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.

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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.

We are grateful to Dr R Foster, Pfizer Central Research, for devising the methodology and providing the capsules of oxamniquine.

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Clostridium difficile and its toxin in healthy neonates

Clostridium difficile and its associated toxin are related to pseudomembranous colitis but their presence in the stools of healthy neonates has been intriguing and demanded further study.[1] This strictly anaerobic bacillus was first described in 1935 in the stools of four out of 10 normal breast fed infants in the first 10 days of life.[2] It is rarely found in healthy adults.[3] We reported a pilot study[4] showing a 30% incidence of *C difficile* in infants aged under 1 month. This present study clarifies the time related colonisation of normal babies with this organism.

Methods and results

Stool samples from 59 healthy babies, none of whom had received antibiotics, were taken on three occasions during the neonatal period. All faecal samples were examined for neutralisable *C difficile* toxin by the use of Hep 2 cells at an initial dilution of 1/10. All samples were inoculated into cooked meat broth supplemented with cysteine, haemin, and menadione and incubated for 48 hours at 37°C. Gas liquid chromatography was performed on ether extracts of the culture medium supernatant. Those samples showing a peak for isocaproic acid were subcultured on to *C difficile* agar containing cycloserine and cefoxitin (Oxoid), and colonies of the *C difficile* were tested for toxin production. The results were analysed according to the method of feeding, delivery, length of ruptured membranes before delivery, and the ward in which the babies were nursed until their discharge home. A limited environmental survey was performed on one of the wards. The floor of the nurseries, pieces of equipment, and bed pan macerator were sampled with moistened swabs, which were then incubated in cooked meat broth and subcultured on to *C difficile* agar. Finger impressions from staff were taken directly on to *C difficile* agar.

The results (table) showed an increase in the carrier rate of *C difficile* in the stools of healthy babies in the first 28 days of life. By the end of the fourth week nearly half were colonised. There were no significant differences between breast fed and bottle fed babies; between those born by normal delivery, instrumental delivery (forceps or breech), or caesarean section; or between those born after short rupture of membranes (0-4 hours) and long rupture of the membranes (4-20 hours). There was, however, a significant clustering of positive cases in one of the postnatal wards (ward A) compared with the other two ($p < 0.05$ by the Fisher exact probability test for samples 1 and 2, but no significant difference for sample 3).

Details of C difficile isolations from 59 healthy babies sampled on three occasions after birth

Sample	No (%) of stool samples with *C difficile*				No (%) with toxin in culture medium			
	Ward A (n = 27)	Ward B (n = 10)	Ward C (n = 22)	Total (n = 59)	Ward A (n = 27)	Ward B (n = 10)	Ward C (n = 22)	Total (n = 59)
1 (day 1 or 2)	4 (15)	0 (0)	0 (0)	4 (7)	0 (0)	0 (0)	0 (0)	0 (0)
2 (days 5 to 7)	9 (33)	1 (10)	2 (9)	12 (20)	2 (7)	0 (0)	1 (5)	3 (5)
3 (days 21 to 28)	15 (56)	3 (30)	8 (36)	26 (44)	3 (11)	2 (20)	3 (14)	8 (14)

Comment

The clustering we found may indicate that the organism is acquired from the environment rather than from the birth canal of the mother, or that one colonised baby may easily contaminate a ward with the spore forming organisms. Samples from the hands of staff and from equipment did not yield *C difficile*. Babies and nursing staff did not move from one ward to another. Only the medical staff attended all three wards. All the babies went home between the second and 10th day of life.

In none of the stool samples was the cytotoxin of *C difficile* found. This is in contrast to the results of Viscidi *et al*, who found toxin in about one quarter of cases.[3] In our study some strains of *C difficile* did, however, produce toxin in culture medium. Of the samples taken during the fourth week of life 26 yielded *C difficile* and, of those, eight produced toxin in culture. Probably the environment plays an important part in the production of *C difficile* toxin and this may be why the administration of antibiotics enhances the toxin producing ability of the organism in vivo. Further studies are necessary to elucidate the environmental factors which encourage toxin formation in vitro and in vivo.

The isolates of *C difficile* were indistinguishable by colonial morphology, antibiotic sensitivity, and fatty acid pattern on gas liquid chromatography. It has been suggested that analysis of stool specimens by gas liquid chromatography is a useful screening test for the presence of *C difficile*.[5] We examined stool specimens after preliminary incubation in cooked meat broth and of 177 samples screened for *C difficile* by gas liquid chromatography 52 were positive but only 42 could be confirmed as containing the organism by further culture. All 10 cases not so confirmed were from bottle fed babies. Organisms giving a positive trace for isocaproic acid included *C sporogenes*, *C sordellii*, and *C bifermentans*. This finding calls into question the use of gas liquid chromatography as the sole method of screening for the presence of *C difficile* in clinical practice.

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