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FATAL CASE OF MARROW APLASIA AFTER TREATMENT WITH CARBIMAZOLE

THE EFFECT OF A.C.T.H.

BY

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Carbimazole ("neo-mercazole"; 2-carbethoxythio-1-methylglyoxaline) must now be added to the long list of drugs that may cause marrow aplasia with depression of all the blood-forming elements.

The incidence of marrow depression due to anti-thyroid drugs is relatively low and is still decreasing as less toxic preparations become available. A report on the treatment of 150 patients with carbimazole by Doniach (1953) stresses the absence of any toxic effects in her cases, and only mild toxic reactions were found to follow treatment of 14 patients with this drug by Lawson and Barry (1951). Poate (1953), in a survey of nine cases, states that carbimazole in therapeutic doses does not interfere with the leucocytes. In a recent study on the clinical effects and toxic reactions of carbimazole, Bartels (1953) found that 3 of his 52 patients treated with this drug developed toxic manifestations. Two of these were skin reactions, the third had agranulocytosis, which however, cleared up within 14 days after discontinuation of the drug.

Rosenbaum and Reveno (1953) reported a case of agranulocytosis and toxic hepatitis secondary to methimazole ("mercazole"), the forerunner of carbimazole, and referred to two instances of agranulocytosis due to this drug (Croke and Berry, 1952; Specht and Boehme, 1952). In the experience of Davidson (1953), who discusses the use of methimazole in 44 patients, this drug is definitely less toxic than methylthiouracil, and, although slightly more toxic than propylthiouracil, the incidence of severe toxic reactions is of the same order of magnitude as with the latter drug. The overall incidence of toxic reactions with methimazole is given by various workers as 4.5–6%, that of agranulocytosis as 0.15%.

The following case is, we believe, the first example of a fatal marrow aplasia following the use of carbimazole.

Clinical History

A married woman aged 23 was admitted to hospital on June 8, 1953, suffering from severe thyrotoxicosis. Her B.M.R. was 74%. As she had suffered from extensive bilateral bronchiectasis for several years, surgical treatment for her thyrotoxicosis was considered undesirable, and she was put on carbimazole, 10 mg. three times a day, on June 19. She was discharged from hospital a fortnight later and continued as an out-patient with carbimazole in the same dosage as her sole medication. When seen a month after discharge her thyrotoxicosis was under control and she felt much better.

On August 12, just under eight weeks after beginning carbimazole she noticed red patches on her skin and was coughing up more blood from her bronchiectatic cavities than ever before. The drug was discontinued and she was admitted to hospital. Purpuric haemorrhages were found over most of her body and on her mucous membranes. There was no soreness of her throat, but she had a pyrexia of between 101 and 103° F. (38.3 and 39.4° C.). Hess's test was strongly positive. A blood count on the day of admission showed: haemoglobin, 64%; red cells, 4,110,000; white cells, 4,000, with a normal differential count; platelets, 61,000; bleeding and clotting times, normal.

Four days later her haemoglobin had fallen to 54%, her white count to 1,000 cells with 29% polymorphs, and her platelets to 25,000. She was transfused with 2 pints (1,140 ml.) of fresh blood. Her bone marrow taken at this time showed marked agranulocytosis and only one megakaryocyte in three films. Electrophoretic examination of the serum, both before and after the first transfusion, failed to reveal the presence of any α_2 -globulin such as may be present in certain cases of purpura (Bernfeld and Stefanini, 1951).

Treatment directed to the control of infection consisted of penicillin for one week, which was then replaced by aureomycin, 500 mg. six-hourly, and this was continued throughout the rest of her illness. She was given approximately 2 pints (1,140 ml.) of fresh blood at weekly intervals for the next eight weeks.

Cortisone was begun on August 23, 11 days after the onset of purpura, the initial dose being 100 mg. six-hourly, followed on the next and subsequent days by 50 mg. six-hourly. As she made no detectable response the cortisone was replaced by adrenocorticotrophic hormone (A.C.T.H.) with a dosage of 40 mg. six-hourly. After starting cortisone the patient's condition was reasonably satisfactory and her temperature settled on aureomycin, but she continued to get crops of petechiae, although Hess's test had become negative before cortisone was started. Her blood picture, which was examined daily, remained unchanged. The platelets were virtually absent, her haemoglobin was maintained in the region of 50% with transfusions, and her white cells remained round about 1,000, with 20 to 30% polymorphs.

This state of affairs continued for 17 days, during which time the dose of A.C.T.H. was gradually reduced from 40 mg. six-hourly to 15 mg. twice daily, as supplies were running out. Her temperature rose to 101° F. (38.3° C.) and she had a haemoptysis of 12 oz. (340 ml.). A fresh supply of A.C.T.H. was obtained and her condition improved, but the drug was running short by October 3, and was tailed off and discontinued on October 7. Three days later her temperature, which had been rising, reached 102° F. (38.9° C.); she had a haemoptysis of 16 oz. (450 ml.), and several smaller ones. Her condition became critical. Her pulse rate rose to 140 a minute, and her blood pressure fell from its normal level of 130/80 to 90/50. The bleeding from her lungs was stopped by two transfusions of 2 pints and 1 pint (1,140 and 570 ml.) of blood respectively, but she remained desperately ill.

The next day A.C.T.H. was again obtained and 30 mg. was given intramuscularly with a further pint (570 ml.) of fresh blood. Two hours later her general condition was better, her colour improved, and her pyrexia began to settle. The A.C.T.H. was continued in doses of 15 mg. six-hourly, and a week later, on October 19, her blood count showed the first sign of improvement; haemoglobin, 72%; red cells, 3,890,000; white cells, 3,000 (60% polymorphs); 60 nucleated red cells per c.mm.; platelets 10,000.

The figures of her blood count remained round about the same level and on November 6 A.C.T.H. was stopped. On this occasion after withdrawal of A.C.T.H. her temperature did not rise or her condition deteriorate and her blood count had remained substantially the same, although transfusions of 2 pints (1,140 ml.) were required every two to three weeks instead of weekly. Her bone marrow on November 9 appeared completely aplastic, but the drop in cells was mainly in the red-cell series, her white blood count being constant at 2,000–3,000 and her platelets 10,000–50,000 per c.mm. Her condition appeared to improve for a time, but remained precarious throughout. The haemorrhagic incidents became more frequent. She was admitted for a further transfusion, developed a cerebral haemorrhage, and died before any effect of a new supply of cortisone could take place. She died on December 28—that is, 139 days after the onset of her blood disorder.

Post-mortem examination revealed a pale and fatty bone marrow, the presence of petechial haemorrhages in most organs, and a cerebral haemorrhage on the right side. Bronchiectasis, fatty degeneration of the liver, and deposition of haemosiderin in the liver and spleen were found. No significant histological changes were present in the endocrine organs.

Discussion

It is the experience of several workers that marrow function usually returns spontaneously in about a week after discontinuing the offending drug (Hutt and Lee, 1953). We felt at first that both cortisone and A.C.T.H. were of no value in the management of this case, but, as the aplastic condition of her marrow persisted and she did not deteriorate clinically, we began to think that it might be having a life-saving effect. Coincidentally with the reduction in the dose of A.C.T.H. to an ineffective level she developed on two occasions a pyrexia and severe haemoptysis, and on the second was desperately ill. On both occasions when an effective dose of A.C.T.H. was restarted her general condition improved in a matter of hours.

We found no evidence that cortisone and A.C.T.H. had any effect in hastening recovery of normal marrow function. Sternal marrow puncture was not used throughout as a guide to the amount of regeneration, as daily blood counts showed no signs of recovery and the patient was having to endure many but inevitable needle pricks and discomforts. We felt, however, that we were giving cortisone and A.C.T.H. a proper trial, as they were not begun until 11 days after the onset of purpura and the discontinuation of carbimazole. We suggest that these drugs would have produced signs of regeneration of the marrow after a course lasting 72 days if they were capable of bringing about such an effect.

Summary

A fatal case of marrow aplasia secondary to carbimazole is reported. It is believed that this is the first recorded example due to this drug.

Cortisone and A.C.T.H. were given for 72 days, and on two occasions when the dose was reduced the patient immediately became extremely ill with pyrexia and haemoptysis. A third attempt at withdrawal of the drug was achieved without untoward effects, but only after the peripheral blood picture had shown some improvement over a period of 18 days.

It is believed that cortisone and A.C.T.H. kept this patient alive while they were being administered, but no evidence was found that either of them assisted in the regeneration of the marrow.

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PRURITUS AND ITS MANAGEMENT*

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Pruritus implies the peculiar uncomfortable sensation of itching, which leads to the physical response of scratching but is not associated with any inflammatory changes of the skin. As with love, it is difficult to know where it is bred, in the skin or in the head; whether in the nerve endings or in the accelerated appreciation of the sensation. It may even originate in the cerebral cortex.

Whether one itches may depend on the degree of attention paid to somatic sensation. We know that if we are obliged to keep still at attention, within a few minutes an intolerable itch is likely to develop, often near one of the orifices.

Itching is very easily suggested. The sight of a head infested with crawling lice will induce in the novice a crawling itching feeling over the skin, which might even be localized to the same area.

The pleasurable element of itching is a matter of common experience. According to Jowett, Socrates dilates in his dialogues on the sensual pleasure of itching and scratching. The back scratcher of the Chinese, so finely carved in the shape of a hand or a claw, indicates the artistic appreciation of the instrument and equally the pleasure it gives when used.

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