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SHORT REPORTS

Agranulocytosis associated with malaria prophylaxis with Maloprim

Dapsone is an important drug in the treatment of leprosy and bullous dermatoses, particularly dermatitis herpetiformis, and has been used in prophylaxis against chloroquine resistant *Plasmodium falciparum* malaria, usually combined with pyrimethamine. Side effects include skin reactions and haematological disorders such as haemolytic anaemia and methaemoglobinaemia.[1] Dapsone may also cause agranulocytosis during treatment and when used in malaria prophylaxis,[2 3] where a mortality of 40% has been recorded.[2] Pyrimethamine does not appear to have been associated with agranulocytosis.

We report seven cases of agranulocytosis, with three deaths, in persons taking Maloprim (dapsone 100 mg and pyrimethamine 12·5 mg) as prophylaxis against malaria in a dose of two tablets a week.

Case reports

Between January 1980 and December 1981 seven cases of agranulocytosis occurred in people taking Maloprim or within days of stopping the drug (see table). Two of the patients (cases 3 and 4) were brother and sister and all except one (case 5), who had suffered a transient cerebral ischaemic attack three years before and was taking salicylic acid daily, were otherwise well and not taking any other drugs.

Full haematological data were not available in cases 2 and 3, as these patients were admitted to hospital in Latin America and died four and three days after admission. Case records showed that one of these patients (case 3) had "agranulocytosis" and a bone marrow smear reported as showing "severe depression." In neither case were bacterial cultures carried out despite the patient in case 3 dying in "septic shock."

Three patients (cases 1, 5, and 7) were given adequate antibiotic treatment according to in vitro testing of isolated bacteria. Case 4 was treated with gentamicin and piperacillin intravenously. In cases 1, 4, and 7 the patients were also given buffycoat transfusions. The antimicrobial chemotherapy in the three patients who died (cases 2, 3, and 6) may not have been adequate, since blood cultures were not obtained and isoxazolylpenicillin but no aminoglycoside or modern broad spectrum penicillin or cephalosporin was used.

Comment

Maloprim was the only factor that could be identified as causing the agranulocytosis in these seven patients. Their symptoms developed seven to nine weeks after beginning Maloprim, and the mortality (three deaths) agrees with that reported for dapsone.[2] We assume that the agranulocytosis was due to the dapsone in Maloprim, as a weekly dose of 175 mg reportedly causes agranulocytosis,[2] and all seven of these patients were taking 200 mg a week. In vitro data show a dose dependent toxic effect on the granulopoiesis promoted by hydrogen peroxide and mediated by a metabolite of dapsone.[5] The manufacturer's recommended dose of one tablet of Maloprim a week does not appear to have been associated with agranulocytosis; nevertheless, the low dose of pyrimethamine per tablet and the short half life of dapsone might suggest that two doses a week would be necessary for effective prophylaxis.[4]

The incidence of agranulocytosis due to dapsone given as prophylaxis against malaria has been estimated as one in 5000[2]; and according to the Swedish National Board of Health and Wellfare there were about 15 000 prescriptions for Maloprim during the period that these patients became ill, yielding an incidence of about one in 2000.

Thrombocytopenia was not a feature of the drug reaction reported here. One case of thrombocytopenia associated with a twice weekly dose of Maloprim has, however, been reported to the Swedish Adverse Drug Reactions Advisory Committee.

Maloprim given in a dose of one tablet twice a week may cause agranulocytosis; the use of the lower dose of one tablet weekly or alternative drugs is advocated in persons travelling to areas in which chloroquine resistant *P falciparum* malaria is endemic.

Clinical and pathological data in patients suffering from Maloprim associated agranulocytosis

Case No	Sex and age	Duration of Maloprim treatment (weeks)	Presenting symptoms	Bacteriological findings	Haematological picture on presentation: White cell count ($\times 10^9$/l) (% polymorphs)	Platelet count ($\times 10^9$/l)	Haemoglobin (g/l)	Bone marrow	Outcome
1	M 64	8	Fever and boil on neck	*Staphylococcus aureus* in boil; blood cultures sterile	0·1 (2)	68	120	Absence of granulocytes; erythroid series and megakaryocytes normal	Recovered after 3 weeks
2	F 27	8	Sore throat, earache, and fever	None	?	?	?	Numerous myeloblasts, arrest at promyelocyte stage; erythroid series and megakaryocytes hyperactive	Died 4 days after admission to hospital in Latin America
3	F 49	8	Sore throat and fever	None	?	?	?	"Severe depression"	Died 3 days after admission to hospital in Latin America
4	M 47	8	Sore throat and fever	Blood cultures sterile	0·7 (0)	362	125	Absence of myelopoiesis; erythroid series and megakaryocytes normal	Recovered after 3 weeks
5	M 74	8	Fever, jaundice, and lymphadenopathy	Coliforms in blood	0·2 (0)	165	104	Absence of myelopoiesis; hypoplastic erythropoiesis; megakaryocytes normal	Recovered after 3 weeks
6	F 67	9	Sore throat and fever	Throat culture, normal flora	0·3 (0)	118	98	Absence of myelopoiesis; hypoplastic erythropoiesis; megakaryocytes increased	Died after 4 days in hospital
7	F 32	7	Malaise, fever, and pain in left sternomastoid	*Staph aureus* in blood	0·3 (0·1)	300	120	Absence of myelopoiesis; erythroid series and megakaryocytes normal	Recovered after 3 weeks

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Unusual case of peripheral venous occlusion

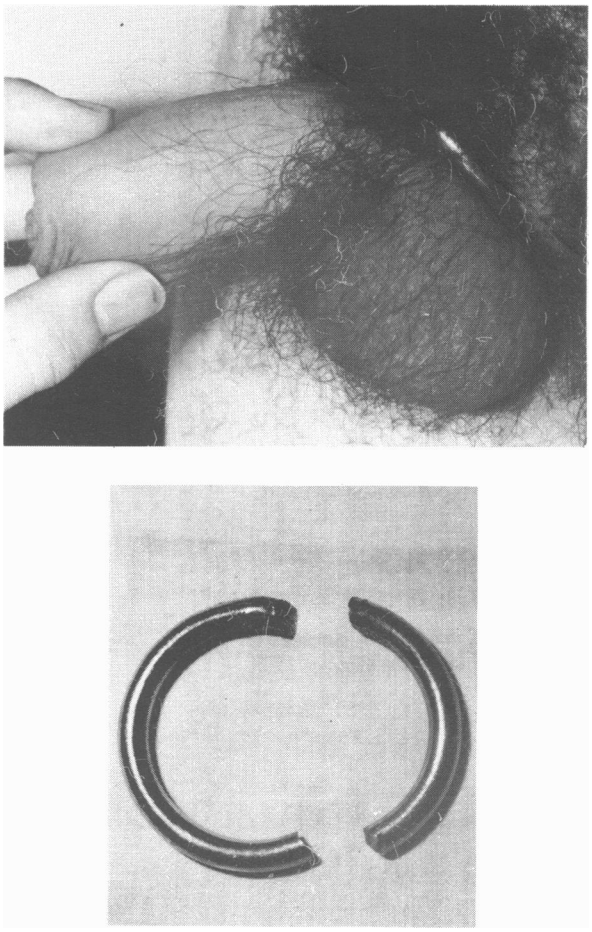
We describe a case in which the use of a proprietary sexual aid necessitated surgical intervention to effect its removal. Investigation showed these items to be in common usage.

Case history

A 21 year old man presented to the accident and emergency department on the morning of 24 December 1981. For three years he had been in the habit of using a so called "cock ring." The device consisted of a simple metal ring which was fitted around the base of the penile shaft proximal to the scrotum before erection. Erection would cause the ring to tighten, thus occluding venous return and resulting in maintenance and prolongation of the turgid state of the penis.

Having recently mislaid his usual ring, the patient had purchased a new one, which he had used for the first time the previous night, some 12 hours before presentation. Although enjoying satisfactory intercourse, he had been unable to remove the ring either immediately after the act or on waking the next morning. The ring was causing pain and he was unable to urinate.

Examination showed the penis to be congested and semierect (figure). There was moderate scrotal oedema and the ring was firmly in situ around the base of the penile shaft, obstructing venous return. All attempts to pull the ring off were unsuccessful. A rotary cutter used to remove rings after finger injuries made no progress and finally broke. Eventually the ring was cut in two places with a hacksaw, the patient sustaining a small scrotal laceration in the process. The ring (figure) was 5 cm internal diameter and the metal 0·8 cm in cross section.



Above: Appearance at presentation. Below: The ring after removal.

Comment

Similar rings are apparently readily found in shops supplying sexual aids in and around central London. They are available in various sizes and no warning is supplied. The possibility of the reported complication of the use of these rings is inherent in their mode of action. In more extreme cases they could conceivably cause penile ischaemia or even necrosis.

We think that rings of this type should be withdrawn from circulation, and since there seems to be a demand they should be replaced by models with a clasp and hinge mechanism for rapid release. Alternatively they might be made of rubber or a similar elastic material, which could be stretched if necessary.

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Identical twins with identical vesicoureteric reflux: chronic pyelonephritis in one

It is well established that chronic pyelonephritic scarring occurs predominantly in kidneys drained by ureters in which vesicoureteric reflux occurs in childhood.[1] Most of such ureters develop a competent vesicoureteric valve during follow up periods of at least 10 years,[2] so that only a few adults with pyelonephritic scarring still show reflux.[3] Reflux of sufficient severity to be associated with renal scarring is inherited as an autosomal dominant with high penetrance.[4] Controversy continues as to whether reflux per se causes renal scarring during a period of high vulnerability in early childhood or whether the kidney is only damaged when the refluxing urine is infected.[3] We describe identical twins in whom bilateral vesicoureteric reflux persisted into adult life, only one of whom developed chronic pyelonephritis, suggesting that an environmental factor is required before reflux leads to scarring.