SHORT REPORTS

Rifampicin-induced non-responsiveness to corticosteroid treatment in nephrotic syndrome

The nephrotic syndrome in childhood is usually of the minimal-change variety. At least 95% of children with this lesion respond to adequate corticosteroid treatment. Failure to respond is an indication for renal biopsy to exclude a more sinister glomerular lesion. We report the case of a boy whose failure to respond was not due to progressive glomerular disease but to a drug interaction.

Case report

A 6-year-old boy, son of an Irish mother and Pakistani father, presented to a local hospital with abdominal pain. He had microscopic haematuria but no proteinuria and the urine was sterile. An intravenous pyelogram and micturating cystogram were normal. The pain subsided spontaneously and no definite diagnosis was made. Six months later he was admitted to the Nottingham Children's Hospital with a four-day history of swelling of the limbs and abdomen. He was oedematous but normotensive. There was pronounced proteinuria and intermittent microscopic haematuria. The results of investigations were as follows: 24-hour urinary protein 1.1 g/l; serum albumin concentration 13 g/l; differential protein clearance 0.10, 0.11 (highly selective proteinuria 0.1); serum C3 1.78 g/l; serum C4 0.56 g/l; serum creatinine 40 μ mol/l (0.45 mg/100 ml); blood urea 4 mmol/l (24 mg/100 ml).

Nephrotic syndrome was diagnosed. Spontaneous remission occurred over the next nine days. He was then inadvertently given BCG vaccination. Five days later the nephrotic syndrome relapsed. Treatment with prednisolone 2 mg/kg/day was started. To prevent possible dissemination of the vaccine rifampicin plus isoniazid were also given. Over the next four weeks there was no response: oedema and hypoalbuminaemia persisted. By then the dose of prednisolone had been increased to 3 mg/kg/day. A renal biopsy was indicated, but the patient had not become Cushingoid and so the possibility of a drug interaction was investigated. The plasma half life of prednisolone was found to be 1.29 hours. This was estimated by standard pharmacokinetic techniques¹ measuring the decline in prednisolone plasma concentration after an oral dose on an empty stomach of 10 mg prednisolone dissolved with 10 μ Ci tritiated prednisolone in 10 ml water. The prescribed corticosteroid was withheld on the day of the study. Rifampicin and isoniazid were then discontinued and treatment with prednisolone continued at the original dose of 2 mg/kg/day. Within 13 days the patient was in remission. Four weeks after discontinuing rifampicin the plasma half life of prednisolone had increased to 2.17 hours in agreement with mean data obtained in 22 children.² A renal biopsy specimen at a later date has confirmed the diagnosis of a minimal-change lesion, and the boy has continued to respond to corticosteroids. Full pharmacokinetic data calculated by standard equations¹⁻³ are shown in the table.

Prednisolone pharmacokinetics with and without rifampicin treatment

Study 1			Study 2		
Rifampicin treatment			Rifampicin withdrawn		
$t_{1/2}$ (h)	Volume of distribution (l)	Plasma clearance (l/kg/h)	$t_{1/2}$ (h)	Volume of distribution (l)	Plasma clearance (l/kg/h)
1.29	15.7	0.34	2.17	15.9	0.20

Assume 100% drug availability in study 2, and equivalent V_d per kg body weight in both studies.

Comment

Edwards *et al*⁴ first described a reduction in the pharmacological half life of cortisol in a patient with tuberculous Addison's disease being treated with replacement cortisone and rifampicin. Similarly, progressive loss of renal allograft function has been attributed to increased degradation of methylprednisolone during treatment with rifampicin.⁵ We believe ours is the first case where the interaction between prednisolone and rifampicin has been verified by measuring the half life of prednisolone by a reliable pharmacokinetic technique. There are a few occasions where corticosteroids and antituberculosis drugs may be used together—for example, tuberculous meningitis.

Similarly, the increased incidence of tuberculosis in patients receiving corticosteroids is well recognised. Rifampicin is now a major anti-tuberculosis drug. Its hepatic microsomal enzyme-inducing properties should be more widely appreciated.

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¹ Pickup, M E, *et al*, *European Journal of Clinical Pharmacology*, 1977, **12**, 213.

² Green, O C, *et al*, *Journal of Pediatrics*, 1978, **93**, 299.

³ Gibaldi, M, and Perrier, D, *Pharmacokinetics*, p 37. New York, Marcel Dekker, 1975.

⁴ Edwards, O M, *et al*, *Lancet*, 1974, **2**, 549.

⁵ Buffington, G A, *et al*, *Journal of the American Medical Association*, 1976, **236**, 1958.

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Haemolytic anaemia caused by overheated dialysate

Haemodialysis is a potentially hazardous procedure but complications due to technical failure are uncommon. We report one such rare and potentially fatal complication.

Case report

A 57-year-old man who had been treated with home dialysis for two years was admitted with a three-day history of vomiting. He dialysed for 10 hours twice weekly on a Meltec multipoint kidney (1.05 m²) with a single pass Dylade B3A proportionating machine. He was pale with yellow sclera. Blood investigations showed a haemoglobin concentration of 3.4 g/dl (5.4 g/dl one week earlier). The peripheral blood contained fragmented and polychromatic red cells, microspherocytes, and 16 nucleated red cells/100 white cells. Reticulocytes were 21.2% and some red cells contained Heinz bodies. Serum bilirubin concentration was 45 μ mol/l (2.6 mg/100 ml). A direct anti-globulin test was negative. A G6PD screen was normal. His dialysis four days before admission had been uneventful. There was no history of exposure to oxidant drugs or chemicals. The patient's proportionating machine appeared to function satisfactorily. The results of tap water and dialysate analyses (including copper measurements) were normal. Six units of packed red cells were given during the next two weeks as blood films showed continuing red cell regeneration and a falling haemoglobin. The cause of the haemolytic anaemia remained obscure, and after three weeks' haemodialysis in hospital he returned home.

One hour after starting dialysis at home he felt unwell and began to vomit bloody fluid. He completed a 10-hour dialysis. The next day he walked 400 metres to the hospital, where he was found to be jaundiced and afebrile. The whole blood haemoglobin concentration was 4.1 g/dl but the packed cell volume was only 0.03 (3%). The true haemoglobin concentration was 1.1 g/dl and the plasma haemoglobin 3.0 g/dl. The peripheral blood film showed many tiny red cells and cell fragments with 8 nucleated red cells/100 white cells. Reticulocyte count was 2.5%. The platelet count was 23×10^9 /l ($23\,000/\text{mm}^3$), but there were no other gross abnormalities of the coagulation system. The plasma potassium concentration was 3.4 mmol(mEq)/l.

He was immediately dialysed and given two units of whole blood. Four hours later a 3.4 l partial exchange transfusion was carried out. After that the blood haemoglobin concentration was 7.0 g/dl and the plasma haemoglobin 1.7 g/dl. His subsequent recovery was uneventful and he has now returned to home dialysis. The cause of the haemolysis was not discovered until the patient remarked that the tubing returning blood from the dialyser was hot during the dialysis that preceded his second admission. The Dylade

proportionating system was dismantled and a gas leak found in the Cambridge Bourdon tube type dialysate temperature gauge which caused the needle pointer to register about 20°C too low. The fault had come on over a period of time and, unfortunately, it had been assumed that the Cambridge gauge was indicating the true dialysate temperature. Therefore the back-up temperature alarm system and the dialysate heater were adjusted to maintain the Cambridge gauge recording in the range 35–41°C. Probably, however, the dialysate was much hotter (possibly as much as 58°C).

Comment

There are three reports of patients exposed to overheated dialysate. Fortner *et al*¹ reported the death of a patient who developed gross haemolysis after accidentally dialysing with a bath at 55°C. Two patients had chronic haemolysis after being exposed to 47°C dialysate for 95 minutes² and 50°C for 110 minutes³ respectively.

In-vitro experiments⁴ have shown morphological changes in red cells heated to >51°C, regardless of the time of exposure. Temperature <47°C produced no morphological changes, irrespective of the duration of exposure, and intermediate temperatures caused changes that were dependent on both temperature and exposure time. Heat-damaged canine erythrocytes reinjected into dogs suffered acute haemolysis if heated to >51°C and chronic haemolysis if heated to between 47°C and 51°C.⁴ We think that our patient's two episodes show both types of heat-induced haemolysis.

¹ Fortner, R W, *et al*, *Annals of Internal Medicine*, 1970, **73**, 443.

² Berkes, S L, *et al*, *Annals of Internal Medicine*, 1975, **83**, 363.

³ Hecht, B, *et al*, *Annals of Internal Medicine*, 1975, **83**, 902.

⁴ Ham, T H, *et al*, *Blood*, 1948, **3**, 373.

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Maternal serum and amniotic fluid concentrations of alphafetoprotein in epidermolysis bullosa simplex

Maternal serum and amniotic fluid alphafetoprotein (AFP) concentrations have been used since 1972 in diagnosing neural tube defects in the fetus.^{1,2} These concentrations are raised in congenital abnormalities of the gastrointestinal tract, kidney, and other sites.³ We report here, for the first time, a case of epidermolysis bullosa simplex, an autosomal dominant condition, in which the AFP concentrations were raised.

Case report

A 21-year-old primigravida with no significant medical or family history was first examined at 16 weeks gestation. The date of conception was uncertain, so the gestational age was assessed by clinical examination and measuring the fetal biparietal diameter and the head/abdominal circumference. The maternal serum AFP concentrations at 16, 17, and 18 weeks gestation were 150, 165, and 160 µg/l—well above the upper limit of normal (90, 100, and 124 µg/l respectively). The AFP concentration in the amniotic fluid at 20 weeks gestation was 26.5 mg/l, which was within the normal range (upper limit 28 mg/l). A live female infant weighing 2.48 kg was born at 39 weeks after an uncomplicated spontaneous labour. She had blistering and superficial skin loss over the legs, wrists, and abdomen affecting 20% of the total skin area. No bullae were present on the head, neck, back, soles, or palms. The pattern of the lesions suggested epidermolysis dystrophica of the autosomal dominant type, and healing was associated with superficial scarring. Epidermolysis bullosa simplex was diagnosed by electron microscopy. The basal lamina remained intact. Cleavage occurred at the level of the basal epidermal cells, which showed varying stages of disintegration.⁴

The widespread lesions on the limbs presenting at birth are an unusual but recognised feature of epidermolysis bullosa simplex. Healing may be associated with scarring.⁵ There were no other congenital abnormalities and the karyotype was normal. During the neonatal period the lesions improved

with topical corticosteroid treatment only and the baby was discharged home after 21 days. AFP concentrations in the bullous fluid and neonatal serum were 6.0 and 5.6 mg/l respectively, indicating transudation of serum.

Comment

This is the first report of raised serum AFP concentrations in a case of epidermolysis bullosa simplex. Raised concentrations have been described in a patient with skin necrosis and duodenal atresia of the fetus,⁶ but the atresia could have accounted for the rise in this case. The raised AFP concentration in maternal serum probably resulted from transudation of fetal serum into the bullae and subsequent rupture thereof into the amniotic fluid cavity. Trans-mission from amniotic fluid would account for the raised serum levels at around 17 weeks gestation. The amniotic fluid concentration three weeks later, however, was near the upper limit of normal. The explanation for this could be that there had been no recent rupture of bullae. Our case suggests that AFP assay might be of value in patients who have already had an infant with epidermolysis bullosa. They could be screened at around 17 weeks gestation and the diagnosis confirmed by fetoscopy.

We thank Dr R A J Eady for the electron microscopy report.

¹ Brock, D J H, and Sutcliffe, R G, *Lancet*, 1972, **2**, 197.

² Leighton, P C, *et al*, *Lancet*, 1975, **2**, 1012.

³ Clarke, P C, *et al*, *British Journal of Obstetrics and Gynaecology*, 1977, **84**, 285.

⁴ Pearson, R W, and Spargo, B, *Journal of Investigative Dermatology*, 1961, **36**, 214.

⁵ Pearson, R W, in *Dermatology in General Medicine*, ed T B Fitzpatrick, p 626. New York, McGraw-Hill, 1971.

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Rupture of spleen at colonoscopy

Colonoscopy is now a routine procedure in many hospitals. Complications on the whole are few and consist mainly of perforation of the bowel and haemorrhage after polypectomy. Injuries to other viscera seem to be very rare. We report a case in which both spleen and liver were damaged.

Case report

A 33-year-old woman presented with an 18-month history of diarrhoea accompanied by sharp central abdominal pain and a feeling of distension. She was passing 10 to 15 stools daily with mucus and occasionally fresh blood. She was tender in the umbilical region, and at sigmoidoscopy a nodular area was seen in the upper rectum. Biopsy showed active chronic colitis affecting the mucosa and superficial submucosa, possibly of the Crohn's type. A barium enema was normal. The patient was admitted for colonoscopy.

The preoperative haemoglobin level was 13.2 g/dl. The bowel was prepared with 4 litres of 5% mannitol by mouth. On examination under light sedation with diazepam and pentazocine there was obvious colitis in the sigmoid colon and descending colon with some scattered ulcers and oedema in the transverse colon. The caecum was reached without undue difficulty and was normal. Samples of tissue were taken for biopsy. Four hours later the patient complained of severe abdominal pain, predominantly in the left hypochondrium. On examination she had a tender, silent abdomen. Plain radiographs showed no evidence of pneumoperitoneum. Initial management was conservative, with analgesics and intravenous fluids. Her condition remained stable over the next two days and she passed a loose stool. On the third day her pain increased, with radiation to the left shoulder-tip. She appeared pale, although not shocked. The haemoglobin level had fallen to 4.5 g/dl. She was therefore transfused and prepared for surgery.