extraction of a ureteric calculus. She was started on 200 mg of trimethoprim twice daily in accordance with our policy of prophylaxis against urinary infection. She soon developed a cutaneous erythematous reaction, which progressed rapidly to florid toxic epidermal necrolysis. Although she had denied any allergies at the initial clerking it subsequently emerged that she did have a history of reaction to trimethoprim.

We have treated over 2000 patients for urinary calculi at the London Stone Clinic. Most received trimethoprim, and this was the only case of epidermal necrolysis. In view of its widespread use doctors should be aware that trimethoprim is capable of causing toxic epidermal necrolysis.

Idiosyncratic reaction resembling toxic epidermal necrolysis caused by chloroquine and Maloprim

Mr P A PHILLIPS-HOWARD (London School of Hygiene and Tropical Medicine, London WC1E 7HT) and Dr J WARWICK BUCKLER (City Hospital, Nottingham) write: Serious cutaneous reactions have been associated with the combination of pyrimethamine and sulfadoxine (Fansidar) used for malaria chemoprophylaxis.[1 2] We report a rare and severe idiosyncratic cutaneous reaction to chloroquine and the combination of pyrimethamine and dapsone (Maloprim).

A 59 year old white British man visited the Republic of South Africa in May 1986. He started a prophylactic regimen of chloroquine 300 mg (Nivaquine, May and Baker Ltd) weekly and pyrimethamine 12·5 mg and dapsone 100 mg (Maloprim, Wellcome Foundation Ltd) one tablet weekly, taking both on the same day five days before he set off. Concurrent drugs were 1 g of aspirin and 40 mg of propranolol daily. He had taken these continuously for the past decade with no untoward effect.

Within 24 hours of arrival he developed bullous erythema on exposed skin areas. Symptoms resembling sunburn subsided over two to three days. A second dose of the same regimen was taken one week after the first. Within three to four hours he developed giant bullae affecting the soft palate, uvula, and epiglottis. A single oral dose of 5 mg of dexamethasone was given to relieve oedematous swelling of his pharynx.

Some of the lesions ulcerated and the skin exfoliated on large areas of the limbs and trunk. Nikolsky's sign was positive: superficial layers of skin could be rubbed off with light pressure. There was severe lassitude and he felt feverish. The chemoprophylaxis was stopped after the second dose, but the skin changes took 10 days to resolve and left scars on the legs.

Inquiries to the drug companies found no similar reports, suggesting no association with batch impurities. The clinical manifestations closely resembled toxic epidermal necrolysis,[3] although it was not possible to confirm the diagnosis by biopsy. No other cases attributed to prophylaxis with chloroquine and the combination of pyrimethamine and dapsone have been reported to the Committee on Safety of Medicines in Britain (personal communication).

The temporal association strongly implicates malaria chemoprophylaxis, but the evidence about which drug was the cause is incomplete. Patch testing was rejected because this would reflect only sensitisation to surface allergens, and prick testing was considered to be too dangerous. The patient had travelled extensively and had taken the combination of pyrimethamine and dapsone on at least 20 previous occasions without complication. This was, however, the first time he had taken chloroquine.

Serious cutaneous adverse reactions have been associated with dapsone,[4] sulphonamides,[5] and chloroquine[6] at high doses. Severe skin reactions to prophylactic doses are extremely rare. Recently, a case of severe dapsone syndrome was attributed to the combination of pyrimethamine and dapsone taken once weekly in addition to chloroquine.[7] Toxic epidermal necrolysis, with a positive Nikolsky's sign, has been reported during treatment with chloroquine alone.[8]

1 Miller KD, Lobel HO, Satriale RF, *et al.* Severe cutaneous reactions among American travellers using pyrimethamine-sulfadoxine (Fansidar) for malaria prophylaxis. *Am J Trop Med Hyg* 1986;**35**:451-8.
2 Hellgren U, Rombo L, Berg B, *et al.* Adverse reactions to sulphadoxine-pyrimethamine in Swedish travellers: implications for prophylaxis. *Br Med J* 1987;**295**:365-6.
3 Goldstein SM, Wintroub BW, Elias PM, *et al.* Toxic epidermal necrolysis. *Arch Dermatol* 1987;**123**:1153-5.
4 Browne SG. Toxic epidermal necrolysis. *Br Med J* 1961;i:550-3.
5 Bergoend H, Loffler A, Amar R, Maleville J. Reactions cutanées survenues au cours de la prophylaxie de masse de la méningite cérébro-spinale par un sulfamide long-retard (à propos de 997 cas). *Ann Dermatol Venereol* 1968;**95**:481-90.
6 Biilmann-Petesen ML. Exfoliative erythroderma after chloroquine treatment. *Ugeskr Laeger* 1959;**121**:579-80.
7 Grayson ML, Yung AP, Doherty RR. Severe dapsone syndrome due to weekly Maloprim. *Lancet* 1988;i:531.
8 Kanwar AJ, Singh OP. A report of toxic epidermal necrolysis after the ingestion of one tablet of chloroquine *Indian J Dermatol* 1978;**21**:73-7.

Acyclovir malabsorption

Dr A MINDEL and Ms O CARNEY (Academic Department of Genitourinary Medicine, University College and Middlesex School of Medicine, London W1N 8AA) write: Little is known about the exact site of absorption of oral acyclovir, although it is presumed to be absorbed over the entire length of the small intestine. We recently saw a patient with recurrent genital herpes whose terminal ileum had been removed at surgery. She failed to respond to suppressive oral acyclovir in a dose up to 400 mg four times a day and was found to have malabsorption of the drug. Adequate therapeutic concentrations were obtained and the recurrences suppressed when the dose was increased to 800 mg four times a day.

A 22 year old woman presented in December 1986 with a history of recurrent genital herpes. Her attacks occurred every five to six weeks and each lasted five to 10 days. These had been occurring since mid-1985. In 1979 her appendix had been removed after several months of abdominal pain. In 1980 she presented with acute abdominal pain and was found to have small bowel obstruction due to adhesions. At surgery 0·6 m of terminal ileum was removed, although the ileocaecal valve was preserved. After surgery she complained of intermittent diarrhoea. In 1986 she had extensive gastrointestinal investigations. Her weight was constant and there was no evidence of malabsorption; albumin, folate, and vitamin B_{12} concentrations were normal. In February 1987 she was given suppressive oral acyclovir for recurrent genital herpes at a dose of 200 mg four times daily, but her recurrences continued with unchanged frequency and severity. In June the dose was increased to 400 mg four times daily, with little success. Her plasma acyclovir concentration was measured two hours after the last oral dose and found to be 0·32 μmol/l (normal 5·21 (SD 1·32) μmol/l—see table) (P D Whiteman *et al*, second international acyclovir symposium, 1983). We therefore increased the dose to 800 mg four times a day. At this dose the peak serum value was 3·34 μmol/l (normal 8·16 (1·98) μmol/l).[1] From August to December she had no recurrences and we reduced her dose to 800 mg twice daily; a few days later she had a breakthrough recurrence. She immediately returned to the higher dose and was subsequently free of recurrence.

Maximum plasma acyclovir values (μmol/l) taken two hours after last dose

Dose (mg)	Our patient	Experimental*
200 mg	Not measured	3·02 (0·50)
400 mg	0·32	5·21 (1·32)
800 mg	3·34	8·16 (1·98)

*Mean (SD) (P D Whiteman *et al*, second international acyclovir symposium, 1983).

Frequently occurring genital herpes may be controlled with suppressive oral acyclovir.[1-3] On 200 mg four times a day recurrences are rare and the few that occur will be minor and short lived.[1] If a patient fails to respond to treatment there are several explanations to be considered. Is the medication being taken; are the recurrences herpes or some other genital complaint—for example, candida; could the patient have a drug resistant strain (already reported in immunocompromised patients)[4]; and is the drug being absorbed? The possibility of poor absorption should be borne in mind particularly if the patient has had abdominal surgery. Our patient had no other obvious evidence of malabsorption. This suggests that acyclovir may be absorbed over only a very limited region of the bowel and that the problem may be overcome by increasing the total daily dose.

We thank Dr Lancaster-Smith from the Sloane Hospital in Kent for permission to report this case and Dr Holdich from the Wellcome Research Laboratories radioimmunoassay section, Beckenham, Kent, for measuring the serum acyclovir concentrations.

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3 Straus SE, Takiff HE, Seidlin M, *et al.* Suppression of frequently recurring genital herpes. A placebo-controlled double blind trial of oral acyclovir. *N Engl J Med* 1984;**310**:1545-50.
4 Burns WH, Saral R, Santos GW, *et al.* Isolation and characterisation of resistant herpes simplex virus after acyclovir therapy. *Lancet* 1982;i:421-3.

Sterile abscess formation by continuous subcutaneous infusion of diamorphine

Drs P J HOSKIN and G W HANKS and Sister I D WHITE (Continuing Care Unit, Royal Marsden Hospital, Sutton, Surrey SM2 5PT) write: Continuous subcutaneous infusion of diamorphine and antiemetic drugs in patients with advanced cancer is generally free from complications apart from minor induration and erythema at the skin site.[1] We have observed a severe local reaction with sterile abscess formation at the site of infusion in two patients who received a subcutaneous infusion using a Graseby MS series syringe driver and a 25 gauge Vygon butterfly infusion set.

A 70 year old woman received aqueous diamorphine over 22 days in a dose increasing from 30 to 100 mg/h. Solutions of 60 to 222·5 mg/ml were infused at rates of 0·3 to 0·5 ml/h. Frequent changes of site were required (mean every 2·5 days, range 20 hours to 5 days) because of a severe reaction consisting of extensive induration and fluctuant swelling at the injection site. The site of infusion, concentration of diamorphine, and volume of infusate did not influence this reaction; nor did the addition of chlorpromazine or methotrimeprazine. Biopsy specimens taken from each of nine sites about 16 hours after death showed histological appearances typical of a sterile abscess. Swabs from fluid drained from each site grew only normal skin flora.

A 42 year old woman received aqueous diamorphine increasing from 83·3 to 200 mg/h. Solutions of 125 to 240 mg/ml were delivered at rates of 0·6 to 0·8 ml/h. Within 24 hours the infusion site became painful with erythema, induration, and a fluctuant mass. The site was changed to the opposite thigh, where a similar reaction developed. Fluid obtained from surgical drainage of the abscesses grew only normal skin flora.

The development of sterile abscesses after subcutaneous injection has been reported previously with chlorpromazine[2] (M Lacomme, May and Baker abstract No 54107, 1953). In the cases reported here simple aqueous solutions of diamorphine hydrochloride without preservative were used, and the addition of phenothiazines in the first case did not affect the reaction. The only common feature was the use of relatively high doses of diamorphine. This has previously been associated with increased local skin irritation[1 2] but not with abscess formation. The infusion system is commonly used and has not been associated with specific reactions. This idiosyncratic response to subcutaneous infusion of aqueous diamorphine is unusual. Early recognition of such complications and use, whenever possible, of the rectal route as the first alternative to oral treatment are recommended.

We thank Dr R L Carter for performing the histological examination.

1 Nicholson H. The success of the syringe driver. *Nursing Times* 1986;**82**:49-51.
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