Acute intravascular haemolysis associated with cephalixin therapy

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CEPHALEXIN, a new semi-synthetic antibiotic derived from cephalosporin C, has the same basic nucleus and the same range of activity as its predecessors, cephalothin and cephaloridine but has the advantage that it can be given orally. As this drug is relatively new, few side-effects have been described.

The following case report is of a boy, aged 14 years, who developed acute intravascular haemolysis while taking cephalixin.

Case history

The patient was a severely affected haemophilic with no antihaemophilic factor (AHF) activity detectable in his plasma. He sustained a rupture of the ureter, multiple fractures of ribs and large haematoma of head, arms and legs, as the result of a crushing injury. This was associated with intraperitoneal bleeding and a fall in haemoglobin from 15 to 6.2/100 ml. Surgery to the ureter was undertaken under cover of cryoglobulin precipitate, a potent concentrate of antihaemophilic factor prepared by cold precipitation of human plasma (Pool, Hershgold & Pappenhagen, 1964). Four units of donor blood were transfused to bring the haemoglobin to 12 g/100 ml. No serological abnormalities were detected at the time of performing the matching tests. The infusions of cryoprecipitate were continued for 32 days to allow complete healing of the ureter, skin incision and the drainage tube tracks. On the sixth postoperative day the patient developed haematuria and a haematoma of the thigh at the site of an intramuscular injection when the AHF activity of the plasma fell below the haemostatic level. This was the only time the patient had any evidence of bleeding during the postoperative period.

During anaesthesia the patient aspirated gastric content and developed a pneumonitis of the left lower lobe and collapse of the right upper lobe. This was treated with ampicillin, 1 g/day for 9 days, then with cephalixin, 2 g/day for 13 days (Fig. 1).

Blood urea was elevated to 50 mg/100 ml immediately after surgery but rapidly fell to normal and

FIG. 1. Postoperative course of the patient showing the relation of antibiotic therapy to haemoglobin levels (H) and the reticulocyte count (R).

at the time cephalixin was administered ranged from 20-25 mg/100 ml.

Nine days after the start of cephalixin therapy the patient's plasma was noted to be brown in colour and the following results suggestive of acute intravascular haemolysis were obtained; methaemalbumin 2.34 mg/100 ml, plasma haemoglobin 6 mg/100 ml, reticulocyte count 5%, total bilirubin 1.6 mg/100 ml. Direct broad spectrum antihuman globulin (Coombs') test using a standard slide technique was negative and the osmotic fragility of the red blood cells was normal. Haemolysis increased and maximum values were seen on the thirteenth day of cephalixin therapy when the reticulocyte count was 13%, the methaemalbumin 3.47 mg/100 ml and the plasma haemoglobin 8.9 mg/100 ml. The serum complement level was normal. The maximum serum level of cephalixin obtained during this time was of 10 µg/ml, 3 hr after an oral dose of 500 mg and this occurred on the twenty-third postoperative day. Serum proteins were slightly elevated, the total being 8.7 g/100 ml with an albumin of 4.6 g/100 ml (55%) and globulin of 4.1 g/100 ml (45%). Electrophoresis of plasma proteins showed elevation of the gammaglobulin fraction to 2.4 g/100 ml (25.4%).

β -globulin 8.5%, α_1 -globulin 8% and α_2 -globulin 3.1% were within normal limits. Plasma fibrinogen was grossly elevated at 1067 mg/100 ml.

Since it is reported (Kosakai & Miyakawa, 1970) that the direct antiglobulin test on the red blood cells of patients receiving cephalosporins varies, depending upon the particular drug given and the particular antihuman globulin reagents and technique employed, it was decided to attempt to enhance the sensitivity of the method by using a two-stage method modified from that of Cohen & Nelken (1964). The patient's thrice washed red blood corpuscles collected soon after cessation of cephalixin therapy were incubated at room temperature with goat antihuman serum, washed to remove free serum and followed by a rabbit antigoat serum on a slide. Careful attention was given to finding the optimal dilutions for the rabbit antigoat and goat antihuman sera. The patient's cells tested by this technique gave a positive reaction, control sensitized and unsensitized cells reacting satisfactorily. No irregular blood group antibodies were detected in the patient's serum. Direct antiglobulin reactions were performed using specific goat antihuman IgG immunoglobulin and anti- β_2C component of complement with negative results. This is in agreement with Molthan, Reidenberg & Eichman, 1967, who reported the coating on the cells of their patients to be non-specific protein in nature.

Cephalixin was stopped at this time and thereafter the levels of plasma haemoglobin, methaemalbumin and the reticulocyte count fell and haemoglobin level rose to normal.

Discussion

All members of the cephalosporin group of drugs are known to bind normal plasma proteins to red cells *in vitro* and so produce a positive direct antiglobulin test (Kosakai & Miyakawa, 1970; Mine *et al.*, 1970). The antiglobulin reaction is dependent on the type of antiserum used and in *in vitro* experiments the incidence of positive tests rises with the concentration of the drug.

Molthan *et al.* (1967) reported positive direct Coombs' tests in 75% of patients receiving cephalothin. This finding was confirmed by Gralnick, Wright & McGinniss (1967) who showed that 40% of patients on cephalothin developed a positive Coombs' test. In these series, patients with impaired renal function had a high incidence of positive tests probably because of the high blood cephalothin concentrations and because azotaemic red cells were more easily sensitized. The incidence of positive tests was also higher in patients with hypoalbuminaemia.

A similar result was reported by York & Landes (1968) and Foord (1970) in patients receiving cephaloridine. In the latter study involving sixty-five

patients, the overall incidence of positive Coombs' tests was 15% but all the positive tests occurred in the group of patients receiving over 4 g of cephaloridine/day. This gave an incidence of 26% in this group. Perkins, Saslaw & Billmaier (1967) reported similar observations in patients receiving cephalothin or cephaloridine. Girdwood (1971) reviewing the notifications to the Safety of Drugs Committee cites eight examples.

At least five cases of positive Coombs' tests have been recorded after cephalixin therapy. Two cases are quoted by Foord (1970), one of these being in a monkey and one case by Fass, Perkins & Saslaw (1970). Also Erikssen, Midvedt & Bergan (1970) report that two out of five patients on cephalixin developed a positive Coombs' test as determined by a 'tube' technique although the slide test was negative.

Positive Coombs' tests in patients on cephalosporins have been regarded as laboratory curiosities and of no significance with regard to haemolytic anaemia, however, two cases of acute haemolysis have been described (Kaplan, Reisberg & Weinstein 1968; Foord 1971). The first patient received cephaloridine, and the second cephalixin. Both patients had however received penicillin therapy prior to the cephalosporin and both had impaired renal function. The incidence of cross-sensitization reactions between penicillin and cephalosporins is probably between 10 and 15% (Ky *et al.*, 1970), but varies widely according to the criteria chosen.

The case presented here is complicated by the prior administration of ampicillin, the elevation of the gamma-globulin and the high fibrinogen level, but renal function, plasma albumin and the plasma level of cephalixin were all within normal limits. During the whole of this haemolytic episode and for 10 days thereafter, the patient received cryoglobulin precipitate and had no evidence of bleeding. Withdrawal of the cephalixin was associated with cessation of haemolysis.

The evidence available suggests that in this instance, despite the low dosage, cephalixin therapy resulted in acute intravascular haemolysis.

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An unusual case of acrodystrophic neuropathy

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THIS rare condition is characterized by progressive loss of sensation which usually occurs first and is most severe in the lower limbs, but may eventually become widespread. Thévenard (1953) reviewed 100 cases reported up to that time and since then others have been reported by Ogden, Robert & Carmichael (1959); Pallis & Schneeweise (1962); Walker (1955); and Spillane & Wells (1969). It may occur as a familial disease, when it is often transmitted as an autosomal dominant character but other forms of inheritance can occur (Denny-Brown, 1951).

The familial form is characterized by recurrent, painless ulcers starting on the feet, usually in early adult life, with ultimate severe destruction of the feet and often of the lower legs. Sensation is usually first affected in the territory of one first sacral root, and in the earlier stages there is dissociated sensory loss, temperature sensibility being more extensively and severely impaired than pain, which is in turn lost more than touch. As more adjacent roots become involved this dissociation becomes less marked.

Sporadic cases also occur and it has been suggested that in these there tends to be a more widespread involvement of the sensory roots, an earlier onset of ulceration of the feet and lack of progression of the sensory neuropathy (Ogden, Robert & Carmichael, 1959). Nerve deafness and lightning pains in the limbs may occur in either form.

The essential pathological change appears to be degeneration of the cells in the posterior root ganglia, and of their fibres both distal and proximal to the ganglia (Denny-Brown, 1951). The anterior roots are not involved; neither does there appear to be any primary involvement of muscle.

The cause is unknown and Denny-Brown (1951) has suggested that this may represent one end of a spectrum of conditions affecting nerve roots, the analogous disease of the anterior roots being the classical radicular form of peroneal muscular atrophy.

The patient here reported, a single woman now aged 60 years, presented with unusually extensive sensory loss and some other features of interest.

Case history

The details of this patient's early history are vague, but it is known that although her hands and feet appeared normal at birth she did not walk until the age of 3, and then only with difficulty. She later developed ulcers on the plantar and dorsal aspects of the feet, and the feet gradually became deformed, requiring an operation at about the age of 16 years. At a later date bone was discharged spontaneously from both feet. By the age of 30 she was unable to stand or walk. She has noted shooting pains in the upper limbs and repeated infections of the fingers over many years, and at the age of 50 her right index