

concentration ( $r=0.61$ ,  $p<0.05$ ). Patients with a serum creatinine concentration greater than  $250 \mu\text{mol/l}$  did not develop hypophosphataemia. No correlation existed between the lowest plasma phosphate concentration and the dose of paracetamol; time after ingestion; blood urea, serum potassium, or blood glucose concentration; prothrombin time; grade of coma; serum osmolality; rate of dextrose infusion; or volume of dextrose or mannitol infused. Plasma phosphate concentrations on admission and the lowest concentrations attained were not significantly different between survivors and non-survivors.

Supplements of phosphate were given intravenously to two patients whose plasma concentrations were  $0.01$  and  $0.06 \text{ mmol/l}$ , respectively. In other patients low phosphate concentrations returned to normal spontaneously but without a consistent improvement in other biochemical or haematological variables. Urinary phosphate concentration was reduced ( $1.1$  and  $1.4 \text{ mmol/l}$ ) in the two patients in whom it was measured, but the maximum tubular reabsorption of phosphate was also decreased ( $0.05$  and  $0.38 \text{ mmol/l}$ ; normal range  $0.80$ - $1.35 \text{ mmol/l}$ ).

## Comment

This is the first record of hypophosphataemia in acute liver failure induced by paracetamol; it occurred in most of the patients and was severe ( $<0.3 \text{ mmol/l}$ ) in more than one third. At this level hypophosphataemia produces impaired oxygen transport and tissue hypoxia, abnormal leucocyte function, depressed platelet numbers and function, generalised muscle weakness, and disorder of the central nervous system<sup>1,5</sup>; these are frequent complications of acute liver failure. The similarity of the effects of liver failure and hypophosphataemia on the central nervous system (irritability, muscle weakness, dysarthria, confusion, and coma) suggests that phosphate depletion may be important in hepatic encephalopathy, and a progressive defect of phosphate metabolism in brain tissue of patients with chronic liver disease was shown recently by nuclear magnetic resonance spectroscopy.<sup>4</sup>

The cause of hypophosphataemia in acute liver failure remains unclear. None of the recognised causes of moderate ( $0.3$ - $0.7 \text{ mmol/l}$ ) hypophosphataemia<sup>1</sup> correlated with the phosphate concentrations in our patients. The reduced maximum tubular reabsorption of phosphate in two patients suggests an increased loss of renal phosphate, perhaps due to a direct effect of paracetamol, although the correlation between plasma phosphate and creatinine concentrations suggests that renal failure may protect against hypophosphataemia. Because of the serious clinical implications of phosphate imbalance in acute liver failure the homeostatic mechanisms of bone and renal phosphate reabsorption in this condition need to be studied urgently. Plasma phosphate concentrations should be monitored carefully during infusion of glucose in patients with liver failure.

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## Skin reactions and fever with indapamide

Indapamide is an antihypertensive agent structurally related to the benzothiazide diuretics. Skin reactions are not described in the data sheet produced in either the United Kingdom or the Netherlands, and we are not aware of any published case reports. We describe 16 cases of rash, some accompanied by fever, attributed to this drug and reported to the Netherlands Centre for Monitoring of Adverse Reactions to Drugs. A further 188 cases of skin reactions ascribed to intake of indapamide

(photosensitivity reactions (seven) excluded) had been reported to the World Health Organisation Collaborating Centre for International Drug Monitoring programme up to April 1987.

## Details of patients

The table summarises the clinical details of the Dutch cases. Interestingly, the skin reaction was accompanied by painful micturition in case 13 (also during rechallenge). All patients had taken  $2.5 \text{ mg}$  indapamide daily as treatment for hypertension, and, except in case 13, the reactions occurred in those taking it for the first time. In all cases the rash subsided within 14 days of indapamide being stopped, mostly without treatment. Only three patients were treated with antihistamines. Eight patients had also taken other drugs, but these were continued except in case 3, in which chlorthalidone was changed to epitizide and triamterene. Eleven patients later took chlorthalidone, (hydro)chlorothiazide, epitizide, frusemide, or clopamide without a relapse.

## Skin reactions attributed to indapamide notified to the Netherlands centre

Case No	Age and Sex	Adverse reaction	Time between starting drug and onset of reaction (days)	Rechallenge (time (days) to onset of reaction)
1	58 F	Generalised erythematous rash	6	<1
2	80 F	Generalised maculopapular rash, malaise	4	ND
3	60 F	Rash maculopapular, malaise, fever ( $38^\circ\text{C}$ )	8	ND
4	73 F	Generalised rash, nausea	9	ND
5	58 F	Generalised rash	12	ND
6	42 F	Generalised rash	8	ND
7	70 F	Generalised erythematous rash, arthralgia, fever ( $40.4^\circ\text{C}$ )	11	ND
8	51 M	Rash	$\leq 2$	<1
9	80 F	Morbilloform rash, Quincke's oedema, hypotension	15	ND
10	70 M	Generalised urticaria, fever ( $38.5^\circ\text{C}$ )	10	ND
11	78 F	Erythematous rash, fever ( $39^\circ\text{C}$ )	9	ND
12	59 F	Rash	13	ND
13	57 M	Generalised erythematous rash, urticaria	Same day	<1
14	43 F	Generalised maculopapular rash	12	ND
15	60 F	Rash	9	ND
16	73 F	Generalised morbilliform rash, fever ( $39^\circ\text{C}$ )	10	ND

ND=Not done.

In the World Health Organisation's series there were eight skin reactions of a possibly more serious type, such as erythema multiforme (four cases) and epidermal necrolysis (two). Fever occurred in nine cases. (As details of individual cases are not available in the World Health Organisation's database these reports should be interpreted with caution.)

In the Netherlands database 36% of all adverse reactions reported to indapamide (42) were skin reactions, as against 17% of those to chlorthalidone (87), 14% to (hydro)chlorothiazide (28), and 8% to frusemide (74). In the World Health Organisation's database these figures were 19% for indapamide (1087), 8% for chlorthalidone (1090), 11% for (hydro)chlorothiazide (2796), and 13% for frusemide (4811).

## Comment

The Dutch cases were studied in detail, a follow up being done in every case, and clearly indapamide may cause skin reactions. A causal relation is strongly suggested by the temporal relation between intake and the onset of the adverse reaction and by the rapid recovery after indapamide was stopped. The positive reaction to rechallenge in three cases supported the likelihood that indapamide was causative. The usual latent period of 8-12 days suggests sensitisation, and the accelerated reaction to rechallenge favours an immunological mechanism. Moreover, indapamide is related to the sulphonamides, which are a known cause of allergic reactions. Hence we believe that the active ingredient is the cause, as we are not aware of any allergenic excipients. Cross sensitivity between thiazides has been reported,<sup>1</sup> yet despite indapamide's close structural resemblance to chlorthalidone, frusemide, clopamide, epitizide, and (hydro)chlorothiazide none of the patients treated with these agents showed a relapse. This suggests that the allergic reaction is directed not against the sulphonamide side chain but possibly against a reactive intermediate.

In both the Netherlands and in the World Health Organisation databases comparisons of suspected adverse reactions to indapamide, chlorthalidone, (hydro)chlorothiazide, and frusemide showed a high prevalence of rashes with indapamide. Nevertheless, these figures are based on data obtained by

voluntary reporting, and no conclusions can be drawn about the comparative incidence of adverse effects to different drugs. Our data show that indapamide may cause skin reactions, and the Dutch experience suggests that cross sensitivity to other thiazides is probably rare. Rashes with indapamide were frequently reported, but whether these are relatively frequent can be confirmed or disproved only by further study.

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## Measles in adults: a prospective study of 291 consecutive cases

Since the introduction of measles vaccine in the mid-1960s the incidence of the disease has declined significantly.<sup>1,2</sup> As a result unvaccinated children born in the early 1960s were not exposed to large scale epidemics and grew to

after the fourth day of admission. None of the patients had overt jaundice. Serum creatine phosphokinase activities were abnormally high in 94 (41%) of the patients; isoenzyme assays showed that the increase in activity was limited to the MM fraction—that is, it was of muscle origin. Complications of measles that developed during the study were keratitis (31 patients), sinusitis (11), otitis media (11), and pneumonia (6).

### Comment

Several features seemed to characterise the measles syndrome in adults in the community. Firstly, liver function was impaired in 86% of our patients, and this should therefore be regarded as a characteristic symptom in adults rather than a complication. This is in contrast with the findings of Gavish *et al*, who concluded that the incidence of measles hepatitis is close to 4%, assuming that milder forms of measles were not associated with hepatitis.<sup>4</sup> Secondly, gastrointestinal symptoms—namely, vomiting, diarrhoea, and abdominal pain—occurred in one third of our patients. Thirdly, musculo-skeletal symptoms—namely, myalgia, arthralgia, and back pain—were fairly common, and the incidence of raised serum creatine phosphokinase activity (a possible indication of viral myositis) was 41%. Fourthly, Koplik's spots persisted for on average three to five days, although in 15% of the patients they were present on the seventh day of the disease, five days after the rash developed. Finally, photophobia was reported in only 1% of patients; the commonest eye complaint was pain that was not affected by light (78%).

These features in adults differ from the symptoms of measles in childhood: symptomatic enteritis or enterocolitis is rare in otherwise healthy children<sup>5</sup>; musculoskeletal symptoms have not been reported; Koplik's spots have usually resolved by the end of the second day of the rash<sup>5</sup>; and photophobia is a classic symptom in children.

We are indebted to Mrs J Misch for her invaluable help in collecting and analysing the data and in preparing this manuscript.

### Symptoms, physical findings, and results of blood tests in adults with measles

Symptom	No of patients (n=291)	Physical findings	No of patients (n=291)	Blood test	No of patients (n=230)
Fever	291	Rash	291	AST (nmol/s/l):	
Cough	282	Conjunctivitis	279	Normal*	75
Malaise	264	Pharyngitis	275	2× Normal	84
Sore throat	264	Lymphadenopathy	246	3× Normal	30
Coryza	243	Koplik's spots	188	≥4× Normal	41
Eye pain	228	Aphthous stomatitis	34	LDH (nmol/s/l):	
Headache	219	Splenomegaly	32	Normal*	67
Nausea	159	Abdominal tenderness	15	2× Normal	147
Myalgia	102	Hepatomegaly	7	3× Normal	15
Vomiting	101			4× Normal	1
Abdominal pain	97			CPK (nmol/s/l):	
Diarrhoea	93			Normal*	136
Ear pain	72			2× Normal	51
Hoarseness	70			3× Normal	18
Arthralgia	69			≥4× Normal	25
Pruritus	47			Bilirubin (μmol/l):	
Back pain	32			Normal*	211
Dysuria	8			2× Normal	19
Photophobia	3			Leucocyte count:	
				Normal*	157
				<4.0×10 <sup>9</sup> /l	73

AST=Serum aspartate transaminase. LDH=Lactate dehydrogenase. CPK=Creatine phosphokinase.

\*Normal ranges: AST ≤330 nmol/s/l; LDH ≤3670 nmol/s/l; CPK ≤1170 nmol/s/l; bilirubin ≤17 μmol/l; leucocyte count 4.0–10.8×10<sup>9</sup>/l.

adulthood without acquiring the disease. Reports of measles in young adults began to appear during the late 1970s,<sup>3</sup> but these were mainly of patients admitted to hospital and did not show the clinical picture of the disease in the community. After an outbreak of measles in Israel in 1982 the surgeon general issued an order whereby all soldiers with the disease, regardless of its severity, were admitted to hospital. This permitted a prospective study of consecutive adults with measles.

### Patients, methods, and results

Measles was diagnosed clinically in 291 patients and confirmed in 100 of these by a fourfold rise in serum antibody titre to the virus on haemagglutination inhibition. In four cases only a twofold rise was found. Medical history, the results of physical examination, and laboratory data were recorded for each patient on admission on a standard form. Further results of examinations and laboratory tests were subsequently recorded every 48 hours. Blood tests were performed for the first 230 patients within 48 hours after admission.

The table shows the clinical symptoms, physical findings, and results of laboratory tests. Serum aspartate transaminase and lactic dehydrogenase activities were found to be abnormally high in 155 (67%) and 163 (71%) of the patients, respectively. These figures increased to 173 (75%) and 198 (86%) respectively

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