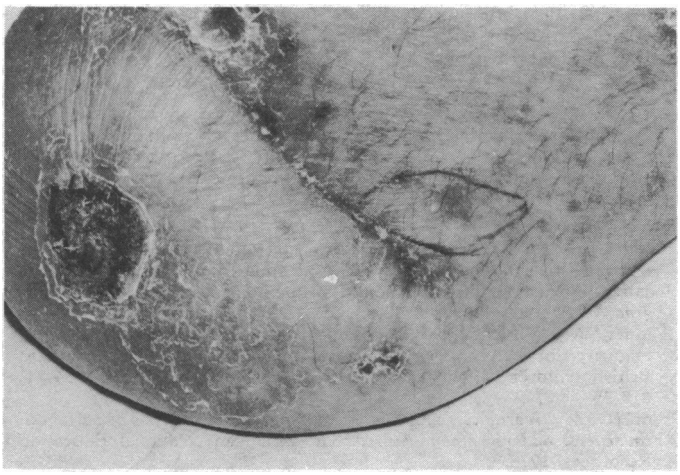
gation disclosed an ankle pressure index of 0·7, indicative of peripheral vascular disease. This index is a ratio of the systolic pressure of the posterior tibial artery at the ankle to that of the brachial artery and is normally greater than 1·0. There was no history of any skin disorder. Results of investigations were: haemoglobin concentration 11·6 g/dl, normochromic normocytic pattern; erythrocyte sedimentation rate 83 mm in the first hour; blood glucose concentration 14·3 mmol/l (257·4 mg/100 ml); and normal urea and electrolyte values. He was started on glibenclamide 5 mg daily and referred for surgical treatment.

The great toe was amputated but, unfortunately, this failed to heal and he had a below knee amputation three weeks later. He made a good postoperative recovery and underwent early rehabilitation with a prosthesis, which is the policy for diabetic amputees. He continued with glibenclamide and was given no other medication. Two months postoperatively and after several weeks of active rehabilitation he developed a blistering eruption over the amputated stump (figure). These clear, tense blisters developed on normal skin. Biopsy



Appearances of stump (below knee) two months after amputation.

showed a large subepidermal blister with a strong inflammatory component including numerous eosinophils. Direct immunofluorescence showed deposition of IgG along the basement membrane extending into the roof of the blister. These are the findings of bullous pemphigoid, but circulating antibasement membrane antibody was not detected on two separate occasions. The patient responded to rest and topical steroid treatment with clobetasol propionate ointment, and mobilisation was recommended. This caused a recurrence of the blistering eruption, remaining localised to the amputated stump, and final control was achieved only with oral prednisolone 15 mg daily. At no time did the eruption become generalised.

Comment

There are many skin problems which can affect the amputee who wears a prosthesis. The skin is exposed to frictional trauma and the tightly fitting socket of the prosthesis prevents air circulating, trapping perspiration. These factors increase the likelihood of skin complications, and contact dermatitis, eczemas, epidermoid cysts, bacterial and fungal infections, chronic ulcers, and verrucous hyperplasia have been reported.[1] The diabetic patient has additional hazards: there is an increased susceptibility to infection, and below knee amputations heal less well than above knee amputations.[2]

Localised bullous pemphigoid has been reported occurring around the scar of a previous injury to the leg,[3] and some cases of bullous pemphigoid have been observed to start with a localised group of blisters before the generalised eruption.[4] There is no increased incidence of bullous pemphigoid in diabetes, however, and there have been no previous reports of the eruption confined to the skin of the amputated stump. The aetiological relevance of trauma is difficult to assess, but blistering due to trauma alone results in skin separation in the granular zone of the epidermis without positive immunofluorescence findings.[5]

We thank Dr J D Ward for permission to report this case.

[1] Levy SW. Skin problems of the leg amputee. *Prosthet Orthot Int* 1980; 4:37-44.
[2] Steinberg FU. Rehabilitation of the diabetic amputee. In: Levin ME, O'Neal LW, eds. *The diabetic foot*. 3rd ed. St Louis: C V Mosby Co, 1983:303-29.
[3] Sparrow GP, Moynahan EJ. Localised pemphigoid. *Br J Dermatol* 1976; **95**, suppl 14:27.
[4] Sneddon IB, Church RE. Diagnosis and treatment of pemphigoid. Report on 22 cases. *Br Med J* 1955;ii:1360-3.
[5] Sulzberger M, Cortese TA Jr, Fishman L, *et al*. Studies on blisters produced by friction. *J Invest Dermatol* 1966;**47**:456-65.

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Asthma associated with N-acetylcysteine infusion and paracetamol poisoning: report of two cases

Intravenous infusion of *N*-acetylcysteine has been shown to be effective and safe for paracetamol poisoning. Side effects are said to be few and serious complications rare.[1-3] We, however, describe two patients with a history of asthma in whom an asthmatic reaction occurred after treatment.

Case reports

Case 1—An 18 year old woman was admitted to the emergency centre after having swallowed over the previous seven hours 65 tablets of Di-gesic containing a total of 21 g paracetamol and 2·1 g propoxyphene. She had a history of frequent "bronchitic" cough and hay fever and had been taking antihistamines by mouth and beclomethasone and cromoglycate by inhalation. Physical examination elicited only general weakness and tiredness. Intravenous infusion of *N*-acetylcysteine was begun according to a standard protocol.[1] After infusion of 9 g over 15 minutes she developed increasing tachypnoea, central cyanosis, and diffuse bilateral wheezing. Peak expiratory flow rate was 180 l/min and arterial blood gas values (pH 7·43) were: oxygen pressure 10·2 kPa (77 mm Hg), carbon dioxide pressure 4·4 kPa (33 mm Hg), bicarbonate concentration 22 mmol (mEq)/l, and base excess −1·0 mmol (mEq)/l. The infusion was stopped and the patient responded to intravenous aminophylline infusion and salbutamol inhalation. She remained well over the next three days and was discharged. Her serum paracetamol concentration on admission was 84 mg/l, which fell further after admission.

Case 2—A 16 year old girl weighing 91 kg was admitted to the emergency centre one and a half hours after swallowing 50 tablets of Panadol, which contained a total of 25 g paracetamol. She had a history of asthma as a child and had been treated with salbutamol and beclomethasone inhalation. Infusion of *N*-acetylcysteine was instituted according to the usual protocol. After receiving 13·5 g over 15 minutes she had a severe attack of bronchial asthma. The infusion was stopped and she responded to intravenous aminophylline infusion. After a week of obervations in the ward (during which time no clinical or biochemical evidence of liver dysfunction appeared) she was transferred to the psychiatric service. Her serum paracetamol concentration on admission and two and a half hours later were 203 and 125 mg/l respectively.

Comment

Paracetamol, singly or in combination with other drugs in proprietary preparations, is one of the most popular and easily available analgesic and antipyretic agents, and accounts for an increasing number of attempted suicides in Australia and Britain.[3] Hepatotoxicity is the most serious complication and a major cause of morbidity and mortality in these cases.[4] In recent studies Prescott *et al* have shown *N*-acetylcysteine to be effective and safe in the treatment of this condition.[1] Intravenous administration is preferred to the oral route, which has the disadvantage of unreliable absorption due to the use of oral activated charcoal and to vomiting. Vomiting often occurs in such cases as a result of other drugs ingested or is induced as a therapeutic measure.

N-Acetylcysteine is now available for intravenous use. The indications and methods of administration have been described[1] and are adopted in this hospital. Prescott and colleagues recommended

immediate treatment for any patient presenting within eight hours of ingesting more than 7·5 g paracetamol and that it should be continued or terminated as guided by the serum paracetamol concentration subsequently available. Side effects are said to be few and uncommon and include nausea, vomiting, hypokalaemia, metabolic acidosis, and mild thrombocytopenia. Rarely have these required withdrawal of treatment. Breen *et al* reported one case of rash necessitating withdrawal.[3] Walton and colleagues reported one patient who developed an anaphylactoid reaction with rash, hypotension, and bronchospasm.[5] No case of isolated bronchospasm has been reported.

Our two patients were asthmatics who developed bronchospasm after infusion of a loading dose of *N*-acetylcysteine. Arguably the asthmatic attack might have resulted from paracetamol ingestion or from the emotional stress that precipitated or accompanied admission to hospital, but we think that the timing of the onset of symptoms in relation to the infusion makes the latter highly suspect. Asthma has not been reported after paracetamol poisoning. The temporal sequence of events strongly suggests that the intravenous infusion of *N*-acetylcysteine precipitated the attack in these two patients. Alternatively, an interaction between paracetamol and *N*-acetylcysteine might have led to bronchospasm. The underlying mechanism is unexplained. Though bronchospasm is well recognised to occur after local bronchial instillation of *N*-acetylcysteine by inhalation (Mucomyst), such reaction is considered to be a local irritant rather than systemic effect.

We conclude that the possibility of inducing severe bronchospasm should be borne in mind when using *N*-acetylcysteine to treat paracetamol poisoning in asthmatic subjects. Should more similar side effects be reported with this treatment, the recommendation of administering *N*-acetylcysteine before the serum paracetamol concentration is known may need reconsideration.

We thank Dr H Copeman and Dr V Turner for allowing us to report on their patient.

[1] Prescott LF, Illingworth RN, Critchley JAJH, *et al.* Intravenous *N*-acetylcysteine: the treatment of choice for paracetamol poisoning. *Br Med J* 1979;ii:1097-1100.
[2] Oh TE, Shenfield GM. Intravenous *N*-acetylcysteine for paracetamol poisoning. *Med J Aust* 1980;i:664-5.
[3] Breen KJ, Bury RW, Desmond PV, *et al.* Paracetamol self-poisoning. *Med J Aust* 1982;i:77-9.
[4] Prescott LF, Wright N, Roscoe P, Brown SS. Plasma paracetamol half life and hepatic necrosis in patients with paracetamol overdose. *Lancet* 1971;i:519-22.
[5] Walton NG, Mann TAN, Shaw KM. Anaphylactoid reaction to *N*-acetylcysteine. *Lancet* 1979;ii:1298.

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Synergy of concurrent low dose oxamniquine and praziquantel in schistosomiasis

Laboratory studies suggest that concurrent low dose administration of oxamniquine (Vansil) and praziquantel (Biltricide) is likely to be highly effective in the single dose treatment of schistosomiasis.[1] We have conducted a dose finding study of this coadministration regimen in *Schistosoma haematobium* and *S mansoni* infections.

Subjects, methods, and results

The study was conducted in schoolchildren from the Lilongwe District, Malawi. One population (school 1) comprised 57 subjects (37 boys, 20 girls; are range 6-14 years, mean 9·2) infected with *S mansoni*, and the other population (school 2) comprised 66 subjects (56 boys, 10 girls; age range 9-20 years, mean 14·0), 60 of whom were infected with concomitant *S mansoni* and *S haematobium*, four with *S mansoni*, and two with *S haematobium*.

S mansoni infection was assessed by determining the faecal egg load on at least two separate occasions using a thick smear technique.[2] *S haematobium* was assessed on midday urine samples using a filtration technique.[3] Post-treatment assessments were made on single specimens obtained at one and three months (and at six months at school 2).

Subjects from school 1 were allocated to two nominal dosage schedules of oxamniquine plus praziquantel on the basis of egg counts: 4·0+8·0 mg/kg, and 7·5+10·0 mg/kg. The mixed infection population (school 2) was similarly allocated to doses of oxamniquine and praziquantel: 7·5+15·0 mg/kg, and 10·0+20·0 mg/kg.

Egg counts were expressed as group mean values using square root transformation. Efficacy was expressed as percentage reduction in mean egg count for each treatment group. The two infections were assessed separately, so that subjects harbouring both parasites were used for the assessment of efficacy against each.

Pretreatment *S mansoni* egg loads in the population (school 1) infected with this parasite only were higher than in the other population carrying concomitant *S haematobium* (see table). This explains the higher mean egg counts for *S mansoni* shown in the first two columns of the table. A dose response was observed at each post-treatment assessment, with high levels of efficacy (≥93% egg count reduction) up to six months after treatment with oxamniquine and praziquantel 7·5+15·0 mg/kg or 10·0+20·0 mg/kg.

Mean pretreatment egg counts and percentage egg count reductions after treatment of schistosomiasis infections with concurrent low doses of oxamniquine and praziquantel

	Combined treatment groups: oxamniquine + praziquantel (mg/kg)					
	Ox 4·0 Pr 8·0	7·5 10·0	7·5 15·0	10·0 20·0	7·5 15·0	10·0 20·0
	S mansoni				*S haematobium*	
No of infections treated	29	28	31	33	32	30
No reassessed:						
1 Month	22	24	26	30	29	27
3 Months	8	14	24	27	27	26
6 Months	0	0	16	25	15	23
Mean pretreatment egg counts* of No reassessed:						
1 Month	495	624	328	241	135	270
3 Months	555	539	345	220	147	248
6 Months			376	260	89	331
Mean egg count reduction after treatment (%):						
1 Month	43	78	99	99·7	99	99·7
3 Months	0	59	93	97	99	99·9
6 Months			95	96	97	99·2

**S mansoni* as ova/g; *S haematobium* as ova/10 ml.

Side effects occurred in four subjects (3%). Two reported abdominal pain and headache, one noted a rash 24 hours after treatment, and one with mixed infection reported dizziness eight hours after treatment.

Comment

These results show the high efficacy of simultaneous oxamniquine and praziquantel in low single doses of 7·5 and 15·0 mg/kg, respectively, against *S mansoni* and *S haematobium*. These doses are considerably lower than those used in Malawi for each drug administered alone—oxamniquine 30 mg/kg (Teesdale, Chitsulo, and Pugh, unpublished data), praziquantel 40 mg/kg.[4]

The combined treatment was well tolerated, side effects being of low incidence and self limiting. Our impression is that a higher incidence and a greater severity of side effects are found in these areas with very heavy *S mansoni* infections after treatment with either oxamniquine or praziquantel administered alone.

Low dose coadministration could confer a cost advantage with the potential benefit of an increase in tolerance without loss of efficacy. There would be further grounds for continued interest if resistance to a single schistosomicide ever became established. While it might be argued that low dosage could result in the emergence of resistance, this issue has usually been raised in connection with suppressive treatment. The question of resistance cannot be excluded in view of the increasing popularity of population based chemotherapy programmes.[5]

Our results have been confirmed by a Zambian study, in which the additional assessment of laboratory safety parameters was satisfactory (Njelesani and Ekue, unpublished data). Further studies are planned in Sudan, Kenya, and Zimbabwe to confirm efficacy and tolerance of oxamniquine and praziquantel 7·5+15·0 mg/kg.