SHORT REPORTS

Piroxicam poisoning

Piroxicam is a potent non-steroidal anti-inflammatory drug. Experience with overdosage is limited. We describe a patient who took a large dose of piroxicam.

Case report

A 25 year old Chinese man weighing 46 kg was admitted to hospital about two hours after ingesting 56 capsules of 10 mg piroxicam, 97 tablets of 125 mg griseofulvin, and about 10 tablets of 100 mg fentiazac. He had been suffering from psoriatic arthropathy affecting both knee and ankle joints and had been taking piroxicam 30 mg daily for nine months. Other analgesics, including aspirin, paracetamol, fentiazac, and indomethacin, had also been prescribed at various times. He had bought griseofulvin over the counter thinking that his skin condition was a fungal infection. Feeling depressed about his chronic illness and being unemployed, he attempted suicide.

On examination he was drowsy and responded only to pain. There were no other neurological abnormalities, and the abdomen was soft and not tender. Blood pressure was 130/90 mm Hg, pulse 82 beats/minute, respiration 18 breaths/minute, and temperature 36.5°C. Gastric lavage was performed. An antacid and intramuscular injections of vitamin K₁ 10 mg daily were given. There were no important complications of the haemopoietic system and renal function, and serum electrolyte concentrations were normal. Results of liver function tests, however, were abnormal: alkaline phosphatase 112 IU/l, γ -glutamyl transferase 19 IU/l, albumin 19 g/l, globulin 51 g/l, serum aspartate aminotransferase 25 IU/l, and serum alanine aminotransferase 48 IU/l. Piroxicam serum concentrations were 23.5 mg/l, 14.6 mg/l, and 4.7 mg/l at 12, 36, and 84 hours respectively after admission (figure).

Serum concentrations of piroxicam after admission.

His conscious level gradually improved after admission. After 12 hours he could respond to simple verbal commands, and he became fully conscious after two days. From 14 to 60 hours after admission he had episodic involuntary movements of the lips and jaw and myoclonic twitching of his limbs. Each episode lasted about five seconds, and he remained conscious during such attacks. No muscle relaxant was given because the twitches were transient.

No other complications were observed, and he made an uneventful recovery from his overdose after four days, although his arthritis flared up and required further treatment.

Comment

This is the first reported case of piroxicam overdosage in man with documented serum concentrations. The dose ingested was more than 20 times the usual daily maintenance dose of 20 mg. The highest serum concentration of piroxicam measured was 23.5 mg/l at 12 hours after admission, which is about 10 times the usual therapeutic concentration of 1-3 mg/l.¹ He had also taken a large dose of griseofulvin, but unfortunately blood concentrations were not available. Fentiazac is a non-steroidal anti-inflammatory drug with antipyretic and

analgesic properties. The usual daily dosage is 400 mg. The amount of fentiazac absorbed after gastric lavage would probably be small and of little importance.

The main signs were altered consciousness and muscle twitchings. The exact causes of these were unknown, but griseofulvin has been associated with dizziness, mental confusion, irritability, and impaired coordination.² Side effects of piroxicam have occasionally included headache and dizziness, although their incidences in double blind comparative studies have been lower than those reported with indomethacin.³ Thus the drowsiness and muscle twitchings could not be definitely attributed to piroxicam.

Gastrointestinal bleeding is usually the major side effect of most non-steroidal anti-inflammatory drugs. Piroxicam seemed to be well tolerated since the patient did not complain of gastric discomfort or gastrointestinal bleeding despite a history of gastric erosions. On admission a tendency for bleeding was expected in view of his deranged liver function and the inhibiting effect of piroxicam (as with many other non-steroidal anti-inflammatory drugs) on platelet aggregation induced by adenosine diphosphate,⁴ but no bleeding tendency was observed.

Griseofulvin and piroxicam are both metabolised mainly by the liver. Despite the impaired liver function the biochemical variables did not indicate further deterioration. The serum half life of piroxicam (figure) was about 35 hours, which corresponded to that in a normal subject taking the recommended dose.⁵

We thank Pfizer for help in estimating the blood piroxicam concentrations in this patient.

¹ Wiseman EH. Piroxicam (Feldene): pharmacokinetics and the clinical management of inflammation. *Eur J Rheum Inflam* 1978;1:338-45.

² Roger HJ, Spector RG, Trounce JR. *A textbook of clinical pharmacology*. Sevenoaks: Hodder and Stoughton, 1981:696.

³ Davis J, Dixon ASTJ. Efficacy and safety of piroxicam compared with indomethacin in the management of rheumatoid arthritis. *Am J Med* 1982;72:27-30.

⁴ Weintraub M, Case K, Kroening B, Bosmann HB. Effects of piroxicam on platelet aggregation. *Clin Pharmacol Ther* 1978;23:134-5.

⁵ Makisara P, Nutotio P. Pharmacokinetic and clinical study of piroxicam. In: *Piroxicam*. International Congress Series No 1. London: Academic Press, 1978:25-30.

(Accepted 18 May 1983)

Department of Medicine, United Christian Hospital, Kowloon, Hong Kong

GEORGE C C LO, MB, MRCP, physician

Advanced Semiconductor Materials Plating Ltd, Kowloon, Hong Kong

JOHN Y W CHAN, MB, MRCP, consultant physician

Correspondence to: Dr George C C Lo, Grey Hospital, Greymouth, New Zealand.

Prophylactic topical acyclovir for frequent recurrent herpes simplex infection with and without erythema multiforme

Reactivation of herpes simplex virus infection may cause cold sores, sometimes so frequently as to be distressing. A few patients suffer the disabling skin complication of erythema multiforme after each episode of reactivation. We have reported successful prophylactic use of topical acyclovir in one such patient¹ and have now evaluated this form of treatment in a double blind controlled crossover trial.

Methods and results

Patients were admitted to the trial who had had at least five attacks of reactivation of herpes simplex infection per year or three attacks in the

preceding three months. A preparation of 5% acyclovir in modified aqueous cream (containing 40% propylene glycol) or cream alone was applied twice daily to all areas where herpes lesions occurred. Patients received 16 weeks of each treatment consecutively in random order and they were assessed at monthly intervals for the frequency of herpes simplex lesions or erythema multiforme and for compliance.

Eighteen patients entered the trial but two failed to complete it. Five patients had had herpes simplex lesions alone and 11 had had lesions followed by erythema multiforme. Twelve of the patients had had herpes lesions in the orofacial area and four had had lesions in the genital area or buttocks. Subtyping of the herpes virus was not carried out. For the entire group of patients, the mean number of episodes of herpes virus infection and erythema multiforme occurring with each treatment were compared with Wilcoxon's signed rank test. The proportion of patients having episodes of herpes infection and erythema multiforme with each treatment were compared with Fisher's exact test. These tests were performed on patients receiving placebo first, on those receiving acyclovir first, and on all the patients combined.

There was no significant difference between the mean number of episodes or the proportion of patients having episodes of viral reactivation or of erythema multiforme during acyclovir or placebo treatment (table). The results were not influenced by the order in which acyclovir or placebo was

Comparison of number of herpes simplex virus lesions and episodes of erythema multiforme occurring during acyclovir and placebo treatment

	Placebo	Acyclovir
<i>All patients</i>		
Mean number of episodes*:		
herpes virus infection	3.3	3.7
erythema multiforme	1.2	1.1
Proportion of patients with episodes:		
herpes virus infection	10/16	14/16
erythema multiforme	5/11	8/11
<i>Placebo followed by acyclovir</i>		
Mean number of episodes:		
herpes virus infection	3.7	3.8
erythema multiforme	2.2	1.6
Proportion of patients with episodes:		
herpes virus infection	5/9	9/9
erythema multiforme	4/6	5/5
<i>Acyclovir followed by placebo</i>		
Mean number of episodes:		
herpes virus infection	2.7	3.6
erythema multiforme	0.3	0.5
Proportion of patients with episodes:		
herpes virus infection	5/7	5/7
erythema multiforme	1/6	3/6

*Mean number of episodes per patient in 16 weeks.

given. Episodes of reactivation of herpes virus did not correlate with recorded failure of compliance. No adverse reactions were recorded during the trial despite the application of the cream for 32 weeks, of which 16 were with acyclovir.

Comment

After the early apparent success of acyclovir in one patient the failure of this trial to show that topical prophylactic acyclovir can prevent attacks of herpes virus infection and erythema multiforme is disappointing. Topical treatment was chosen for this trial as we thought that it was likely to offer the safest form of continuous prophylaxis. In the early treatment of herpes labialis acyclovir cream was shown significantly to shorten the duration of lesions and, when the treatment was started before vesicles developed, to increase the number of lesions aborting.² In a study in initial and recurrent genital herpes acyclovir cream significantly shortened the healing of all lesions (Kinghorn GR, *et al*, unpublished observations). In studies of the use of 5% acyclovir ointment in primary genital herpes virus infection Corey *et al* showed that symptoms were less severe and virus shedding was curtailed but that the appearance of new lesions was not prevented and there was little effect on recurrent disease.³

The failure of topical acyclovir to prevent herpes simplex virus lesions suggests that concentrations of acyclovir were inadequate at the site of virus replication either because of inadequate penetration or because of insufficiently frequent application. At least one patient observed the development of "escape" lesions outside the treatment area. This was not specifically assessed during the trial and, as with compliance, their occurrence may have been more frequent. The development of mutants of herpes virus resistant to acyclovir is a further possibility which has not yet been tested.

The successful use of intravenous acyclovir in preventing herpes virus infections in immunocompromised patients⁴ would support the observation that maintenance of adequate tissue levels of the drug is

important. With this in mind we are investigating the use of oral acyclovir to achieve better suppression of the formation of lesions and, we hope as well, the more serious erythema multiforme.

- Kennedy CTC, Leigh IM, Ridgway HA, Wansbrough-Jones MH, Bridgen D. Treatment of erythema multiforme secondary to herpes simplex by prophylactic topical cyclovir. *Br Med J* 1981;283:1360-1.
- Fiddian AP, Yeo JM, Stubbings R, Dean D. Successful treatment of herpes labialis with topical acyclovir. *Br Med J* (in press).
- Corey L, Nahmias AJ, Guinan ME, Benedetti JK, Crechlow CW, Holmes KK. A trial of topical acyclovir in genital herpes simplex virus infections. *N Engl J Med* 1982;306:1313-9.
- Saral R, Burns WH, Laskin OL, Santos GW, Lietman PS. Acyclovir prophylaxis of herpes-simplex-virus infections. *N Engl J Med* 1981;305:63-7.

(Accepted 24 May 1983)

St George's Hospital, London SW17 0RE

H A FAWCETT, MB, MRCP, registrar

M H WANSBROUGH-JONES, MSC, MRCP, consultant physician

Wellcome Research Laboratories, Beckenham, Kent

A E CLARK, BSC, clinical research associate

St John's Hospital for Diseases of the Skin, London WC2

I M LEIGH, MB, MRCP, senior registrar

Correspondence to: Dr M H Wansbrough-Jones.

Effect of thalidomide on orogenital ulceration

Severe recurrent oral and genital ulceration may be difficult to treat, but a recent report suggested that thalidomide may be used in Behçet's syndrome.¹ We report the effect of thalidomide in three patients with severe orogenital ulceration.

Case reports

CASE 1

A 20 year old white woman had an eight year history of recurrent severe mouth and vulval ulcers, which failed to respond to multiple systemic and topical antibiotics and antifungal treatment. Trials of colchicine and cytotoxic drugs were unsuccessful, and only prednisolone in excess of 30 mg daily influenced the disease. Results of investigations were mostly normal except for an increased alkaline phosphatase activity of 332 IU/l (normal 46-190 IU/l). Anticomplementary activity was detected in the serum, suggesting the presence of circulating immune complexes, and the plasma complement degradation product (C₃d) concentration was raised.

She was admitted and, with full informed consent, given thalidomide 200 mg twice daily for five days followed by 100 mg twice daily. Three weeks after admission she was discharged taking thalidomide 200 mg each evening. Improvement continued over the next month: the mouth ulcers healed completely and only one small vulval ulcer remained. The alkaline phosphatase activity also returned to normal. Concern regarding the long term use of thalidomide led to its withdrawal and replacement with clofazimine 200 mg twice daily, though this had previously been ineffective. Over the following 10 weeks the vulval and oral ulcers returned. She was readmitted and given thalidomide 400 mg each evening. The ulcers healed over the next four days, and thalidomide was again withdrawn.

CASE 2

A 29 year old white woman had an eight year history of oral and vaginal ulcers, which were controlled only with high doses of prednisolone. Results of investigations were mostly normal except that the C₃d concentration was increased.

With full informed consent she was admitted and started on thalidomide 200 mg twice daily for five days; the prednisolone dosage was gradually reduced. Within a week ulcers that had been present for up to two months were healing, and she was discharged taking thalidomide 200 mg at night. A month later no ulcers remained and the dose was reduced to 100 mg daily. After a further two weeks she developed more ulcers, which rapidly cleared when the dose was increased to 150 mg daily. She remained free of ulcers for the first time in eight years, and over the next six weeks the dose was reduced to zero. The component degradation product concentration returned to normal. Her condition relapsed one week after thalidomide was stopped but responded to a further short course of treatment.