PAPERS AND ORIGINALS

Sulphinpyrazone in acute myocardial infarction: studies on cardiac rhythm and renal function

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Summary and conclusions

Ninety-eight patients with acute myocardial infarction were randomly allocated to receive sulphinpyrazone 200 mg four times daily or placebo on admission to a coronary care unit. Twenty-four-hour electrocardiogram tape recordings showed no significant reduction in serious arrhythmias in the sulphinpyrazone-treated group. In addition to the expected fall in serum urate concentration, patients taking sulphinpyrazone showed a persistent increase in their serum urea and creatinine concentrations when compared with those in the placebo group ($p < 0.05$ and $p < 0.01$ respectively). These differences could not be accounted for by differences in the extent and severity of the infarction between the two groups.

These results suggest that sulphinpyrazone has no discernible antiarrhythmic effect in acute myocardial infarction.

Introduction

Sulphinpyrazone was developed as a uricosuric agent but was found to prolong platelet survival and modify in-vitro platelet behaviour,[1] so its potential as an antithrombotic agent began to be examined. When it was given to patients 25-35 days after a myocardial infarction a reduction in sudden death was observed in the first few months after the start of treatment.[2] The importance of this finding has been debated[3] but three additional questions arise from the results reported by the Anturane Reinfarction Trial (ART) group. Firstly, if sudden death is caused by arrhythmia rather than thrombosis[4] does sulphinpyrazone possess antiarrhythmic properties, since preliminary studies on dogs showed that pretreatment with sulphinpyrazone may prevent ventricular fibrillation after coronary arteyr occlusion?[5] Secondly, if the reduction in mortality in the ART, with its 25-35-day entry point, did result from an effect on arrhythmias, will this effect be even more valuable if treatment is begun immediately after myocardial infarction? Finally, if a powerful uricosuric agent is given to patients soon after infarction how will it affect serum urate concentration and renal function?

To answer these questions we have carried out a placebo-controlled double-blind study of sulphinpyrazone in patients with acute myocardial infarction.

Patients and methods

The study was conducted in the coronary care units of the City and University Hospitals, Nottingham. Patients admitted to either unit within 24 hours after a typical history of myocardial infarction and with an initial electrocardiogram diagnostic or highly suggestive of an acute myocardial infarction were considered for the study. Patients already taking an antiarrhythmic drug (other than digoxin) were excluded. If a cardiac tape recorder was available the patient was randomised as soon as possible after admission to receive either sulphinpyrazone 200 mg four times daily or matching placebo tablets. Treatment was continued for 10 days or until the patient was discharged from hospital, whichever was the sooner. Patients could be withdrawn from the study at the discretion of the admitting consultant physician. Antiarrhythmic drugs were not given routinely.

From sequential electrocardiograms and serum enzyme measurements the patients were categorised as follows: (*a*) definite myocardial infarction—unequivocal Q-wave changes in the electrocardiogram with serum enzyme activities over twice normal; (*b*) probable infarction—either unequivocal Q-wave changes in the electrocardiogram or serum enzyme activities over twice normal; (*c*) possible infarction—an abnormal electrocardiogram with sequential changes and an increase in serum enzyme activities not exceeding twice normal; and (*d*) ischaemic heart disease—a past history of myocardial infarction or angina but without sequential changes in the electrocardiogram or enzyme activities during the stay in hospital.

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ELECTROCARDIOGRAM TAPE RECORDING

Twenty-four-hour tape recordings were made with Medilog recorders (Oxford Instruments). The first tape was started as soon as possible after the patient had been admitted to the study and the second tape was recorded in the general medical ward between the fifth and eighth days. The tapes were analysed visually with a Medilog DA-11 electrocardiogram analyser without knowledge of the patient's treatment group or final diagnosis. All abnormal rhythms were tabulated and the ventricular arrhythmias classified as serious or less serious.[6]

Serious ventricular arrhythmias included (*a*) ventricular tachycardia—three or more consecutive beats of ventricular origin separated by not more than 500 ms (heart rate exceeding 120 beats/min); (*b*) couplets—two consecutive ventricular beats separated by not more than 500 ms; and (*c*) R-on-T phenomenon—ventricular ectopic beats occurring on the T wave of the preceding sinus beat, where the RR′ :QT ratio was less than 0·85.

Less serious ventricular arrhythmias included (*a*) multiform ventricular ectopic beats occurring in the same hour of recording; (*b*) idioventricular rhythm—three or more consecutive ventricular beats with intervals exceeding 500 ms (heart rate less than 120/min); (*c*) bigeminy—alternate sinus and ventricular beats separated by a fixed interval; (*d*) frequent ventricular ectopic beats—isolated ventricular beats occurring more frequently than 30/hour; and (*e*) occasional ventricular ectopic beats—isolated ventricular beats occurring less frequently than 30/hour.

BLOOD TESTS

Blood samples were taken on admission for serum urea, creatinine, electrolyte, and urate measurements, and additional estimates were made at the discretion of the physician in charge. Sufficient repeat estimations of urea, creatinine, and electrolyte values were available to permit longitudinal analysis in about half the patients in each treatment group. The serum urate concentration was measured again just before the patient was discharged.

STATISTICAL ANALYSIS

The χ^2 test with Yates's correction was used to compare the results of the 24-hour cardiac tape analysis. A univariate, repeated-measures method was used to assess the significance of the changes in the biochemical estimations.

Results

Of the 98 patients admitted to the study, 49 were allocated to receive sulphinpyrazone and 49 to receive placebo. Table I shows the comparability of the two groups on admission to the units and the mean delay between the onset of symptoms, treatment, and electrocardiogram tape recording. Forty-three patients in each group began treatment within eight hours of the onset of symptoms.

Table II shows the diagnoses and treatment in hospital in the two groups. A similar number of patients in each group were treated for heart failure or sinus bradycardia and a few in both groups received additional antiarrhythmic treatment after episodes of symptomatic ventricular arrhythmias. Only one patient was withdrawn from the study (a 76-year-old man in the sulphinpyrazone group who was withdrawn in the first 24 hours after a cardiac arrest complicated by complete heart block). Throughout the study there were no overt complications that could be attributed to sulphinpyrazone.

TABLE I—*Comparability of treatment groups on admission*

	Placebo group (n = 49)	Sulphinpyrazone group (n = 49)
No of men	39	39
No of women	10	10
Mean age in years (± SEM)	55 ± 1*	58 ± 1*
No with past history of:		
Infarction	9	8
Angina	10	6
Hypertension	10	5
Mean time in hours (± SEM) from onset of symptoms to:		
Treatment	5·2 ± 0·5	5·2 ± 0·5
Tape recording	6·6 ± 0·6	6·2 ± 0·5

*Unpaired t test: $p < 0{\cdot}02$.

TABLE II—*Diagnoses and treatment in two treatment groups while in hospital*

	Placebo group (n = 49)	Sulphinpyrazone group (n = 49)
Myocardial infarction:		
Definite	41	39
Probable	4	8
Possible	3	1
Anterior	27	29
Inferior	20	16
Uncertain	1	3
Ischaemic heart disease	1	1
Mean No of days in coronary care unit (± SEM)	2·3 ± 0·1	2·6 ± 0·2
Mean No of days in hospital (± SEM)	9·2 ± 0·6	9·4 ± 0·5
Drugs given in hospital:		
Digoxin	5	5
Diuretics	18	15
Atropine	5	3
Lignocaine	1	2
Disopyramide	1	3

TAPE ANALYSIS

On a simple presence-absence basis about 70% of patients had "serious" ventricular arrhythmias in the coronary care units and 25% in the medical ward; there were no significant differences between the two treatment groups. To facilitate comparison we reanalysed all the 24-hour tapes which had at least 18 hourly periods of recording and from this obtained the number of hourly blocks in which the various arrhythmias appeared. Of the 49 tapes in each group that were recorded in the coronary care units, 43 (88%) in the placebo group and 39 (80%) in the sulphinpyrazone group were suitable for analysis. In the general ward, 44 patients in the placebo group had a second 24-hour tape recording (one patient had died, two refused, and two had gone home), and 37 (84%) of these tapes were suitable for hourly analysis. In the sulphinpyrazone group 36 tapes were recorded in the general ward (four patients had died, four had gone home, and one had been withdrawn), and 30 (83%) of these were suitable for hourly analysis. All the tapes recorded in the general ward were obtained between the fifth and eighth days in hospital, the mean being six days in both groups.

TABLE III—*Number of patients in each treatment group with specified arrhythmias and mean number of hourly blocks in which arrhythmias noted in coronary care units and general ward*

		Ventricular ectopics			Ventricular tachycardia	R-on-T	Couplets	Supraventricular ectopics	Supraventricular tachycardia
		<30/h	>30/h	Multiform					
In coronary care units									
No (%) of patients	placebo group (n = 43)	42 (98)	21 (49)	25 (58)	20 (46)	5 (12)	30 (70)	40 (93)	6 (14)
	sulphinpyrazone group (n = 39)	38 (97)	21 (54)	26 (67)	20 (51)	7 (18)	27 (69)	37 (95)	6 (15)
Mean No of blocks	placebo group	14	4	10	3	2	5	13	3
	sulphinpyrazone group	13	6	8	3	2	6	13	3
In ward									
No (%) of patients	placebo group (n = 37)	24 (65)	3 (8)	4 (11)	1 (3)	1 (3)	4 (11)	26 (70)	4 (11)
	sulphinpyrazone group (n = 30)	25 (83)	6 (20)	6 (20)	2 (7)	2 (7)	7 (23)	26 (87)	5 (17)
Mean No of blocks	placebo group	6	13	10	1	1	7	9	2
	sulphinpyrazone group	6	10	11	1	1	6	12	3

Table III shows the number of patients in each group in whom the various arrhythmias were observed, together with the mean number of hourly periods in which they occurred. There were no significant differences between the two groups. Table IV shows the numbers and percentages of the total hourly coronary care unit records in which the arrhythmias were observed. Again there were no significant differences between patients given placebo and those given sulphinpyrazone.

TABLE IV—*Number (%) of hours in which specified arrhythmias were observed in recordings taken in coronary care units*

	Placebo group (n = 43)	Sulphinpyrazone group (n = 39)
No of recorded hours	1012	919
Ventricular ectopics <30/h	588 (58)	494 (53·7)
Ventricular ectopics <30/h	84 (8·3)	126 (13·7)
Ventricular ectopics Multiform	250 (24·7)	208 (22·6)
Ventricular tachycardia	60 (5·9)	60 (6·5)
R-on-T	10 (0·9)	14 (1·5)
Couplets	150 (14·8)	162 (17·6)
Supraventricular ectopics	520 (51·3)	481 (52·3)
Supraventricular tachycardia	18 (1·8)	18 (1·9)

During treatment, two patients in the placebo group had an episode of ventricular fibrillation (both on day 1), as did three patients in the sulphinpyrazone group (on days 1, 4, and 8). Two patients who had received sulphinpyrazone had fatal episodes of ventricular fibrillation (days 13 and 14 respectively). One patient in each group had a fatal asystolic arrest during the first 48 hours in the coronary care unit, and four patients showed transient complete heart block in the sulphinpyrazone group but none in the placebo group.

ant changes in serum sodium, potassium, or bicarbonate concentrations. Sulphinpyrazone did, however, produce a significant and persistent increase in serum urea and creatinine concentrations (table V). The extent of these increases was not correlated with the initial concentration of urate or with the size of its reduction by sulphinpyrazone.

Discussion

In contrast to the studies on dogs reported by Moschos *et al*,[5] we found no discernible antiarrhythmic effect of sulphinpyrazone in patients with acute myocardial infarction. The dogs, however, were pretreated with the drug before coronary artery ligation so the area of infarction would already have been exposed to sulphinpyrazone, whereas in our study the agent could be given only after the event so the delivery of sulphinpyrazone to the ischaemic area would be impaired. The late entry point in the ART and their decision to exclude from analysis events that occurred within six days of starting treatment make their study more directly comparable with the animal experiments than ours.

The early divergence of mortality in the two ART groups and the lack of any subsequent additional differential between them has prompted investigators to consider new early-entry trials. The results from our studies on renal function suggest that further small-scale studies must be undertaken before larger numbers of patients with acute infarction can be entered into outcome-and-survival trials. Acute infarction itself may have adverse effects on renal function,[7] but we could not detect any difference in the indices of severity or of haemodynamic performance between our placebo-treated and sulphinpyrazone-treated groups that could account for our findings on urea and creatinine concentrations. We therefore conclude that it is the drug itself that produces the increase in urea and creatinine concentrations.

No overt renal problems arose during our trial, but as the urea and creatinine concentrations were still significantly increased at the sixth to tenth days, a longer study is required to determine the duration of this effect and to characterise the underlying mechanism. The relation between renal function and dosage should also be ascertained, since the dose used in the ART and in our more limited study was higher than the doses recommended for uricosuric purposes in gout and higher than the dose (400 mg daily) first shown to prolong platelet survival in man.[1]

TABLE V—*Mean (± SEM) serum urate, urea, and creatinine concentrations in patients for whom complete longitudinal results were obtained*

	Placebo group			Sulphinpyrazone group		
Day:	1	3	6-10	1	3	6-10
Urate (mmol/l)	0·35 ± 0·02	—	0·34 ± 0·03	0·36 ± 0·03	—	0·15 ± 0·02***
Urea (mmol/l)	5·5 ± 0·3	(n = 21) 6·2 ± 0·5	6·0 ± 0·4	5·9 ± 0·5	(n = 26) 9·2 ± 1·1	9·7 ± 1·4*
Creatinine (μmol/l)	102·7 ± 5·5	(n = 21) 97·3 ± 7·8	97·1 ± 6·8	99·9 ± 4·5	(n = 25) 137·2 ± 24·2	128·8 ± 12·2**

Significance of difference between means on day 1 and days 6-10: * < 0·05; ** p < 0·01; *** p < 0·001.
Conversion: SI to traditional units: Serum urate: 1 mmol/l ≈ 16·8 mg/100 ml. Serum urea: 1 mmol/l ≈ 6 mg/100 ml. Serum creatinine: 1 μmol/l ≈ 0·01 mg/100 ml.

DEATHS

Five patients given sulphinpyrazone and one given placebo died during the 10-day treatment period. In the placebo group the patient died on day 2 from an asystolic arrest. In the sulphinpyrazone group two patients died on day 1 (one from intractable ventricular fibrillation and the other from an asystolic arrest), one patient died on day 2 in cardiogenic shock, and two patients died on days 4 and 8 (complete heart block complicated by ventricular fibrillation, and cardiogenic shock terminated by ventricular fibrillation respectively). In addition, there were three other deaths in hospital among patients who had received sulphinpyrazone. These occurred on days 13 (recurrent ventricular tachycardia and fibrillation), 18 (cardiogenic shock), and 30 (refractory heart failure).

BIOCHEMICAL CHANGES

Twenty-one patients in the placebo group and 26 in the sulphinpyrazone group had complete biochemical data which permitted comparison of values on entry, on day 3, and at some stage between days 6 and 10. There were no significant differences between these two subgroups in age and sex distribution, history of cardiovascular morbidity, peak cardiac enzyme activities, drugs given for heart failure while in hospital, or duration of stay in hospital. We observed the expected and highly significant reduction in serum urate concentration in response to sulphinpyrazone and there were no signific-

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Actinomyces-like organisms in cervical smears from women using intrauterine contraceptive devices

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Summary and conclusions

Cervical smears from 293 users of intrauterine contraceptive devices attending family planning clinics in East Fife, Dundee, and Angus were stained by Papanicolaou and Gram's methods and examined for actinomyces-like organisms. Of the 128 women using plastic devices, 40 gave smears positive for these organisms. In contrast only two positive smears were obtained from the 165 women using devices containing copper and none from a control group of 300 women taking oral contraceptives. Colonisation was more common in women whose plastic devices had been in situ for over two years. Correlations between the presence of these organisms and recorded incidences of pain and both clinical and cytological evidence of inflammation of the lower genital tract were highly significant ($p=0.00001$, $p<0.00001$, and $p<0.00001$ respectively).

The results suggest that plastic intrauterine contraceptive devices predispose to colonisation by actinomyces-like organisms, particularly after long-term use. Hence if the apparently bacteriostatic action of copper devices is confirmed these should probably be more widely used.

Introduction

With the widespread use of modern intrauterine contraceptive devices genital actinomycosis is becoming increasingly common.[1-3] In Britain several actinomycotic tubo-ovarian abscesses have been reported,[4 5] and in North America many cases of serious pelvic infection have occurred, including systemic dissemination of the organisms and one death.[2 6 7]

Gupta in 1972 was the first to identify cytologically colonies of actinomyces-like organisms in cervical smears from women using intrauterine contraceptive devices and, later, with a fluorescent antibody technique, classified most of these as *Actinomyces israeli*.[8-10] By 1978 Gupta *et al* had identified 540 such cases.[11] Jones *et al*[12] rescreened 300 cervical smears from women using these devices and found actinomyces-like organisms in 25·5% of smears from women attending public health and family planning clinics and 8% of smears from private patients.

To our knowledge the following report is the first retrospective epidemiological study of the clinical importance of cervical colonisation by these organisms and of their association with various types of intrauterine contraceptive devices.

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Patients and methods

Between March 1978 and March 1979 cervical smears were examined from 293 women using intrauterine contraceptive devices and from a randomly selected control group of 300 women taking oral contraceptives. All women were attending family planning clinics in three adjacent districts (East Fife, Dundee, and Angus). The policy for taking smears differed slightly among the districts, though most of the women were tested at intervals of one to two years. In Fife smears were taken only when the cervix was clinically healthy. If cervicitis was suspected samples were examined bacteriologically. In Angus, in addition to routine cervical smears, cytology was used to confirm a clinical suspicion of cervicitis. In Dundee there was no definite policy.

Of the 293 intrauterine contraceptive devices being worn, 128 were plastic (108 Saf-T-coil, 15 Lippes loop, 2 Dalkon shield, 1 Ota's ring, 2 unknown) and 165 contained copper (157 Gravigard, 8 Cu-T).

METHODOLOGY

Cervical smears were taken under direct vision with an Ayre spatula modified by one of us and the occupational therapy department, Royal Dundee Liff Hospital, to enable the tip to be inserted into the endocervical canal of most parous women (fig 1). Smears were stained by the standard Papanicolaou method and examined by one cytology screener for actinomyces-like organisms and inflammatory changes. Smears positive or suspicious for these organisms were decolorised, washed, restained by Gram's method, and re-examined and the findings categorised as follows.

Positive (positive or suspicious on Papanicolaou staining and Gram-positive)—Dense aggregates (microcolonies) of bacillus-like organisms seen with feathering at edges (fig 2). Occasionally smaller, more loosely arranged aggregates (classified as suspicious) observed. After Gram staining, typical branching, beaded, slender Gram-positive filaments seen.

Suspicious (positive or suspicious on Papanicolaou staining and Gram-negative)—After Gram staining, branching and beaded organisms not seen but bacilli of non-branching type or fungal mycelia observed.

Negative—No evidence of actinomyces-like organisms detected on Papanicolaou staining.

Statistical significances were assessed with χ^2 tests for 2×2, 3×2, and 4×2 contingency tables for two-sided departures from the null hypothesis. In the 2×2 case the continuity correction was applied.