SHORT REPORTS

Oral (E)-5-(2-bromovinyl)-2'-deoxyuridine in severe herpes zoster

(E)-5-(2-bromovinyl)-2'-deoxyuridine (BVDU) is a nucleoside analogue that inhibits the replication of herpes simplex virus type 1 (HSV-1) in cell culture (primary rabbit kidney) at a concentration of 0.01 mg/l, but does not affect normal cell metabolism at concentrations up to 100 mg/l.¹ BVDU has also been found effective in the local and systemic treatment of HSV-1 skin lesions, and its associated mortality, in athymic nude mice¹ and in the local treatment of HSV-1 keratitis in rabbits.² The compound is readily absorbed when given orally to mice³ or rabbits. BVDU doses of 500-1000 mg/kg body weight/day are well tolerated by mice, even if administered over 20 days.⁴

Recently we have found that BVDU is also highly active against varicella zoster virus, inhibiting the cytopathogenicity of this virus in human skin fibroblast cultures at a minimum concentration of 0.004 to 0.04 mg/l. We now report on a clinical study with oral BVDU in the treatment of four patients with severe localised or disseminated herpes zoster.

throughout, 10 times higher than the serum drug concentrations, which suggests that BVDU is actively excreted by the kidney.

Comment

Oral treatment with BVDU caused prompt recovery of patients with severe herpes zoster. Existing lesions regressed within the first few days after the start of BVDU treatment, and no new lesions developed while the patients were taking BVDU. There was no evidence of drug toxicity in bone marrow, liver, kidney, or any other organ. The beneficial effects obtained with BVDU in the systemic treatment of herpes zoster are reminiscent of those reported with acyclovir.⁵

A practical advantage of BVDU is that it can be administered orally apparently with high efficacy. The clinical value of BVDU as a systemic anti-herpes agent has to be confirmed by carefully controlled studies. Our preliminary results should provide the necessary impetus for such studies.

We thank Dr R Busson and Professor H Vanderhaeghe (Rega Institute) for the synthesis of BVDU.

Clinical details of four patients with herpes zoster given oral BVDU

Case No	Age (years)	Sex	Location of lesions	Duration of lesions before treatment (days)	Underlying disorder	Other antiviral treatment
1	47	F	Thoracic	2	Metastatic breast carcinoma	None
2	54	M	Thoracic	6	Non-Hodgkin's lymphoma	Zoster immune globulin
3	60	F	Disseminated	2	Metastatic breast carcinoma	None
4	68	F	Cervical	5	Hyperthyroidism	BVDU eye drops (0.1%)
			Ophthalmic	0.5		
			Disseminated			

Case reports

All four patients that were treated with BVDU (table) had severe localised or disseminated herpes zoster lesions, and three out of the four had a malignant disorder for which they had been given intensive chemotherapy.

BVDU was administered by mouth at 7.5 mg/kg body weight/day (three or four capsules of 125 mg BVDU daily, eight or six hourly) for five days. Informed consent was obtained from all patients. The patients were examined daily during treatment and at regular intervals afterwards. Complete blood count; urea, creatinine, and electrolyte concentrations; and activities of liver enzymes (aspartate transaminase, alanine transaminase, and γ -glutamyl transpeptidase) were measured at the first, third, and fifth day of treatment. Drug concentrations in serum and urine were measured by bioassay, based on the inhibition of HSV-1 cytopathogenicity in cell culture.³

In all four patients progression of vesicle formation was completely arrested within 24 hours of starting treatment with BVDU: no new lesions developed during treatment, and the lesions which had developed before treatment healed briskly. For those patients (cases two and four) who presented with dissemination of the herpes zoster lesions, the prompt response to treatment was also reflected by a dramatic improvement in their general condition: fever resolved within 24 hours of starting treatment with BVDU. In case 4, where dissemination had occurred just before treatment, the newly formed lesions disappeared completely within two days of treatment. None of the patients who were treated with BVDU experienced any discomfort or showed any signs of drug toxicity. The biochemical and haematological blood values remained unchanged during the observation period. Plasma and urine concentrations of BVDU were measured in cases 1 and 3; the serum drug concentrations varied from 1 to 1.5 mg/l from one to three hours after BVDU administration. This concentration is about 100 times higher than the minimum effective dose required to inhibit VZV replication in cell culture. The urine drug concentrations were 10-15 mg/l

¹ De Clercq E, Descamps J, De Somer P, Barr PJ, Jones AS, Walker RT. (E)-5-(2-Bromovinyl)-2'-deoxyuridine: a potent and selective anti-herpes agent. *Proc Natl Acad Sci USA* 1979;76:2947-51.

² Maudgal PC, De Clercq E, Descamps J, et al. (E)-5-(2-Bromovinyl)-2'-deoxyuridine in the treatment of experimental herpes simplex keratitis. *Antimicrob Agents Chemother* 1980;17:8-12.

³ De Clercq E, Descamps J, De Somer P, Barr PJ, Jones AS, Walker RT. Pharmacokinetics of (E)-5-(2-bromovinyl)-2'-deoxyuridine in mice. *Antimicrob Agents Chemother* 1979;16:234-6.

⁴ De Clercq E, Descamps J, Maudgal PC, et al. Selective anti-herpes activity of 5-(2-halogenovinyl)-2'-deoxyuridines and 2'-deoxycytidines. In: Collier LH, Oxford J, eds. *Developments in antiviral therapy*. London: Academic Press (in press).

⁵ Selby PJ, Powles RL, Jameson B, et al. Parenteral acyclovir therapy for herpesvirus infections in man. *Lancet* 1979;ii:1267-70.

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Voluntary chlorine inhalation: A new form of self-abuse?

In many forms of self-abuse noxious substances are inhaled. Although accidental exposure to chlorine gas from mixing household cleaning agents has been reported,¹ this patient inhaled chlorine for pleasure.

Case report

In November 1978 a 41-year-old electrician began mixing Vim and Ajax cleaning powders with water and sniffing the fumes released. He would occasionally heat the mixture to produce more fumes and would also smear the mixture over his arms. He was referred to the outpatient department in March 1979 with a six-week history of headache, sore eyes, swollen legs, and lethargy. He had no history of psychiatric illness or other forms of self-abuse, though he did smoke 20 cigarettes a day.

He had severe conjunctival injection, central cyanosis, a raised jugular venous pressure, gross oedema, and ascites. The heart was enlarged, the pulmonary second sound accentuated, and a third heart sound was audible.

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Blood oxygen and carbon dioxide pressures during three admissions. Results are given under days after admission in each month

Pressure (kPa)	Month of admission											
	March				July				December			
	0	2	6	12	0	2	4	8	0	2	4	8
Oxygen	5.4	5.7	7.1	10.0	4.5	7.3	7.2	8.3	6.0	7.3	7.0	8.8
Carbon dioxide	8.7	8.8	6.7	6.0	9.6	9.7	7.1	5.1	9.3	7.9	5.6	5.6

Conversion: SI to traditional units—1 kPa $\approx$ 7.5 mm Hg.

Results of other investigations were: haemoglobin concentration 16.5 g/dl; packed cell volume 0.65 (65%); and peak expiratory flow rate (PEFR) 60 l/min (predicted value 535 l/min). A chest radiograph showed enlargement of the heart, and an electrocardiogram showed right axis deviation, right ventricular hypertrophy, and biatrial enlargement. Results of echocardiography showed that the right ventricular cavity was dilated; there was good left ventricular function, a normal mitral valve, and a small pericardial effusion. Cardiac catheterisation gave the following results: pulmonary artery pressure 80/50 mm Hg; mean right atrial pressure 22 mm Hg; and right ventricular pressure 80/20 mm Hg.

The table shows the severe hypoxia and hypercapnoea on each of his three presentations after further chlorine inhalation. After treatment on each occasion with diuretics, bronchodilators, digoxin, and oxygen he improved and his PEFR rose from 60 l/min to 200 l/min. Other tests at his best in hospital showed a forced expiratory volume in litres of 1.1 l (predicted value 4.8 l).

During the months in which he was no longer inhaling chlorine gas his heart size returned to normal and diuretics were stopped.

Comment

Vim and Ajax contain trichlorocyanuric acid, sodium carbonate, and sodium tripolyphosphate. When mixed with water chlorine is released and hypochlorite is formed in solution; hypochlorite reacts with protein to release chloramine, a respiratory tract irritant.

Acute exposure to high concentrations of chlorine results in headache, dyspnoea, coughing, lacrimation, and later the development of pulmonary oedema.² In patients studied soon after exposure, airways obstruction and hypoxaemia due to ventilation perfusion imbalance have been shown.² The pathological findings in fatal cases of acute chlorine poisoning include congestion of the tracheal mucosa, sloughing of the alveolar walls, and pulmonary oedema.³ In workers chronically exposed to concentrations of chlorine of under one part per million no appreciable ventilatory impairment has been shown.⁴

This case is unusual because the patient repeatedly inhaled chlorine for the pleasant effect he claimed to experience. He has developed pulmonary hypertension for which we have found no other cause, and although the physical signs improve after stopping chlorine inhalation they recur immediately his behaviour relapses.

I thank Dr A M Holmes for her advice and her permission to report this case.

¹ Faigel HC. Mixtures of household cleaning agents. *N Engl J Med* 1964; 271:618.

² Jones FL. Chlorine poisoning from mixing household cleaners. *JAMA* 1972;222:1312.

³ Warrack AJN. Another domestic hazard. *Med Sci Law* 1978;18:93-5.

⁴ Chester EH, Gillespie DG, Krause FD. The prevalence of chronic obstructive pulmonary disease in chlorine gas workers. *Am Rev Respir Dis* 1969;99:365-73.

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Psychiatric morbidity and physical toxicity associated with adjuvant chemotherapy after mastectomy

Doubt has been cast on claims that adjuvant combination chemotherapy causes little physical toxicity and psychiatric morbidity in patients with breast cancer (Bush H *et al*, unpublished observations).^{1 2}

This prompted us to compare the psychiatric morbidity in women treated with a combination of cyclophosphamide, methotrexate, and 5-fluorouracil (CMF) with that found in patients given melphalan or no further treatment. We also examined the relation between this morbidity and physical toxicity.

Patients, methods, and results

Half the weeks in a 24-month period were randomly selected. Women admitted in these weeks were included in the trial if their axillary lymph nodes were found at mastectomy to have been invaded by breast cancer (63 women), and they were randomised to receive CMF, melphalan, or no treatment (control subjects).

Trained interviewers administered the present-state examination shortly after surgery and three months and 12 to 18 months later to determine the incidence of psychiatric morbidity.³ They used a four-point scale (none to severe) to rate any physical toxicity, as did the clinicians following up these patients. Of the 63 patients, 59 completed all assessments.

Psychiatric morbidity—Of the 26 patients treated with CMF, 20 experienced an anxiety state compared with four of the 15 given melphalan and nine of the 18 control subjects (table). Depressive illness occurred more often in

Presence or absence of psychiatric morbidity judged to require treatment in patients with breast cancer. Figures in parentheses give percentage of treatment group showing morbidity

Treatment group	Anxiety*		Depression†		Sexual problems‡		Overall morbidity§	
	+	-	+	-	+	-	+	-
Mastectomy alone	9 (50)	9	9 (32)	19	5 (50)	5	9 (50)	9
Mastectomy and melphalan	4 (27)	11	5 (33)	10	3 (38)	5	5 (33)	10
Mastectomy and CMF	20 (77)	6	20 (77)	6	14 (70)	6	21 (81)	5

Significance of difference between numbers of patients showing morbidity and numbers of patients not showing morbidity at: * $\chi^2 = 10.1$, df = 2, $p < 0.01$; † $\chi^2 = 8.0$, df = 2, $p < 0.02$; ‡ $\chi^2 = 4.4$, df = 2, NS; § $\chi^2 = 9.9$, df = 2, $p < 0.01$. CMF = Cyclophosphamide, methotrexate, and 5-fluorouracil.

patients given CMF (20 patients) than in the melphalan group (five patients) or control group (nine patients). Fourteen of the 20 patients given CMF who had a satisfactory sex life before mastectomy subsequently experienced a severe loss of interest compared with three of the eight patients given melphalan and five of the 10 control subjects. Twenty-one patients treated with CMF developed psychiatric morbidity during follow-up. Fewer patients given melphalan (five) and fewer control subjects (nine) did so.

Physical toxicity—The clinicians and interviewers judged that 20 of the patients given CMF had experienced moderate or severe physical toxicity such as nausea or hair loss. Of these, 18 developed an anxiety state compared with two of the six patients with mild or minimal toxicity. The results for depressive illness were identical. Sexual problems occurred in 13 of the 15 patients with moderate or severe toxicity but in only two of the five patients who escaped it.

Disclosure of toxicity—The interviewers detected the toxicity in 18 of the 20 patients but the clinicians recognised it in only 12. Eight of these 12 reported the toxicity to a medical oncologist but not to the surgeons. Five of the eight patients who did not disclose toxicity failed to complete treatment compared with only two of the 12 who disclosed it.

Comment

Our sample is small, but our findings confirm a high incidence of psychiatric morbidity in patients given CMF and suggest that it is linked to physical toxicity.

The non-disclosure of toxicity is worrying, since it misleads clinicians about the consequences of treatment and results in poor compliance. It may explain the low toxicity reported in earlier studies. The greater honesty of patients with the medical oncologist may have reflected his skill in the use of cytotoxic drugs, his more detailed inquiry into toxicity, his sensitivity to cues given by the patients, and his greater awareness of barriers to communication.⁴