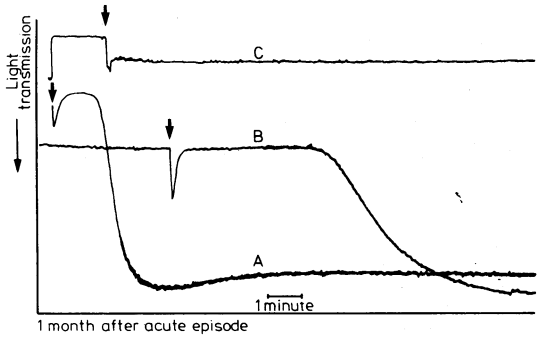
on 40 mg prednisolone daily. Within 48 hours the platelet count returned to normal. She was allowed home after one week and warned to avoid quinine in any form. Six days later she again developed feverishness and malaise and was admitted with widespread purpura. The platelet count was 18×10^9/l (18 000/mm^3). She was still taking 20 mg prednisolone daily. After admission she rapidly improved and her platelets increased to 50×10^9/l (50 000/mm^3) within 24 hours. She denied taking quinine sulphate tablets, but on the evening before admission she took a glass of sparkling bitter lemon. She had first inspected the label and found no mention of quinine among the ingredients.

That the thrombocytopenia was due to quinine-dependent platelet antibodies was confirmed by standard in-vitro tests of platelet factor 3 release (in which the addition of serum containing the drug-dependent antibody to normal platelet-rich plasma shortens the clotting time by releasing platelet factor 3 from damaged membranes) and platelet aggregometry.[3] The latter provides a simple method for detecting drug-dependent antibodies. In this case aliquots of the patient's platelet-rich plasma (PRP) showed increased light transmission with the addition of a quinine solution (containing 715 μg/ml) and tonic water (80 μg/ml) (figure) but no change with bitter lemon (20 μg/ml). A threshold concentration was obtained with a solution of 35 μg/ml. Below that there was no change in light transmission. Subsequent analysis by light microscopy showed that actual lysis of platelets had occurred, which was found to be complement-dependent (figure). PRP with inactivated complement (heated at 56°C for 10 minutes) showed neither lysis nor aggregation, supporting previous findings that immune lysis can occur in the absence of platelet aggregation.[3]



Increase in light transmission of PRP on addition (↓) of solution containing 715 μg/ml quinine (A). After inactivation of complement same solution produced no response (C). Brisk response with tonic water (B) containing 80 μg/ml quinine.

Comment

Quinine is one of the commonest drugs responsible for drug-induced purpura. It is believed to cause thrombocytopenia by an "innocent bystander" mechanism[4] wherein the drug-antibody complex passively attaches to platelets and results in fixation of complement and subsequent lysis. This case shows that minute amounts can induce severe thrombocytopenia in a previously sensitised person. We were therefore surprised to find that none of the major pharmaceutical organisations has a reference list of quinine-containing substances, which is essential information for people who remain at risk for life. We also think that all products containing quinine should be appropriately labelled.

We thank Dr G J R McHardy for permission to report this case, Dr A C Parker for helpful discussion, and Miss Jo Donnelly for typing the manuscript.

1 Belkin, G A, *Annals of Internal Medicine*, 1967, **66**, 583.
2 Horowitz, H L, *et al*, *Transfusion*, 1965, **5**, 336.
3 Deykin, D, and Hellenstein, L J, *Journal of Clinical Investigation*, 1972, **51**, 3142.
4 Shulman, N R, *Journal of Experimental Medicine*, 1958, **107**, 665.

(*Accepted 3 October 1979*)

Department of Haematology and the Drug Information Centre, Royal Infirmary, Edinburgh EH3 9YW
J A MURRAY, MB, MRCP, registrar
I ABBOTT, FIMLS, chief medical laboratory scientific officer
D A ANDERSON, MSC, MPS, principal pharmacist

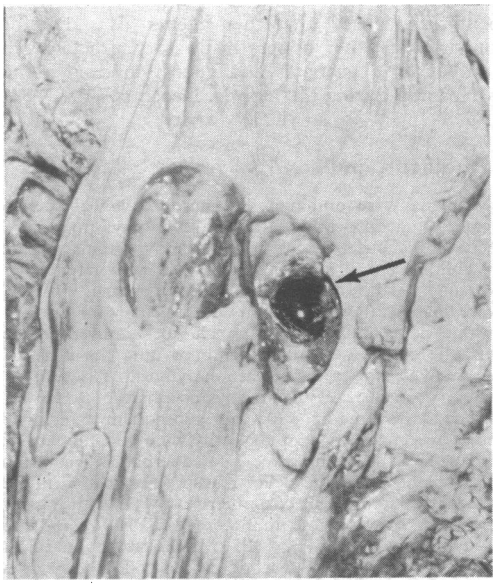
City Hospital, Edinburgh EH10 5SB
A D MORGAN, BSC, MRCP, medical registrar

Atrio-oesophageal fistula complicating mitral valve disease

A man with long-standing mitral stenosis and incompetence of rheumatic origin died suddenly with massive haematemesis resulting from a left atrio-oesophageal fistula. We think this is the first report of this dramatic complication of mitral valve disease.

Case report

A 54-year-old Chinese man had a long-standing history of rheumatic heart disease with mitral stenosis and incompetence. In October 1970 he complained of dyspnoea and was started on digoxin, hydrochlorothiazide, and supplementary potassium in the form of a mixture of potassium chloride 1 g thrice daily. He was regularly followed up at the cardiac clinic and maintained on the above medication. In 1977 he was twice admitted to hospital with epigastric pain and melaena. Barium meal radiography showed a peptic ulcer in the posterior wall of the stomach, for which symptomatic treatment with antacids was given. In November 1978 during a routine follow-up visit the potassium chloride mixture was replaced by the more fashionable slow-release potassium chloride tablets (three tablets daily). In July 1979 he was brought to hospital with a massive haematemesis, which was assumed to be the result of an acute exacerbation of the gastric ulcer. He died within 48 hours of admission without recovering from shock. Necropsy confirmed the presence of severe mitral stenosis and incompetence. There was aneurysmal dilatation of the left atrium with marked thinning of the left atrial wall. The oesophagus was displaced posteriorly and compressed. A fistula 1 cm in diameter just below the carina of the trachea connected the posterior wall of the left atrium to the anterior wall of the oesophagus. Over the mucosal surface of the oesophagus, at the site of the fistula, there was an ulcer 2 cm in diameter (figure). Histological examination of the wall of the fistula showed acute inflammation. There was free flow of blood from the left atrium to the oesophagus. The stomach was grossly distended by a huge blood clot.



Oesophagus with mucosal ulcer and opening of fistula (arrowed).

Comment

Small bowel ulceration is a well recognised complication with enteric-coated potassium chloride,[1 2] and there are reports of slow-release potassium chloride tablets causing oesophageal ulceration in circumstances (left atrial dilation in particular) predisposing to oesophageal stasis.[3 4] Pemberton[3] reported oesophageal ulceration in a 44-year-old woman on Slow-K who had recently had a mitral valve replacement, and all the six patients of Whitney and Croxon[4] with oesophageal ulceration had chronic mitral valve disease and had been treated with slow-release potassium chloride. Presumably the oesophageal compression caused by the dilated left atrium results in stasis of the tablet at the site of obstruction, leading to the release of a local high concentration of potassium chloride which is ulcerogenic. Probably the acute inflammation evoked by the ulcer coupled with pressure necrosis led to the development of the fistula in our patient.

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.

[1] Ashby, W B, Humphreys, J, and Smith, S J, *British Medical Journal*, 1965, **2**, 1409.
[2] Wynn, V, *British Medical Journal*, 1965, **2**, 1546.
[3] Pemberton, J, *British Heart Journal*, 1970, **32**, 267.
[4] Whitney, B, and Croxon, R, *Clinical Radiology*, 1972, **23**, 147.

(*Accepted 9 October 1979*)

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.

[1] Schroder, H, and Campbell, D E S, *Clinical Pharmacology and Therapeutics*, 1972, **13**, 539.
[2] Peppercorn, M A, and Goldman, P, *Gastroenterology*, 1973, **64**, 240.
[3] Hansson, K-A, and Sandberg, M, *Acta Pharmaceutica Suecica*, 1973, **10**, 87.
[4] Sandberg, M, and Hansson, K-A, *Acta Pharmaceutica Suecica*, 1973, **10**, 107.
[5] Hansson, K-A, *Acta Pharmaceutica Suecica*, 1973, **10**, 153.

(*Accepted 17 October 1979*)

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