sodium stibogluconate leishmaniasis cardiac effects

Introduction

Antimony is cardiotoxic. In dogs it reduces myocardial contractile force (Bromberger-Barnea & Stephens, 1965) and in man the trivalent antimonials have been associated with a variety of serious cardiac side-effects including hypotension, bradycardia, ventricular tachycardia, syncope, electrocardiographic changes (deformed P waves, QT prolongation and reduced T wave amplitude) and occasionally sudden death (Honey, 1960; Davis, 1961; Sommers & Rosanelli, 1962; Surawicz, 1970; Sapire & Silverman, 1970; Stemmer, 1976). Sodium stibogluconate, a pentavalent antimonial, was introduced as a safer alternative (Editorial, 1961; Stemmer, 1976) and has now assumed a place of great importance in the treatment of Kala-azar and potentially metastatic cutaneous leishmaniasis due to *Leishmania braziliensis* (Maegraith, 1980; Manson-Bahr, 1982). It is more rapidly excreted than the trivalent compounds but accumulates to a greater extent in the spleen and liver where some conversion to the more toxic trivalent form occurs (Goodwin & Page, 1943; Stemmer, 1976).

Recent years have seen an increase in the incidence of cutaneous leishmaniasis in British Soldiers serving in areas where *Leishmania braziliensis* is endemic. Because of the risk of late mucocutaneous leishmaniasis such patients have all received chemotherapy with sodium stibogluconate. Concern over the cardiac toxicity of this antimonial compound particularly in the light of reports of electrocardiographic changes in patients treated with the drug (Dempsey, 1965; Kaplan *et al.*, 1978) prompted us to undertake a detailed evaluation of the cardiac effects of intravenous sodium stibogluconate using for the first time, modern non-invasive methods.

Methods

British soldiers treated at the Cambridge Military Hospital during 1983 for cutaneous leishmaniasis formed the basis of the study. All had developed the disease in areas where *Leishmania braziliensis* was known to occur and were therefore at risk from late mucocutaneous

leishmaniasis. The clinical diagnosis was confirmed by a positive Montenegro test and either typical histology or parasite culture. All were interviewed and fully examined before treatment. A standard regimen of sodium stibogluconate 600 mg by slow intravenous injection was given daily for 10 days. The patients were recumbent during the injection and for 30 min thereafter but were otherwise fully ambulant. Blood pressure and heart rate were recorded before each injection and at intervals of 5 min for the following 30 min. The following non-invasive investigations were carried out on the day before starting therapy, on the final day of treatment (within 3 h of the final dose of sodium stibogluconate) and 10 days after the last dose:

- Clinical history and examination to elicit the onset of new signs or symptoms

- Biochemical evaluation involving assay of serum urea, MB-creatinine phosphokinase (MB-CPK) and hydroxybutyrate dehydrogenase (HBD)

- Resting 12 lead electrocardiography. The cardiograms were recorded by the same technicians and special care was taken to ensure uniformity of lead position. Measurements of mean ΣR wave amplitude and mean ΣT wave amplitude were taken from a mean of three consecutive beats in each lead using a paper speed of 25 mm/s. Measurements of PR interval, QRS duration and corrected QT interval (QTc) using Bazett's formula were taken from a mean of three consecutive beats in a lead showing well demarcated T waves using a paper speed of 50 mm/s.

- Echocardiography. A Hewlett Packard 77020A phased array 3.5 MHz transducer was used. Examinations were carried out in the left lateral position by a single technician. In all cases visual analysis of wall motion (to exclude regional dyskinesia) was made using two-dimensional echocardiography in the parasternal long and short axis and apical four chamber positions. An M-mode echocardiogram was recorded on photographic paper at a paper speed of 25 mm/s. The left ventricle was visualised using the two dimensional technique in the parasternal short axis position at the level of the mitral valve. An M-mode scan was derived from this with the M-mode cursor intersecting the mitral valve at a right angle in held expiration.

Using a mean of three consecutive systoles the left ventricular internal diameter was calculated in systole (at the peak of inward motion of the posterior wall—SD) and in diastole (at the

electrocardiographic Q wave—DD). Ejection fraction was derived from:

$$EF \% = \frac{(DD)^{-3} - (SD)^{-3}}{(DD)^{-3}} \times 100$$

Fractional shortening from:

$$FS \% = \frac{DD - SD}{(DD)} \times 100$$

and corrected mean velocity of posterior wall thickening/s from:

$$CVWT_{-1} = \frac{\text{Systolic wall thickness} - \text{diastolic wall thickness}}{\text{Diastolic wall thickness} \times \text{contraction time}}$$

All the traces were analysed by one investigator (AH).

- 24 h ambulatory monitoring. An Oxford Medilog recorder with an active lead at V5 and an indifferent lead on the manubrium was used. Analysis was carried out using a Reynolds Medical Electronics Ltd, high speed ECG analyser by a single investigator (AH). Note was taken of the atrial and ventricular ectopic rate and the type and prevalence of other arrhythmias.

- Statistics. The data were converted to logarithms. Pretreatment and on-treatment data and pre-treatment and post-treatment data were compared using Student's *t*-test for paired data.

- Informed consent was obtained from every patient and the protocol was approved by the Army Medical Services Ethical Committee.

Results

Twenty-two male soldiers between the ages of 18 and 31 years were studied. None had evidence of cardiovascular or renal disease before entry into the trial. No new symptoms or signs appeared during treatment. Blood pressure and heart rate were unaffected. There was no evidence of biochemical injury to the myocardium as reflected by release of HBD or MB-CPK into the serum (Table 1).

Electrocardiography

The drug did not provoke any significant changes in PR interval, QRS duration, or R wave amplitude. T wave amplitude however fell in every case. Mean ΣT wave height before treatment was from 41.32 mm (s.e. mean 2.3),

Table 1 Biochemistry (mean (s.e. mean))

Mean value	Pre-treatment	Day 10 of treatment	P value
Urea (mmol/l)	4.6 (0.98)	4.3 (0.92)	> 0.05
Hydroxybutyrate dehydrogenase (iu/l)	279 (59.5)	274 (51.6)	> 0.05
MB-creatine phosphokinase (iu/l)	5.5 (1.2)	4.8 (1.0)	> 0.05

falling to 33.4 mm (s.e. mean 2.1). The change was significant ($P < 0.01$) but normalised by the tenth day after the completion of therapy (40 mm) (Table 2). The effect of QTc interval was analysed in detail because of its importance as a marker of arrhythmogenesis. Mean QTc interval before treatment and on day 10 of therapy were not significantly different (Table 2). QTc interval changes in individuals were generally of small magnitude. In 12 QTc increased by between 1% and 18%; in seven QTc fell by between 1% and 23% while in three it did not change (Table 3). Before treatment one patient had an abnormally long QTc (549 ms) but this fell to 425 ms on therapy. During therapy only one subject had a definitely prolonged QTc (470 ms) while two had borderline high QTc intervals (431 and 427 ms).

Echocardiography

Analysis of two dimensional scans in parasternal long and short axis and apical four chamber view showed uniform left ventricular contraction in all patients before and during therapy. There was no significant change in the derived m-mode parameters of left ventricular contractility (Table 4).

Ambulatory monitoring

No ectopic tachycardias or disturbances of conduction were seen before or during treatment. Eight patients had low levels of ventricular or atrial ectopic activity before treatment

Table 3 Effect of sodium stibogluconate on QTc interval

QTc before treatment (ms)	QTc day 10 of treatment (ms)	% change
364	380	4% ↑
549	425	23% ↓
367	368	0%
396	420	6% ↑
392	370	6% ↓
360	360	0%
374	384	3% ↑
340	360	6% ↑
375	396	6% ↑
388	408	5% ↑
410	427	4% ↑
420	416	1% ↓
340	400	18% ↑
385	387	0%
397	401	1% ↑
353	330	7% ↓
400	373	7% ↓
404	372	8% ↓
424	470	11% ↑
396	431	9% ↑
365	380	4% ↑
389	368	5% ↓

↑ = Increase; ↓ = Decrease.

and 6 on day 10 of therapy. Ectopic activity increased on treatment in four patients and fell in two. In no subject did the ectopic rate exceed 25 ectopics/24 h. No multiform, repetitive or R on T ectopics were seen.

Table 2 Electrocardiography (mean (s.e. mean))

Mean value	Pre-treatment	Day 10 of treatment	P value
PR interval (ms)	152 (5.5)	151 (5.5)	> 0.05
QRS duration (ms)	85 (2.9)	87 (2.9)	> 0.05
QTc interval (ms)	390 (9.04)	392 (8.83)	> 0.05
ΣR waves (mm)	115 (5.3)	111 (5.1)	> 0.05
ΣT waves (mm)	41 (2.3)	33 (2.1)	< 0.01

Table 4 Echocardiography (mean (s.e. mean))

Mean value	Pre-treatment	Day 10 of treatment	P value
Ejection fraction %	71 (2.4)	72 (2.3)	> 0.05
Fractional shortening %	35 (2.3)	35 (1.7)	> 0.05
Corrected mean velocity of posterior wall thickening	2.2 (0.21)	2.3 (0.22)	> 0.05

Discussion

The course of treatment was uneventful. No cardiac signs or symptoms developed and heart rate and blood pressure remained unchanged during and immediately following each injection. There was no evidence of biochemical injury to the myocardium as reflected by release of MB-CPK or HBD into the serum.

Although in dogs, antimony impairs myocardial contractility (Bromberger-Barnea & Stephens, 1965), little information is available regarding the negative inotropic effects in man. In this study indices of left ventricular contractility were measured using M-mode echocardiograms. Providing the left ventricle contracts uniformly and standard measurement techniques are used such scans provide accurate, reproducible data (Roelandt, 1977; Feigenbaum, 1981; Weyman, 1982; Talano & Gardin 1983). There was no significant change in ejection fraction, fractional shortening or corrected mean velocity of posterior wall thickening before and during treatment. However although echocardiography is capable of detecting clinically important changes in left ventricular contractile function the technique is probably insufficiently sensitive to detect very minor changes.

Electrocardiographic abnormalities have been consistently recorded during treatment with antimonials (Honey, 1960; Davis, 1961; Sommers & Rosanelli 1962; Surawicz, 1970; Sapire & Silverman, 1970; Stemmer, 1976). In this study of sodium stibogluconate the drug did not appear to influence PR interval, QRS duration or R wave height. In agreement with others however (Dempsey, 1965; Kaplan *et al.*, 1978) a fall in T wave amplitude was noted in every patient although T wave inversion did not occur. Mean Σ T wave height fell significantly from 41.32 mm to 33.4 mm ($P < 0.01$) but normalised by day 10. This effect although clinically unimportant cannot be ignored as it confirms that even pentavalent antimonials are not entirely innocuous. The effect on QTc interval was studied more closely. It has become apparent that in some circumstances abnormal prolongation of QTc interval is associated with

malignant and potentially lethal ventricular tachyarrhythmias (Coumel *et al.*, 1980; Schwartz, 1980). This is of great importance during antimonial therapy as QT prolongation, malignant ventricular arrhythmias and even sudden death have been reported (Honey, 1960; Davis, 1961; Sommers & Rosanelli, 1962; Surawicz, 1970; Stemmer, 1976). Interestingly the effect on QT interval is not uniform (Davis 1961; Sommers & Rosanelli, 1962). In this study the mean QTc before treatment (390 ms; s.e. mean 8.83) was not significantly different from day 10 of treatment (392 ms; s.e. mean 8.83). Analysis of QTc behaviour in individuals showed a variable and generally small response with shortening in seven (between 1% and 23%), lengthening in 12 (between 1% and 18%) and no change in three. Before treatment only one patient had a QTc prolonged beyond the accepted normal for men of 440 ms (Schwartz, 1980). Interestingly, on therapy shortening to 420 ms occurred. During treatment one patient had a definitely prolonged QTc interval (increasing from 424 to 470) while two had borderline long intervals (431 and 427). Some caution is required in interpreting minor changes in QTc given the intrinsic difficulties and inaccuracies of QTc measurement. Although it is impossible to exclude a change in cell membrane biochemistry a more likely explanation for QTc variation in both directions is chance variation and methodological limitation.

Detailed analysis of 24 h ambulatory cardiograms gave further reassurance regarding the problem of drug induced arrhythmias. No ectopic tachycardias or conduction disturbances were seen. The low level of ectopic activity and the small variations before and during treatment are well within the normal daily variation of premature beat frequency (Barrett *et al.*, 1981).

This study of intravenous sodium stibogluconate shows that in otherwise healthy young men the drug causes no serious cardiac side-effects although minor ECG changes are to be expected.

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