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FATAL APLASTIC ANAEMIA FOLLOWING SULPHAPHENAZOLE (ORISULF) THERAPY

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WINTROBE (1961) classifies sulphonamides among the rarer causes of pancytopenia. Nevertheless, aplastic anaemia due to sulphonamides occurred in 5.3% of Welch's series (Welch, Lewis and Kerlan 1954), 8.7% of Wolff's 334 cases (Wolff and others 1959), and once in Scott's series of 39 cases (Scott, Cartwright and Wintrobe 1959). Similarly the shorter-acting sulphonamide preparations have appeared individually in the literature from time to time as causing aplastic anaemia viz. sulphathiazole (Strauss, 1943; Meyer and Perlmutter, 1942), sulphanilamide and sulphadiazine (Denny and Menten, 1946), sulphabutin (Wagner and Sterz, 1961), and sulphapyridine (Scott and others, 1959). The sulphonated nitrobenzene nucleus of the sulphonamide compounds has been blamed for the bone marrow depression and this indeed would seem to be the case, as structurally related compounds like carbutamide, tolbutamide, acetazolamide and thiosemicarbazone have all been associated with the development of aplastic anaemia. (see Wintrobe (1961) for references).

There have, however, been few reports of this complication following the use of the newer, longer acting sulphonamides.

The first of these drugs, sulphamethoxypyridazine was first reported to have caused aplastic anaemia in 1958 (Holsinger, Hanlon and Welch). A further report followed in 1961 (Johnson and Korst).

A sulphonamide with a similar prolonged action is 3-(p-amino benzene sulphonamido)-2-phenylpyrazole (sulphaphenazole, 'orisulf', 'orisul') which has the following structural formula:—

The case reported here suggests a possible association between the administration of this drug and the development of aplastic anaemia.

Case Report

The patient was a 66-year-old housewife who lived in Jersey. For 15 years she had suffered from asthma and chronic bronchitis. On May 26, 1961, she went to see her general practitioner with breathlessness which had not responded to aminophyllin and ephedrine. Severe bronchospasm was diagnosed and betamethazone prescribed; initially 2 mg was given daily in divided doses, reducing to 0.5 mg daily by the 10th June, 1961 when 'Amesec' was introduced.

In July 1961 a diagnosis of acute bronchitis was made and a 4 day course of 'Orisulf' given—1 g twice a day for the first 2 days, and 0.5 g twice a day for the next two.

The patient was next seen by her doctor on August 16, 1961 when she had had no drugs for 4 weeks. She had been feeling well but petechiae were noticed by the doctor. Ascorbic acid was given pending investigation.

Early in October 1961, in addition to petechiae in the skin and hard palate, there were ecchymoses in the skin and Hess's test was strongly positive. At this time the patient was receiving Histryl spansules (Diphenylpyraline hydrochloride) for vasomotor rhinitis.

Blood count: Hb. 62%; wbc 4,700/cu.mm.; polymorphs 30%, eosinophils 6%, lymphocytes 63%, monocytes 1%, PCV 30%; MCHC 30.5%, platelets 220,000/cu.mm.

On October 25, 1961 the patient was admitted to the General Hospital, Jersey. A few days before her admission she had become lethargic and anorexic and had developed soreness of the tip of her tongue. A further blood count showed: Hb. 26%; wbc 3,200/cu.mm.; reticulocytes 0.3%, PCV 13%; MCHC 29.5%; ESR 75 mm hr (Wintrobe). The sternal marrow was hypoplastic and acellular. An occasional normoblast was present. One myelocyte was seen in 20 /12 inch fields.

In addition to blood transfusions, ACTH, prednisone, iron, ascorbic acid and Vitamin B₁₂ were given. On February 12, 1962, the patient was transferred to the Westminster Hospital for consideration of bone marrow infusion.

On admission the patient was clinically anæmic and there were numerous petechiæ and ecchymoses, especially over upper chest anteriorly, forearms, and buttocks. Petechiæ were seen on the conjunctivæ, buccal mucosa and pharynx. Hess's test was strongly positive. The blood pressure was 140/85 mm Hg and a soft systolic murmur was audible at the mitral area.

Investigations: Blood urea: 40 mg/100 ml. Hb: 54%, Reticulocytes less than 1%, rbc 2,360,000/cu.mm. wbc 3,500/cu.mm. (differential count: neutrophils 16%, lymphocytes 83%, monocytes 1%) ESR 62 mm/hr (Wintrobe); PCV 26%; MCV 110 cu.µ; MCHC 33%.

The bone marrow was very hypoplastic. The total nucleated count was 38,000 cells per cu.mm. The film showed predominantly lymphocytes with an occasional plasma cell. One myelocyte and one nucleated red cell seen. Megakaryocytes were not seen.

Course in Hospital—20 units ACTH were given on February 15, 1962 and on the following day bone marrow was collected from the patient's 16-year-old grandson by multiple bone marrow punctures under general anæsthesia using the technique described by Pegg and Kemp (1960). 300 ml of bone marrow-blood mixture was administered by intravenous infusion. From the day of infusion, prednisone 50 mg. daily in divided doses was given. On February 21, 1962 a further 20 units ACTH were given.

Between March 10—21, 1962 the patient received 6 pints of blood. On March 27 hæmaturia was noted and there was generalised abdominal tenderness. Despite blood transfusion, methicillin and hydrocortisone the patient deteriorated rapidly and died on April 2, 1962.

At autopsy, extensive hæmorrhages were found in the tonsillar fossæ, aryepiglottic folds and pyriform fossæ. There was a large retroperitoneal hæmorrhage arising from both kidneys. Histologically, the bone marrow of the sternum showed almost complete aplasia with many foci of plasma cells and macrophages.

Discussion

Sulphaphenazole has always enjoyed an excellent reputation. An extensive comparative study of sulphaphenazole and five other sulphonamides including sulphamethoxypyridazine was carried out at the CIBA laboratories by Neipp, Padowetz, Sackmann and Tripod, (1958). They showed that sulphaphenazole gave the best-sustained blood concentrations in several animal species, had the best therapeutic effect on mice infected with streptococci and at the same time showed the lowest blood concentrations. The use of 1.0 g/kg. of sulphaphenazole daily for 28 days in rats resulted in no pathological changes in these animals.

Clinical studies followed in man and Essellier, Hunziker and Goldsand (1958) reported that side effects were rare. 174 patients were studied; inclusion bodies were seen in 3, nausea in 'an occasional patient' and urticaria and Quincke's oedema in 1 case each. Orisulf was given to 3 allergic patients but no allergic manifestations followed its use.

Further clinical trials, involving 381 patients in all, showed that the drug was apparently free from toxic and allergic sequelæ while exhibiting a high degree of therapeutic efficiency (Brockhaus, 1958; Rentchnick, 1958; Susset, 1958; Wheatley, 1959). A search through the literature has failed to

reveal a case of aplastic anæmia due to or following the administration of sulphaphenazole. The use of sulphonamides in the prevention of recurrences of rheumatic fever is accepted by many (Rosenberg and Hench, 1946). The longer-acting sulphonamides seem logical contenders for a place in this type of prophylaxis and indeed sulphamethoxypyridazine has been suggested for this purpose by Lepper, Simon and Marienfeld (1957), Schultz and Frank (1958), and Johnson, Matthews and Stollerman (1959). In fact Lepper and his colleagues found one dose per week adequate. Brockhaus (1958) regarded sulphaphenazole as being especially suited to the prophylaxis of rheumatic diseases.

Wheatley (1959) suggests the possible use of this drug in the prophylactic treatment of chronic bronchitis.

The high incidence of toxicity with sulphamethoxypyridazine would appear to make its long term use undesirable. Perhaps, therefore, as sulphaphenazole and the still newer sulphadimethoxine are more widely used, further cases of bone marrow depression will occur and be reported.

The mechanism by which sulphonamides produce marrow aplasia is, however, completely understood. While direct toxicity seems frequently to be responsible, interest in an allergic or auto-immune type of reaction was aroused by the clinical impression that manifestations of allergy are common in patients with aplastic anæmia (Osgood, 1953, and Wolff, 1957).

Wolff (1957) in his series of 334 cases of aplastic anæmia found an incidence of 21.4% of allergy in all cases, but of 62.4% in those cases induced by antibacterial agents. In addition the incidence of an allergic family history was three times as great in the latter group.

It is therefore of some interest that this patient is said to have been an asthmatic and an allergic subject.

Osgood (1953) has postulated that the drug or its metabolite producing the aplastic anæmia behaves as a haptene. Such a mechanism has been demonstrated in thrombocytopenia due to sedormid (Ackroyd, 1949) quinidine (Hirsch and Dameshek, 1950) and other drugs (Beutler, Robson and Bultenwiesser, 1957) and in agranulocytosis due to pyrimidon (Moeschlin, Siegenthaler, Gasser and Hassig, 1954).

It seems possible that the demonstration of cytoagglutinins in a few cases of aplastic anæmia (Dausset, Nenna and Brecy, 1954; Dausset, Nenna, Tseurenis and Bernard 1953; Moeschlin and others 1954a; Matoth, Elian, Nelken and Nevo, 1956; von Weinreich and Muller, 1956), might support a similar mechanism in aplastic anæmia, as suggested by Scott and others (1959).

Although definite proof is lacking it seems at least likely that the aplastic anæmia which this patient developed was due to sensitivity to sulphaphenazole. It is suggested, therefore, that the

routine use of this drug in potentially allergic subjects, e.g. asthmatics, be discontinued.

Summary

A case of aplastic anaemia following upon the use of sulphaphenazole ('Orisulf') is reported. It is believed to be the first case of aplastic anaemia

associated with this drug to be published. The literature is briefly reviewed and it is suggested that the use of this drug in allergic subjects be avoided.

I wish to thank Dr. R. D. Tonkin (under whose care the patient was) and Dr. J. G. Humble for permission to publish the details of this case.

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