

idiopathic thrombocytopenic purpura that 'failed to respond' to splenectomy. Only case 7 could be considered to have a true relapse of the purpura, and he did not have an enlarged accessory spleen.

Despite clinicians' enthusiasm for removing accessory spleens, this operation has produced a remission in less than a third of cases presenting up to 1981.^{3,4} Application of our criteria to these cases suggests that half of those with true relapses of idiopathic thrombocytopenic purpura responded while none who failed to respond to splenectomy did. To this latter group may now be added our own two patients. In 1981 Pawelski *et al*⁵ described 12 patients with apparently true relapses of the purpura after splenectomy, all of whom were cured by splenunculectomy.⁵

Purpura that fail to respond to splenectomy should be distinguished from true post splenectomy relapses. This has not been the case in the past. Although the number of children not cured by splenectomy in our centre is small, we believe that criteria such as ours (platelets $<150 \times 10^9/l$ within six weeks of splenectomy) may identify a group of patients very unlikely

to respond to splenunculectomy. Patients who have had a true relapse of the purpura after apparently successful splenectomy in whom an enlarged accessory spleen is shown may well benefit from its removal.

The authors thank Miss J Gibson for meticulous record keeping and for plotting the platelet counts.

References

- 1 Walker R, Walker W. Idiopathic thrombocytopenia, initial illness and longterm follow up. *Arch Dis Child* 1984;**59**:316-22.
- 2 Hann IM, Wainscoat JB. Recurrent thrombocytopenic purpura associated with accessory spleen. *Arch Dis Child* 1976;**51**:154-6.
- 3 Wallace D, Fromm D, Thomas D. Accessory splenectomy for idiopathic thrombocytopenic purpura. *Surgery* 1982;**91**:134-6.
- 4 Verheyden CN, Beart RW, Clifton MD, Phyllyk RL. Accessory splenectomy in management of recurrent idiopathic thrombocytopenic purpura. *Proceedings of the Mayo Clinic* 1978;**53**:442-6.
- 5 Pawelski S, Konopka L, Zdziechowska H. Recurrence of thrombocytopenia in patients splenectomized for idiopathic thrombocytopenic purpura. *Blut* 1981;**43**:355-60.

Correspondence to Dr M M Reid, Department of Haematology, Royal Victoria Infirmary, Newcastle upon Tyne NE1 4LP.

Received 21 October 1985

Pancytopenia caused by iron-dextran

H HURVITZ, E KEREM, E GROSS-KIESELSTEIN, A BRAND, AND D BRANSKI

Department of Pediatrics, Bikur Cholim General Hospital, Jerusalem, Israel

SUMMARY Pancytopenia after intramuscular iron-dextran treatment occurred in an infant with Down's syndrome. Haematological abnormalities recurred on subsequent challenge. Positive migration inhibiting factor and mast cell degranulation tests support an allergic pathogenesis for the pancytopenia. These side effects have not been reported previously.

Severe, even fatal, allergic reactions are known to occur after parenteral administration of iron-dextran (Imferon). We describe a patient who developed thrombocytopenia, leucopenia, and haemolytic anaemia after intramuscular injection of iron-dextran. These haematological abnormalities recurred on subsequent challenge.

Case report

A 1 year old girl with Down's syndrome was admitted to our department. Blood count showed an

iron deficiency anaemia with haemoglobin concentration 83 g/l, packed cell volume 0.28, mean corpuscular volume 71 fl, leucocytes $8 \times 10^9/l$ (70% neutrophils, 12% band forms, 16% lymphocytes, 2% monocytes), and platelets $165 \times 10^9/l$. Serum iron concentration was 2.3 mM/l (12.7 $\mu\text{g}\%$). Iron binding capacity was 55 mM/l (307 $\mu\text{g}\%$). Intramuscular iron-dextran (30 mg/kg) was given in three divided doses over six days because of feeding problems and poor compliance. Ten days later the haemoglobin concentration rose to 98 g/l, and the reticulocyte count was 4.8%. The leucocyte count was $9.7 \times 10^9/l$ with normal differential count, and the platelet count was $180 \times 10^9/l$. She was discharged home but was readmitted to hospital one month later. Her blood count showed pancytopenia with haemoglobin concentrations 74 g/l, packed cell volume 0.24, mean corpuscular volume 85 fl, leucocytes $3.3 \times 10^9/l$ (49% neutrophils, 4% band forms, 43% lymphocytes, 2% monocytes, and 2% eosinophils), and platelets $50 \times 10^9/l$ (Figure). Direct and indirect Coombs' tests were negative, her glucose-6-phosphate concentration was normal, and

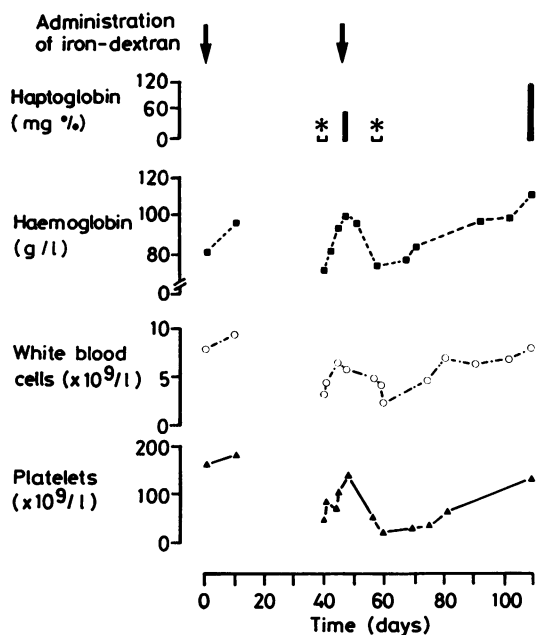


Figure Haematological data after administration of iron-dextran (*undetectable concentration).

her haptoglobin concentration was undetectable. Bone marrow aspirate showed normal reactive hypercellularity of all blood elements.

Serum concentrations of IgG, IgA, IgM, and C3 were 12.35 g/l, 0.67 g/l, 1.21 g/l, and 0.74 g/l, respectively. Antinuclear antibodies, rheumatoid factor, antithyroid, anti-parietal cell, antimitochondrial and anti-smooth muscle antibodies were all negative. Total lymphomononuclear counts ranged between $0.3 \times 10^9/l$ and $3.08 \times 10^9/l$. B and T cell numbers could not be determined; the response to phytohaemagglutinin mitogen, however, was normal, whereas the response to pokeweed mitogen was reduced.

At this stage a challenge with a single dose of 10 mg/kg iron-dextran intramuscularly was performed after informed consent had been obtained from the parents. Two weeks later pancytopenia reappeared with haemoglobin 76 g/l, packed cell volume 0.26, mean corpuscular volume 100 fl, reticulocytes 10%, leucocytes $2.8 \times 10^9/l$ (53% neutrophils, 11% band forms, 26% lymphocytes, 6% monocytes, and 4% eosinophils), and platelets $22 \times 10^9/l$. The haptoglobin concentration dropped again to an undetectable level (Figure).

Tests with iron-dextran for the presence of a migration inhibition factor and mast cell degranulation were positive. Six weeks later the haemoglobin

concentration rose spontaneously to 113 g/l, packed cell volume to 0.39, mean corpuscular volume to 103 fl, leucocytes to $8.1 \times 10^9/l$, platelets to $140 \times 10^9/l$, and haptoglobin concentrations to 1.09 g/l (Figure).

Discussion

Many adverse reactions associated with the administration of parenteral iron-dextran preparations have been described.¹ Local reactions may include pain at the injection site, skin discoloration, and local inflammation. An association between intramuscular iron and subsequent development of soft tissue sarcoma has also been reported.² Adverse systemic reactions may be immediate or delayed and include headache, nausea, vomiting, muscle and joint pain, generalised lymphadenopathy, fever, bronchospasm, and anaphylactic reactions, which may be fatal.¹ The dextran component itself is known to cause immune complex mediated (type III) anaphylaxis in man.³ Berliner *et al* described allergic non-thrombocytopenic purpura after intravenous administration of iron dextran (Imferon) with positive reaction of migration inhibition factor to this drug.⁴ Haematological abnormalities after administration of iron were described, but a non-immune mechanism was suggested as the aetiology: Hamblin and Simmonds described neutropenia associated with treatment with iron and proposed a non-immune mechanism, where the stem cells are diverted from granulocyte production into erythrocyte production.⁵ They alternatively suggested that the iron may have a direct toxic effect on the bone marrow. Fielding and Smith have shown non-immune haemolytic activity of an iron-dextran complex in an *in vitro* model.⁶

We emphasise that immunological disturbances are well recognised in Down's syndrome. Cellular immunity is impaired, as manifested by decreased number and function of peripheral T lymphocytes. There is usually an increase in the concentrations of serum IgG, IgA, and IgD with normal IgM. Cellular immunodeficiency is a known predisposing factor of autoimmunity, and may have contributed to the unusual adverse reaction to the drug in our patient.

Iron deficiency per se may affect immune competence. An additional factor behind the adverse reaction to iron-dextran in our patient may have been a defective host-defence mechanism induced by the iron deficiency itself.

Our patient developed thrombocytopenia, leucopenia (neutropenia and lymphopenia), and haemolytic anaemia after intramuscular administration of iron-dextran. These haematological abnormalities reappeared after a challenge with iron-dextran and were accompanied by positive migration inhibition

factor and mast cell degranulation, suggesting hypersensitivity to this drug.

We thank Ella Livni, PhD, Clinical Laboratory, Beilinson Medical Center, who performed the migration inhibition factor and mass cell degranulation tests and Ms N Alon for her technical help.

References

- 1 Thompson EB. *Iron deficiency, disorders of the blood*. A textbook of clinical haematology. Edinburgh: Churchill Livingstone, 1977;194-5.
- 2 Greenberg G. Sarcoma after intramuscular iron injection. *Br Med J* 1976;i:1508.

- 3 Richter W, Hedin H. Dextran hypersensitivity. *Immunology Today* 1982;3:132-8.
- 4 Berliner S, Shoenfeld Y, Livni E. Allergic purpura following intravenous administration of iron-dextran. *Acta Haematol* 1979;62:178.
- 5 Hamblin T, Simmonds T. Neutropenia and iron therapy. *Lancet* 1976;iii:310.
- 6 Fielding J, Smith GM. The haemolytic activity of an iron-carbohydrate complex. *J Clin Pathol* 1963;16:12-7.

Correspondence to Dr H Hurvitz, Department of Pediatrics, Bikur Cholim General Hospital, Jerusalem, Israel.

Received 14 August 1985

Phenobarbitone prophylaxis of intraventricular haemorrhage

M ANWAR, S KADAM, I M HIATT, AND T HEGYI

Department of Pediatrics, University of Medicine and Dentistry, Rutgers Medical School, New Brunswick, New Jersey, United States of America

SUMMARY Thirty preterm infants (birthweight under 1500 g) were treated with phenobarbitone to examine its effectiveness in reducing the incidence of intraventricular haemorrhage (IVH), the control group comprising 28 infants. The treated group had 57% incidence of IVH and mortality of 13% compared with 68% and 14%, respectively, in controls.

Since barbiturates have been shown to have neuroprotective effects several reports have examined the effectiveness of phenobarbitone in the prevention of intraventricular haemorrhage (IVH) in preterm infants. The conflicting results obtained in these trials led us to re-evaluate this issue using the protocol of Donn *et al*, who showed that phenobarbitone reduced the incidence of IVH.¹

Subjects and methods

We studied 58 preterm infants (birthweight less than 1500 g) who had no congenital malformations and whose mothers had not received phenobarbitone before their delivery. We randomly allocated these infants into control and treatment groups. The two groups were comparable with respect to birthweight, gestational age, race, sex, mode of delivery, and Apgar score. The control group (n=28, birthweight 1120 (SD 218) g) received supportive care only. The treatment group (n=30, birthweight 1119 (SD 264) g) received phenobarbitone for the first

week of life, starting at less than 6 hours of age. We administered phenobarbitone in a loading dose of 20 mg/kg divided into two equal doses administered intravenously 12 hours apart and a maintenance dose of 2.5 mg/kg every 12 hours. We obtained blood concentrations of phenobarbitone before the first maintenance dose and then at 3-5 days of age, and adjusted the dose to achieve phenobarbitone trough blood concentrations of 20-30 µg/ml.

We obtained ultrasound brain scans on days 1, 3, and 7 of life and subsequently at weekly intervals in infants with IVH. Haemorrhages were graded as follows: grade 1, germinal matrix haemorrhage; grade 2, intraventricular haemorrhage with normal ventricle size; grade 3, intraventricular haemorrhage with ventricular dilatation; grade 4, intraparenchymal haemorrhage. The data were analysed by Student's *t* test to compare the means and χ^2 test to compare the proportions in the two groups. Differences were considered significant if the value of *p* was 0.05 or less.

Results

The number of infants in the two groups who required assisted ventilation, treatment with bicarbonate, volume expansion, and indomethacin for patent ductus arteriosus was comparable. In addition, the number of infants who developed hypoxia (arterial oxygen tension <40 mm Hg), hypercarbia (arterial carbon dioxide tension >60 mm Hg), or pneumothorax was also similar. Blood concentrations of phenobarbitone (mean (SD)) before the