HYPERSENSITIVITY TO PARA-AMINOSALICYLIC ACID
A Hazard in the Treatment of Orthopaedic Tuberculosis

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Hypersensitivity reactions against para-aminosalicylic acid have been recorded frequently in the literature. It is the purpose of this report to emphasise the possible occurrence of severe reactions which may result in death if unrecognised. Unlike the chest physician, the orthopaedic surgeon may be unfamiliar with these reactions because he uses the drug much less frequently. Experience with three cases, two of which may well have proved fatal from acute liver damage, prompted the writing of this report.

A comprehensive review of the subject by Simpson and Walker (1960) quotes an incidence of hypersensitivity reactions in up to 5 per cent of patients receiving para-aminosalicylic acid. A double reaction to both para-aminosalicylic acid and streptomycin is sometimes found, but concurrent hypersensitivity to para-aminosalicylic acid, streptomycin and isoniazid is rare.

CLINICAL FEATURES

The clinical presentation of the condition resembles a typical allergic reaction, with the possibility of malaise and headaches, rigors, skin irritation and a "gritty" conjunctivitis. Accompanying these symptoms there is often a high remittent pyrexia and a rash which may be erythematous, maculopapular or vesicular. The rash usually starts on the trunk, but in more severe cases it may involve all areas. After recovery it often leaves a branny desquamation. Alopecia has been known to occur. The time of onset varies between one and eight weeks after the first dose of the drug, the most common time being the third to fifth week. The symptoms usually subside when the drug is discontinued. Acute liver failure is the commonest severe complication and the cause of most of the recorded deaths. The patients usually become jaundiced and present a clinical picture resembling that of infective hepatitis. There is often hepatomegaly and splenomegaly. It is exceptional for jaundice to appear without a previous or concomitant skin reaction. Withdrawal of the drug gives improvement in the clinical state and fading of the jaundice, provided the liver has not been irreversibly damaged. If the condition is not recognised early and para-aminosalicylic acid administration stopped, liver failure will occur.

The haematological findings vary considerably. Leucocytosis with or without eosinophilia is probably the most characteristic finding. Lymphocytosis has been described with abnormal cells like those seen in infectious mononucleosis (Cannemeyer, Thompson and Lichtenstein 1955). Thrombocytopenia is also known to occur (Gregg and Maycock 1960).

Biochemical investigations show a cholestatic type of jaundice accompanied by acute liver cell necrosis. Jaundice may be slight or very pronounced. The alkaline phosphatase is nearly always elevated, and readings of over 50 King-Armstrong units per 100 millilitres have been recorded. Serum turbidity and flocculation tests for parenchymal damage are usually abnormal and are accompanied by changes in the serum proteins, the main one being an increase in gamma globulin giving a lowered or inverse albumin/globulin ratio. The prothrombin time is often prolonged. The few references to sensitive enzyme tests for detecting liver cell damage, namely the levels of the serum glutamic oxalacetic transaminase and the serum glutamic pyruvic transaminase tests, show activities similar to those found in infective hepatitis. Indeed, the whole biochemical course of the reaction closely simulates viral hepatitis, the only important atypical finding being the elevated alkaline phosphatase.
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CASE REPORTS

Three patients suffering from different aspects of hypersensitivity are described.

Case 1—A woman of thirty-two was admitted for treatment of tuberculous disease of the lumbar spine. After two weeks on streptomycin (1 gramme daily) and isoniazid (250 milligrams daily) the psoas abscess was drained and necrotic tissue excised. Four weeks after starting treatment she developed a transient urticarial rash and pain in one knee. This settled in a few days without drug withdrawal. On her discharge from hospital after three months the treatment was changed to para-aminosalicylic acid (12 grammes daily) and isoniazid (250 milligrams daily). There was no immediate reaction but after six weeks she developed sickness and urticaria which progressed to exfoliative dermatitis. There was no clinical or biochemical evidence of liver involvement, but a leucocytosis of 18,000 cells per cubic millimetre with significant eosinophilia developed. The para-aminosalicylic acid was stopped and the rash improved with antihistamines. She was readmitted on two further occasions for operations for the tuberculous lesions and maintained on streptomycin and isoniazid without difficulty over this time. Attempted desensitisation to para-aminosalicylic acid (Smith and Zirk 1961) was unsuccessful, but steroids were not used to assist the process.

Case 2—This patient, a man aged twenty with tuberculosis of a sacro-iliac joint and bilateral pulmonary lesions, presented a typical, severe sensitivity involving the liver and has been described in detail previously (Watts and Griffiths 1964). The reaction developed after one month's treatment with para-aminosalicylic acid (12 grammes daily), streptomycin (1 gramme daily) and isoniazid (250 milligrams daily). Full dosage of para-aminosalicylic acid continued for five days after the onset of jaundice. Marked jaundice and liver failure followed which recovered slowly after withdrawal of para-aminosalicylic acid. A close study of the clinical and biochemical progress of the patient was done after a test dose of para-aminosalicylic acid. This reproduced in character, but not in severity, all the previous symptoms and signs. Desensitisation to para-aminosalicylic acid, as described later, was successful, and the patient has been taking full doses of para-aminosalicylic acid for some months with no ill-effects.

Case 3—This patient presented a complex problem of triple sensitivities to the three standard antituberculous drugs. A girl aged eighteen was admitted for treatment and exploration of a tuberculous lesion of the thoracic spine. Chemotherapy by para-aminosalicylic acid (12 grammes daily), streptomycin (1 gramme daily) and isoniazid (400 milligrams daily) was begun. Three weeks later she felt unwell, vomited and developed an irritant rash and intermittent fever. Streptomycin was stopped but the clinical condition remained unchanged. After a further week all antituberculous drugs were stopped. Despite this her condition deteriorated and she developed nausea, backache and oedema of the legs. Three weeks after the onset of the reaction the rash began to subside but despite this the patient became comatose. Liver function tests showed an alkaline phosphatase of 23 King-Armstrong units per 100 millilitres, with grossly abnormal turbidity reactions and high transaminase values. Although jaundice was not apparent clinically the girl was gravely ill. A petechial eruption developed and the platelet count was only 85,000 per cubic millimetre. Steroid therapy was begun and after a week she recovered consciousness. Over this period jaundice developed with bilirubin 10 milligrams per cent and an inverse albumin/globulin ratio. The thrombotest was 9 per cent of normal. With the improvement in her clinical condition she was weaned from steroids. The platelet count rose to 200,000 per cubic millimetre and the alkaline phosphatase returned to normal. Three weeks later the jaundice had cleared. The serum transaminases were normal, but the thymol turbidity and flocculation and zinc sulphate turbidity were still raised.

Six weeks later she was given a test dose of 200 milligrams of isoniazid. She became feverish and vomited, and the rash reappeared. The condition settled after 50 milligrams of Sparine. After a further ten days a challenge dose of 3 grammes para-aminosalicylic acid was
given which produced an identical result, though the rash was more persistent. After yet another week 0·5 gramme of streptomycin produced an irritant rash within twenty minutes, accompanied by vomiting. Later she noticed that her hair was falling out. No biochemical or clinical evidence of liver damage was found during the test dosing. Four weeks later a course of desensitisation to isoniazid was started. It was only with great difficulty that a dose of 200 milligrams was eventually reached. The dose of isoniazid had to be reduced several times because of a skin reaction.

**DISCUSSION**

**Clinical considerations**—The recognition of the early signs and symptoms of a hypersensitivity reaction to the antituberculous drugs is all-important in these patients, because, as is shown in Cases 2 and 3, serious consequences can ensue from continued administration of the drug after the first signs of a reaction. Cases have been reported in which more prolonged efforts to give para-aminosalicylic have caused complete liver failure and death (Bellamy, Mauck, Hennigar and Wigod 1956). Pyrexia in an otherwise uncomplicated case necessitates close examination of the patient for other likely signs—such as a skin rash or conjunctivitis. If these signs persist or increase with a subsequent dose of para-aminosalicylic acid then the drug should be stopped until an investigation has been done on the lines recommended below. Prompt withdrawal of para-aminosalicylic acid will undoubtedly reduce the risk of more severe complications. The administration of antihistamines appears to have little effect on the hypersensitivity response. Sensitisation to more than one of the therapeutic agents creates difficulties in maintaining an antituberculous régime. Case 3 illustrates this predicament because all three of the drugs had to be withdrawn, thereby creating a lapse in effective therapy for some months whilst the patient was recovering from the initial reaction and undergoing challenge dosing and desensitisation.

**Biochemistry**—Full biochemical findings in Case 2 have been published previously (Watts and Griffiths 1964). The patient in Case 3 also showed a typical picture of liver damage caused by para-aminosalicylic acid, namely, severe jaundice, elevated alkaline phosphatase and transaminase activities, and grossly abnormal turbidity reactions. The most striking feature of this case was the very high activities of the transaminases before the onset of clinical jaundice. Similarly, in Case 2 evidence of subclinical hepatocellular damage was obtained by a rise in the levels of the serum glutamic pyruvic transaminase and other enzymes after the administration of a para-aminosalicylic acid test dose. These facts indicate that there may be considerable liver cell damage before clinical jaundice is detected (Kneebone 1961), and point to the possible use of the serum transaminases as the earliest indicators of hepatic complication in para-aminosalicylic acid hypersensitivity. However, the clinical symptoms remain the surest guide to the onset of a reaction.

**Test dosing**—The giving of a challenge dose of para-aminosalicylic acid to establish a firm diagnosis has been recommended by some authors (Simpson and Walker 1960, Smith 1961), but this can be a hazardous procedure. The nature of the response is unpredictable and may range from only a slight fever to severe and dangerous symptoms (Gupta and Grant 1959). But its usefulness as a diagnostic procedure is amply demonstrated in Cases 2 and 3. In the former the possibility of infective or transfusion jaundice was eliminated, and in Case 3 the triple nature of the sensitivity was revealed only after test dosing. Great care should be taken to ensure that the liver has recovered fully before giving any trial dose. The turbidity tests and serum transaminases should be normal because their continued elevation will indicate the development of a chronic condition (Sherlock 1958). The bromsulphthalein excretion test is also useful in assessing liver integrity. Smith (1961) recommends graded test doses, starting, for example, with 0·1 gramme of para-aminosalicylic acid, increased to 1 gramme if a response is not elicited, and finally to 5 grammes.
Desensitisation—If a diagnosis of para-aminosalicylic acid hypersensitivity has been made and the patient has fully recovered from the initial reaction or that of any subsequent test dose, then a course of desensitisation should be considered. Smith and Zirk (1961) recommend starting with a dose of 10 milligrams of para-aminosalicylic acid which is increased by 10 milligrams per day to 0.1 grammes, then by 0.1 grammes per day to 1 gramme and finally by 1 gramme per day to a full therapeutic dose. If the patient shows signs of a reaction during the desensitisation, there should be a pause in the daily increments until the symptoms disappear. Steroids may be used to help the patient over any symptoms that develop.

This régime was not successful in Case 1, the patient being unable to tolerate more than 200 milligrams of para-aminosalicylic acid. Steroids were not used and the course was stopped as it was felt that para-aminosalicylic acid was not essential to the treatment. In Case 2, although the patient had a severe initial reaction, he tolerated desensitisation well and only two pauses were necessary before he reached a daily dose of 12 grammes. Case 3 was complicated by the sensitivity to all three antituberculous drugs. It was decided to attempt to desensitise her against isoniazid initially as this was the most desirable drug of the three with which to continue therapy. It has been shown in some patients with multiple sensitivity that desensitisation to para-aminosalicylic acid has rendered the patient free from sensitivity reactions to the others (Cannemeyer et al. 1955). It was hoped to assess this in Case 3 by using patch tests before and after desensitisation to isoniazid. However, all patch tests were negative, in spite of the severity of the initial skin reaction. The inadequacy of patch testing in this condition is supported by Smith (1961).

CONCLUSIONS

If a patient on para-aminosalicylic acid shows signs, however slight, of a possible hypersensitivity reaction, which is aggravated by an additional single dose of para-aminosalicylic acid, then all chemotherapy should be stopped immediately. A total white cell count and liver function tests—especially the serum transaminases—should then be done. If hepatic complications occur, liver function should be determined frequently in order to follow the course of the reaction. The serum turbidity tests will probably be the last indices to return to normal. The serum transaminases are especially useful in assessing the presence of subclinical hepato-cellular damage. The possibility of using the serum transaminases as screening tests during the first eight weeks of administration of para-aminosalicylic acid may be considered.

Once the patient has recovered fully from the initial reaction, a test dose of para-aminosalicylic acid may be given under carefully controlled conditions, the least amount to elicit a response being all that is necessary. Close clinical examination of the patient and determination of serum transaminases should be made for at least forty-eight hours after administering the dose. Once the hypersensitivity has been proved, desensitisation to the drug should then be considered.

SUMMARY

1. Attention is drawn to the incidence of hypersensitivity to para-aminosalicylic acid in the course of antituberculous treatment.
2. The clinical features are described with particular reference to hepatic complications.
3. Three cases are presented to illustrate the salient features of the condition.
4. The importance of early detection of the reaction, the giving of test doses and the technique of desensitisation of the patient to para-aminosalicylic acid are discussed.

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REFERENCES


