Medical Memoranda

Reaction to Iron Sorbitol Injection in Three Cases of Malabsorption


To emphasize the potential dangers of parenteral iron two fatal reactions and one severe reaction with subsequent total atrioventricular block after intramuscular administration of iron sorbitol (Jectofer) are described in patients with the malabsorption syndrome.

**Case Reports**

**Case 1.**—The patient was a man aged 35. At the age of 2 years he had been admitted to hospital because of severe diarrhoea. After an asymptomatic period of 20 years he started to have periods of diarrhoea with severe weight loss and anaemia. In 1963 duodenal biopsy showed subtotal villous atrophy. Prednisone, which the patient had been using since 1960, was continued and he was put on a gluten-free diet. In 1965 iron-deficiency anaemia was treated with parenteral iron sorbitol. Two years later, a course of intramuscular iron therapy was started. Ten minutes after the first injection of 100 mg. of iron sorbitol he complained of severe chest pain, sweated profusely, and breathed heavily. A few minutes later he became cyanotic and pulseless. Resuscitation was started immediately, but was unsuccessful. Necropsy showed numerous petechial haemorrhages on serosal surfaces and 800 ml. of bloody fluid in the peritoneal cavity. Atrophy of the intestinal mucosa was also present.

**Case 2.**—The patient, a woman aged 39, had undergone partial resection of the pancreas and pancreaticojunostomy in 1957. She remained well until March 1966, when she was readmitted to hospital with acute pancreatitis. Two weeks later when her hospital symptoms had disappeared intramuscular iron therapy was started. Soon after the first injection she became unconscious. The pulse was irregular and sometimes disappeared. On regaining consciousness she was hypotonic and her E.C.G. pattern had changed to one of right bundle-branch block. Pulmonary embolism was suspected and she was treated accordingly. The next day after a second injection of iron sorbitol her condition worsened. She vomited, had bouts of tachycardia, and was hypotonic. Within a few days she recovered completely, except that the right bundle-branch block remained. Because iron was not thought to have caused these symptoms she received another dose two weeks later, which caused transient nausea. On the following day 10 minutes and a further injection of iron sorbitol she collapsed. Ventricular tachycardia was followed by asystole and she died three hours later. Only congestion of the parenchymatous organs was found at necropsy.

**Case 3.**—The patient was a woman aged 26. In August 1967 malabsorption with complete villous atrophy of the jejunum was diagnosed. An E.C.G. was normal. She was put on a gluten-free diet and given vitamin B<sub>12</sub> and folic acid supplements. Because of vitamin B<sub>12</sub> deficiency, iron and folic acid, intramuscular iron therapy was started. Once a week during the following month she was given 2 ml. of iron sorbitol intramuscularly by a nurse. Half an hour after the sixth injection the patient experienced nausea, chest pain, and dizziness. Her pulse rate was very slow. After lying down her symptoms gradually subsided. The next dose two weeks later was given in two portions 15 minutes apart. Fifteen minutes after the second injection she complained of severe chest pain, sweated profusely, lost consciousness, and had convulsions. Her pulse rate was very slow and convulsive seizures occurred six or seven times. Blood pressure was 75 mm. Hg. The E.C.G. showed complete atrioventricular block, with an atrial rate of 155 and a ventricular rate of 18/min. The QRS complexes showed the configuration of left bundle-branch block. A bipolar pacing catheter was induced transvenously into the right ventricle and the heart was paced artificially. Serum iron was 76 µg. and the total iron-binding capacity 314 µg./100 ml. Serum electrolytes were normal, as were the serum aspartate aminotransferase, serum alanine aminotransferase, and lactic dehydrogenase. On the eighth day the E.C.G. still showed a complete atrioventricular block, but the idiopathic rhythm was of low nodal origin. There were pronounced T-wave inversions in leads II, III aVF, and V<sub>1-4</sub> which gradually disappeared. A second-degree atrioventricular block with 2:1 conduction remained, however, and was still present one year later.

**Comment**

With the iron-sorbitol/citric-acid complex serious reactions are thought to be rare (Que, 1968). These three cases, however, show that it is potentially dangerous. The necropsy findings in Case 1 suggest that the reaction was due to anaphylaxis. The reactions in Cases 2 and 3 might be considered as toxic. The appearance of total atrioventricular block in Case 3 is a peculiar feature. It could be explained by a direct toxic effect of free iron on the heart, since iron deposits in the conductive tissue in transfusion haemosiderosis have been described as a rare cause of total block (Harris et al., 1969). On the other hand, in animal experiments anaphylactic shock has been shown to cause severe cardiac arrhythmias, including total atrioventricular block (Bickel and Fabre, 1954).

Occasionally, parenteral administration of iron to piglets causes the death of most of the piglets in a litter. Vitamin-E deficiency has been suggested as a causative factor, since it lowers the resistance to parenteral iron in piglets and mice.
Treatment with vitamin E will make the resistance normal and even increase it (Tollerz and Lannek, 1964). The possibility exists that patients with malabsorption syndrome have an increased susceptibility to the toxic effects of free iron, and this needs further study.

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Idiopathic Addison’s Disease
Presenting with Hypercalcaemia

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Though Addison’s disease is occasionally cited as a rare cause of hypercalcaemia (Watson, 1966), the association is not mentioned in several of the most authoritative textbooks of medicine. This report concerns a case of idiopathic Addison’s disease which presented with hypercalcaemia.

CASE REPORT

A childless 24-year-old housewife was admitted to hospital in May 1969. At Easter she had begun to develop generalized muscular pains and feelings of faintness. She then became increasingly depressed and subject to outbursts of tears, complained of lethargy, anorexia, and bouts of nausea and vomiting, and more recently had developed polyuria, thirst, and nocturia and a liking for salty food. She had noticed muscular pains in the thighs and lower abdomen and had experienced difficulty in sitting up in bed. In childhood she had undergone criopitomy for raised intracranial pressure. Her past history was otherwise normal and there was no relevant family history. On examination she was depressed. She was not anaemic and had neither buccal nor generalized pigmentation. Corneal calcification was absent. The blood pressure was 95/70 mm Hg. Physical examination was otherwise negative.

Investigations.—E.S.R. 25 mm/hour, blood picture normal. Paul–Bunnell test negative. Urine, routine x-ray films, liver biopsy, and sternal marrow were all normal. Plasma urea 125 mg./100 ml.; sodium 128 mEq/l.; bicarbonate 19 mEq/l.; chloride 94 mEq/l.; potassium 5-2 mEq/l.; calcium 11-8 mg./100 ml. (plasma S.G. 1024); phosphorus 5-2 mg./100 ml.; alkaline phosphatase 6 K.A. units/100 ml.; serum uric acid 9-9 mg./100 ml.; and creatinine clearance 25 ml/min. Twenty-four hour collection of urine contained protein 100 mg., calcium 90 mg., urea 12 g., chloride 36 mEq., sodium 40 mEq., and potassium 37 mEq. Urinary S.G. after overnight fluid deprivation was 1024. Two-hour postprandial blood sugar was 56 mg./100 ml. Antibody studies showed positive cytoplasmic fluorescence for adrenal antibodies, a high titre of thyroglobulin and thyroid cytoplasmic antibodies, and also the presence of gastric parietal cell antibodies. Plasma protein-bound iodine was 7-8 μg./100 ml. and serum vitamin B12 250 μg./ml.

Hydrocortisone 40 mg. t.d.s. was given by mouth. Ten days later plasma calcium, urea, and electrolytes were all restored to within normal limits—the calcium falling in five days, which was an unexpectedly rapid response—the creatinine clearance had risen to 67 ml./min., and her symptoms had disappeared. On discontinuing the hydrocortisone her original symptoms recurred within a week and the previous biochemical abnormalities returned. Plasma cortisol values at midnight and 9 a.m. were 3-9 and 4-5 μg./100 ml. respectively and failed to rise above these subnormal values in response to 50 units of corticotrophin given intramuscularly on three successive days.

Replacement therapy with cortisone acetate 37-5 mg. and fluadrocortisone 0-1 mg. daily was instituted and since then she has remained in excellent health. Plasma calcium, urea, and electrolytes were repeatedly within normal limits after steroid therapy was begun.

COMMENT

Pedersen (1967) pointed out that the clinical pictures of adrenal insufficiency and hypercalcaemia may be identical. In the present case the alterations in plasma calcium paralleled closely those in the clinical state. The mechanism of production of hypercalcaemia is unknown. Hypercalcaemia is a frequent occurrence after adrenalectomy for Cushing’s syndrome (Sprague et al., 1953). On the other hand, cortisone will lower plasma calcium in certain hypercalcaemic states (Connor et al., 1956).

It is stressed that in this patient the original symptoms mimicked those of hypercalcaemia so closely that Addison’s disease was not initially considered as a possible diagnosis. Hence our use of the standard hydrocortisone test in the differential diagnosis. The patient improved so rapidly during the test that our suspicions were aroused and then strengthened when no common cause was found for the hydrocortisone-responsive hypercalcaemia. This situation is very rare. It is the first time that it has been noted at University College Hospital, where the differential diagnosis of patients with hypercalcaemia is a frequent problem.

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