This dramatic but rare fatal complication of mitral valve disease should not be dismissed as a mere academic curiosity. With increasing use of slow-release potassium tablets it may become more common. One of the patients described by Whitney and Croxon died of gastrointestinal haemorrhage and two of their patients had sufficient dysphagia to need feeding jejunostomies. In view of all this it seems desirable to use effervescent potassium chloride or potassium chloride mixture rather than potassium chloride tablets in patients with chronic mitral valve disease complicated by left atrial dilation.

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University Hospital, Kuala Lumpur, Malaysia
E SUMITHRAN, MRCP, MRCPATH, consultant histopathologist
K H LIM, MB, medical officer
H L CHIAM, FRACS, surgeon

Placental and mammary transfer of sulphasalazine

Sulphasalazine (SASP) is widely used as maintenance treatment for ulcerative colitis. Since many of the patients are women in the reproductive age there is the question of the extent to which the drug and its metabolites reach the fetus, and also to what extent they are present in the milk if the treatment is continued throughout pregnancy and the period of lactation. SASP consists of sulphapyridine linked to a salicylate radical by a diazo bond. When taken by mouth only a limited amount is absorbed from the small intestine and most of the drug reaches the colon intact. There it is split at the diazo bond by the colonic bacteria into sulphapyridine (SP) and 5-aminosalicylic acid (5-ASA). The SP is virtually all absorbed and is then metabolised in the usual way of sulphonamides. The 5-ASA is only partly absorbed and is rapidly excreted in the urine so that the serum concentration is very low.[1-2] There is strong evidence that virtually all the complications of SASP therapy are attributable to its SP component.

Patients, methods, and results

Five patients with ulcerative colitis who became pregnant while on maintenance treatment with SASP volunteered to take part in the study, which merely required them to allow additional samples of blood and a sample of milk to be taken for analysis. As is our usual practice, they were continued on SASP in a dose of 0·5 g four times a day throughout their pregnancy and puerperium. Samples of maternal and cord blood and amniotic fluid were collected at the time of delivery. In three of the patients who proceeded to breast-feeding samples of maternal blood and milk were collected one week after delivery. The standard chemical methods[3-5] were used to estimate SASP; SP; N⁴-acetyl-sulphapyridine-O-glucuronide (Ac-SP-Gluc); total-sulphapyridine (total-SP), which represents SP and all its metabolites; and total-5-ASA (free 5-ASA plus acetyl-5-ASA).

Concentrations of SASP and its metabolites in maternal sera and in corresponding cord sera, amniotic fluid, and breast milk. Values are expressed in μg/ml (mean± SD)

	Results in 5 cases			Results in 3 cases	
	Maternal serum	Cord serum	Amniotic serum	Maternal serum	Breast milk
SASP	7·3±4·0	4·2±3·0	0·6±0·5	8·8±1·9	2·7±1·8
Total-SP	10·6±4·6	11·0±4·0	16·0±8·9	19·0±3·1	10·3±1·6
Free-SP	6·7±4·1	4·6±3·0	8·6±5·6	13·8±4·0	6·5±2·2
SP-Gluc	0·0	0·4±0·2	0·6±0·9	0·1±0·2	1·6±2·8
Ac-SP	3·7±2·4	4·9±1·8	4·8±3·4	4·5±2·3	1·4±0·7
Ac-SP Gluc	0·5±0·3	0·6±0·5	1·9±0·7	0·6±0·4	0·8±1·0
Total 5-ASA	<0·5	<0·5	1·2+0·5	Not measured	Not measured

The table shows that SASP crosses the placenta, the mean concentration in the cord serum being half that of the maternal serum. The concentration of SASP in the amniotic fluid was very low. The concentrations of total-SP were identical in the maternal and cord sera. The concentrations of free-SP, however, were significantly lower ($P < 0·02$) and those of total acetylated sulphapyridine (AC-SP+AC-SP-Gluc) were significantly higher ($P < 0·025$) in the cord sera than in the maternal sera. There was no detectable SP-Gluc in the maternal sera but low concentrations were found in the cord sera. The concentrations of total-5-ASA were very low in all types of fluid examined.

Both SASP and SP pass into breast milk. The SASP concentration in the milk was about 30% of that in the maternal serum, while the mean total-SP concentration in the milk was about 50% of that of maternal serum. The various metabolites of SP were present in the milk in roughly the same proportions as in the maternal serum. 5-ASA was not measured in the milk since no satisfactory analytical method was available, but it is likely to be very low as only low serum concentrations are ever found in patients receiving SASP therapy, being 1·0±0·7 μg/ml in our own patients on a dose of 2 g daily.

Comment

Sulphasalazine has been used extensively during pregnancy and no untoward effect on its course or on the fetus has been reported. Our clinical experience at Oxford agrees with this finding. It has been our usual practice for the past 10 years to continue maintenance therapy with SASP throughout pregnancy and the puerperium in patients with ulcerative colitis and we have seen no obvious ill effects on the mother or the child. Nevertheless, this study shows that SASP and its metabolites reach the fetus in concentrations not greatly different from those in the maternal serum. There is therefore a theoretical risk that the fetus might develop complications from the treatment. The concentrations of SASP and its metabolites in breast milk are much lower than those of maternal serum and are unlikely to cause harmful side effects.

We thank our obstetrical colleagues, Professor A C Turnbull and Mr Edward Cope, for their co-operation in this study.

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Nuffield Department of Clinical Medicine, Radcliffe Infirmary, Oxford
A K AZAD KHAN, MB, DPHIL, research fellow
S C TRUELOVE, MD, FRCP, consultant physician

Collapse after oral disopyramide

Disopyramide is electrophysiologically similar to quinidine and has been used to treat supraventricular and ventricular arrhythmias since the late 1960s.[1] Absorption of the oral dose is rapid and almost complete with peak serum concentrations at one to two hours. In five of our patients disopyramide by mouth was followed by severe myocardial depression, hypotension, a rise in venous pressure, and, in four, unexplained severe abdominal pain (table). The following two cases are representative.

Case reports

(1) A 67-year-old man who had had myocardial infarctions developed profound hypotension, sudden severe epigastric pain, dyspnoea, sweating, and raised jugular venous pressure (JVP) after being given disopyramide 400 mg by mouth to revert paroxysmal atrial flutter. He was treated with metaraminol, isoprenaline, and frusemide. Pulmonary embolus was

excluded by pulmonary angiography. Within 12 hours he had fully recovered.

(2) A 39-year-old man with Wolff-Parkinson-White syndrome presented in rapid atrial fibrillation. After disopyramide 300 mg by mouth he developed severe hypotension, cyanosis, raised JVP, and severe epigastric pain. Mesenteric embolus and infarction were diagnosed and an emergency laparotomy was performed. While anaesthetised he developed asystole and could not be resuscitated. No intra-abdominal lesion was found at necropsy.

Comment

Initially we gave 400 mg disopyramide by mouth to revert supraventricular tachycardia with good results.[2] After our first two cases of collapse we reduced the initial loading dose of disopyramide to 300 mg. We used loading doses because they have been recommended for disopyramide (after acute myocardial infarction)[3] and other antiarrhythmic drugs in order to achieve therapeutic blood concentrations rapidly. Recommended daily maintenance doses of disopyramide vary between 300 and 800 mg.[4] Doses ranging from 250 to 400 mg six hourly have been used for ventricular tachycardia.

In our five cases symptoms appeared when maximum serum concentrations would be expected. The serum disopyramide concentration was measured only in the fifth patient: at 6 mg/l it was only slightly above the usually accepted therapeutic range. The adverse effects may have resulted from using standard doses of disopyramide in the presence of myocardial dysfunction or beta adrenoreceptor antagonists, or both. The abdominal pain in four patients was unusual. It was severe and usually epigastric, and in one patient suggested mesenteric embolus and infarction. Its cause remains unexplained. Acute hepatic congestion from cardiac failure was considered but it was found only in one of two patients who had necropsies, and in neither was any other intra-abdominal lesion found. Two patients had ventricular tachycardia. In one it was probably secondary to the use of sympathomimetic agents but in the other it was noted at the time of collapse without any record of abdominal pain. In both it responded to antiarrhythmic therapy, although respiratory depression and impairment of consciousness followed. The sequence of events is similar to that described in cases of fatal overdosage of disopyramide.[5] Atypical ventricular tachycardia or self-terminating episodes of ventricular fibrillation during disopyramide administration have been reported and we have also seen this on two other occasions.

All our patients had enlargement of the heart with or without overt cardiac failure, two had myocardial ischaemia, and three were also taking beta-adrenoreceptor blocking drugs. Disopyramide should therefore be used with great care in patients who have myocardial dysfunction or who are taking other negative inotropic drugs. At present we recommend that they should not be given loading doses of 300-400 mg.

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Department of Cardiology, Royal Melbourne Hospital, Victoria 3050, Australia

E G MANOLAS, MB, registrar
D HUNT, MD, FRACP, assistant director
J T DOWLING, MB, FRACP, assistant director
M LUXTON, MD, FRACP, physician
J K VOHRA, MD, MRCP, assistant physician
G SLOMAN, FRCP, FACC, director

Clinical details in five cases of collapse after taking oral disopyramide

Case No	Age (years) and sex	Weight (kg)	Diagnosis	Arrhythmia	Chest radiograph before collapse		Disopyramide dose (mg)	Time from last dose to collapse (min)	Abdominal pain	Outcome
					Cardiomegaly	pulm congestion				
1	67 M	76	Myocardial ischaemia	Atrial flutter	Yes	Yes	400 (single dose)	90	Yes	Recovery
2	66 M	63	Myocardial ischaemia	Atrial flutter	Yes	No	400 (single dose)*	90	No	Recovery
3	39 M	107	WPW syndrome	Atrial fibrillation	Yes	Yes	300 (single dose)†	60	Yes	Death
4	54 F	51	Aortic valve replacement	Atrial fibrillation	Yes	No	300† 200 (3½ h later)†	60–120	Yes	Death
5	60 M	66	WPW syndrome	Atrial flutter	Yes	Yes	200 (thrice daily)*	150‡	Yes	Recovered

*Ventricular tachycardia during collapse.
†Also taking beta-adrenoreceptor blocking drugs.
‡Serum disopyramide concentration 6 mg/l.
WPW = Wolff-Parkinson-White syndrome.

Vancouver style

All manuscripts submitted to the *BMJ* from now on should conform to the uniform requirements for manuscripts submitted to biomedical journals (known as the Vancouver style).

The *BMJ*, together with many other international biomedical journals, has agreed to accept articles prepared in accordance with the Vancouver style and will be introducing the system from January 1980. The style (described in full in *BMJ*, 24 February, p 532) is intended to standardise requirements for authors and covers text format, presentation of methods and results, use of SI units, and the form of tables and illustrations. All the participating journals have also agreed to introduce a standard form of references.

In future references to papers submitted to the *BMJ* should include: the names of all authors if there are fewer than seven or, if there are more, the first three followed by *et al*; the title of journal articles or book chapters; the titles of journals abbreviated according to the style of *Index Medicus*; and the first and final page numbers of the article or chapter.

Examples of common forms of references are:

[1] International Steering Committee of Medical Editors. Uniform requirements for manuscripts submitted to biomedical journals. *Br Med J* 1979;**1**:532-5.
[2] Soter NA, Wasserman SI, Austen KF. Cold urticaria: release into the circulation of histamine and eosinophil chemotactic factor of anaphylaxis during cold challenge. *N Engl J Med* 1976;**294**:687-90.
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Up to the beginning of October some 100 journals had agreed to accept articles in the Vancouver style, and a full list will be printed early in 1980.