Medical Memoranda

Fatality after Oxyphenbutazone in Still's Disease

Oxyphenbutazone (hydroxyphenylbutazone; "tanderil") was introduced in 1957 and became generally available in 1961. Toxic effects were found to be similar to those of phenylbutazone—namely, leucopenia, thrombocytopenia, rashes, and abnormal liver-function tests. In children it has proved of considerable value in the treatment of rheumatoid arthritis. In doses of 100 mg. daily to children under 7 years of age and 200 mg. for those aged 10–12 years it is effective in the relief of pain and in improving joint mobility and diminishing joint-swelling. It thus allows of an appreciable reduction in the dose of steroids (when these have proved to be necessary) and produces considerable improvement in the children's physical and psychological well-being.

Because of its possible toxic effects it is important that close watch be kept for symptoms such as rash, diarrhoea, or slight jaundice, and that regular blood examination (W.B.C. and platelets) should be undertaken. On the appearance of any abnormality the drug should be discontinued immediately; if this is done recovery is likely to be prompt. Failure to stop treatment may lead to death, as exemplified by the following experience.

CASE REPORT

A boy aged 9 years had suffered from Still's disease since the age of 15 months and his disability was so severe that he had required continuous steroid treatment throughout the course of the disease. All attempts to reduce the dosage had to be abandoned because of the pain and stiffness which rapidly recurred. He had never been really well and had continually had a raised E.S.R. and irregular bouts of fever. On June 4, 1962, he was given oxyphenbutazone, 150 mg. b.d., and paramethasone (of which he had been having 0.5 mg. b.d.) was reduced to 0.25 mg. b.d. His condition improved symptomatically and he was seen on June 14 and again on June 21; on each occasion his blood count was normal. The W.B.C. remained at 6,000/c.mm., with polymorphs 60% on the first occasion and 58% on the second. He was due to attend on June 28 but did not appear; on July 1 his father telephoned to say that the boy was in bed with "infective hepatitis" and the doctor thought it unwise for him to be brought up (because of the infection). However, in the light of his recently changed treatment he was admitted to hospital the next morning for investigation. His general condition was poor; there was moderate jaundice and his temperature was 102° F. (38.3° C.). His E.S.R. was 53 mm. in one hour. His blood count showed Hb 40%, W.B.C. 1,000/c.mm., mainly lymphocytes. He was given 3 pints (1.7 litres) of blood during the next 48 hours and his haemoglobin rose to 62%. His W.B.C. remained at 1,000 with polymorphs 1%, and his platelets were 70,000/c.mm. His condition deteriorated rapidly during the night of July 5 and he became comatose and hyperpyrexial—temperature 108° F. (42.2° C.); he had several convulsions. He died the next day despite intensive supportive therapy.

At necropsy diffuse necrosis of the liver was found, together with ulcerative colitis which had obviously been present for some time, and adrenal atrophy; there was terminal pneumonia. *Staphylococcus pyogenes* being cultured from the lungs. The bone-marrow was markedly hypocellular; late normoblasts were few and were seen in small clumps, but no cells of the leucocyte series were found. Megakaryocytes were numerous and relatively well preserved. It is clear that the drug had affected red-cell formation as well as the white cells; this was reflected clinically in the rapid fall of haemoglobin (from 60 to 40% in 12 days).

This effect on the red cells has been reported previously after phenylbutazone by Venning (1957) and by others.

COMMENT

There can be little doubt that the agranulocytosis, thrombocytopenia, and hepatic necrosis were all due to the oxyphenbutazone; the ulcerative colitis was probably the result of steroids. This boy's clinical history was unusually interesting and prolonged (Gaisford, 1960) and particular importance must be placed on the continued steroid therapy which had virtually destroyed his adrenal cortex.

It was unfortunate that during his initial week of jaundice at home the drug had been continued. As he was a "regular attender" at the out-patient department and was coming up for weekly blood checks the family doctor was, regrettably, not informed about the new treatment and had quite naturally assumed that infectious hepatitis was the most likely cause of his jaundice.

This is the first fatal case recorded following the use of oxyphenbutazone in childhood.

I am indebted to Dr. Don Hilson who first referred this patient to me in 1958, to Dr. H. B. Marsden who performed the necropsy; and to Dr. P. Fowler, of Geigy Pharmaceutical Co. Ltd., for a supply of "tanderil" and for his assistance.

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Sickle-cell Anaemia at Age of 7 Weeks

Haggard and Schneider (1961) have described 26 cases of sickle-cell anaemia which presented in the first two years of life, the youngest at the age of 3 months. The following case is of interest because it presented at the age of 7 weeks with a foetal haemoglobin (Hb F) of 20%.

CASE REPORT

On January 11, 1962, a 7-weeks-old coloured boy was sent to St. Thomas's out-patient department by his general practitioner, who had heard a heart murmur. The parents, Jamaicans, had been in this country for two years and had one other child, a son of 9. None of them had ever had any illness of note.

The baby weighed 5 lb. 9 oz. (2,525 g.) at birth, and at 7 weeks 7 lb. 6 oz. (3,345 g.). He was being breast-fed without difficulty, but the mother said that he had had a cold. On examination he was not clinically anaemic and had a systolic murmur loudest in the third left intercostal space described as "squeaky" that was thought at this time to be functional. The liver was not enlarged, but the spleen was just palpable in the abdomen.

On February 2 he was seen again in the out-patient department, the mother complaining that he had become much worse and was not taking his feeds. He weighed 9 lb. 14 oz. (4,480 g.) and looked very pale. On examination a loud systolic murmur was heard all over the front of the chest. The pulse rate was 120 per minute. In the abdomen a firm liver edge 1 cm. below and a firm spleen 2 cm. below the costal margins were now palpable. The haemoglobin, measured in the out-patient department, was 4.1 g./100 ml. (28%), and gross sickling of the untreated red cells was observed.

The baby was admitted and placed in an oxygen tent. He was treated with digitalis because he was thought to be in cardiac failure precipitated by the upper respiratory infection.

Investigations.—March 2: Hb 4.1 g./100 ml.; P.C.V. 18%; M.C.H.C. 23%; sickling test positive; 20% Hb F

present. Haemoglobin electrophoresis showed a single band of Hb S. March 3: Bilirubin 4.5 mg./100 ml.; blood urea 43 mg./100 ml. March 5: Hb 3.8 g./100 ml.; P.C.V. 14%; M.C.H.C. 21%; reticulocytes 16.2%; W.B.C. 18,300/c.mm. (normoblasts 23 per 100 W.B.C.). March 9: Hb 4.1 g./100 ml.; reticulocytes 50%. March 12: Hb 4.6 g./100 ml.; P.C.V. 17%; M.C.H.C. 26.5%; reticulocytes 40%; W.B.C. 25,900 c.mm. (normoblasts 11 per 100 W.B.C.). X-ray films of the skull and hands showed no abnormality.

His condition improved gradually while he was in the oxygen tent and having digitalis. On March 14 he was given a transfusion of 160 ml. of packed cells and the haemoglobin immediately after was 14 g./100 ml. The next day the cardiac murmur was barely audible.

Investigation of the parents' blood gave the following results. Mother: Hb 15.1 g./100 ml.; Hb F 2.6%; sickling weakly positive; haemoglobin electrophoresis showed haemoglobin A/S. Father: Hb 14.9 g./100 ml.; Hb F 0.81%; sickling positive; haemoglobin electrophoresis showed haemoglobin A/S.

These results support the diagnosis of sickle-cell anaemia for the boy.

COMMENT

This report is of importance, since this condition has only rarely been recorded as occurring before the age of 6 months. In view of the many families from West Africa and the West Indies now in this country, similar cases may occur and might be missed because sickle-cell anaemia would not be considered.

I am grateful to Dr. Dennis Cottom for allowing me to report this case, and would like to thank Dr. G. Wetherley-Mein for his advice.

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Unusual Complication of Glandular Fever

The following unusual occurrence in a case of glandular fever may be found of interest.

CASE REPORT

A student nurse aged 19 was admitted to hospital on November 4, 1960, complaining of a sore throat for 10 days, which had become much worse recently. On examination both tonsils were large and there was considerable peritonsillar and palatal swelling, but with no exudate. The pharynx was red. Both tonsillar glands were enlarged and the tip of the spleen was palpable. A provisional diagnosis of glandular fever was made.

Investigations on day of admission: W.B.C. 7,100/c.mm. (neutrophils 26% lymphocytes 37%, monocytes 3%, atypical mononuclears 34%). E.S.R. 17 mm. in one hour (Westergren). Paul-Bunnell test—unabsorbed serum positive to a titre of 1:5,120; guinea-pig absorbed serum positive to a titre of 1:5,120; ox-cell absorbed serum positive to a titre of 1:160. Throat swab culture: normal flora only.

In the course of the next week the throat became extremely painful and the tonsils very enlarged, meeting in the midline. Further throat swabs on November 9 showed normal flora, no Vincent's organisms, and in particular no beta-haemolytic streptococci. Antibiotics were not given, treatment consisting only of analgesics and sedatives.

On November 10 the patient suddenly complained of an unpleasant taste in the mouth followed by a gush of foul-smelling blood-stained pus. Examination showed that the left tonsillar swelling had disappeared, the right remaining very swollen but with no exudate visible. In view of this it was decided to incise the right peritonsillar swelling. This

produced a large quantity of blood-stained pus, the right tonsil then returning to its normal position. Culture of this material grew only normal throat commensals.

The clinical recovery was dramatic, and the temperature, which had been rising up to 103° F. (39.4° C.), immediately fell to normal (see Chart). She subsequently made an uneventful recovery and was discharged 10 days later.

Chart showing the sudden fall in temperature which occurred immediately after evacuation of the peritonsillar swellings.

COMMENT

In the anginose form of glandular fever it is common for the throat to become secondarily infected, usually with haemolytic streptococci or Vincent's organisms, and peritonsillar abscesses may occur as a result. However, in this case there was no evidence of secondary infection.

Spontaneous rupture without secondary infection is known, for example, in the spleen (Shinton and Hawkins, 1956).

Other cases of suppurating cervical adenitis and retropharyngeal abscesses have been reported (Moir, 1930). Most of these have been thought to be due to secondary infection, but the absence of this has not been well authenticated. Post-mortem examination in some reported fatal cases of glandular fever has shown haemorrhage and necrosis in sections of the cervical glands and tonsils (Custer and Smith, 1948; Shinton and Hawkins, 1956).

We feel that secondary infection is excluded in our case, and suggest that the fever and malaise were probably due to necrotic material under extreme tension, which when relieved resulted in a dramatic recovery.

We believe that the spontaneous rupture of a sterile collection of necrotic material from the peritonsillar region is an unusual occurrence in glandular fever. It is not mentioned by Tidy (1948) or by Bernstein (1940) in his exhaustive review of the literature up to 1940 or in a leading article (*Brit. med. J.*, 1960) dealing with this subject. It is quite possible that many cases have considerable necrosis which absorbs spontaneously, as appearances of almost similar severity are fairly common. However, we are not suggesting that incision of these swellings is indicated in all cases of glandular fever.

We thank Miss T. Turner, the matron of St. Thomas's Hospital, and Dr. H. K. Goadby, honorary physician to the nursing staff, for allowing us to publish this case.

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