manner with signs of pre-eclampsia (the evidence of association varies from 76% to 81%), sudden onset of shock and collapse, haemoperitoneum and a tender mass in the upper quadrant of the abdomen. In addition, the patient was of high parity (94% of the recorded cases have been in patients of high parity), and the age of 40 years was also in keeping; Notelovitz and Crichton found the average age among reported cases to be between 21 - 43 years with an average of 35 years.

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Salicylate Hepatitis

A CASE REPORT

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SUMMARY

A case report of salicylate hepatitis is discussed and a predictable direct drug dosage mechanism is suggested as the pathogenesis. However, a striking eosinophilia and eosinophil infiltration of the portal tract also raises the possibility of a hypersensitivity cholestatic mechanism. Raised transaminase levels in patients on salicylate therapy appear to be a fairly frequent phenomenon which has not been widely stressed. It would seem that a sustained blood salicylate level of 25 mg/100 ml is required to cause an elevated transaminase level, and a level in excess of 30 mg/100 ml is necessary to cause actual hepatitis. Rapid reversal of the elevated transaminases occurs on cessation of salicylate therapy.


The general use of salicylate and its acetyl derivative aspirin in the treatment of rheumatic disease is testimony both to their relatively low toxicity and to their therapeutic efficacy. However, side-effects of salicylate are well known and include gastro-intestinal bleeding, disturbances of the blood clotting mechanism, water retention, allergic reactions in sensitive cases, acidosis and, occasionally, renal papillary necrosis or an increased excretion of renal tubular cells.

Evidence is now accumulating which suggests that salicylates can harm hepatic function. This is not entirely surprising, because salicylate can interfere with a wide variety of metabolic processes. The following case report gives an example of salicylate hepatitis, and may assist in the understanding of the pathogenesis.

CASE REPORT

A Cape Coloured male aged 14 years was admitted to hospital on 9 April 1974 with a clinical diagnosis of acute rheumatic fever. Subsequent investigations supported this diagnosis and treatment was commenced with absolute bed rest, phenoxymethyl penicillin 500 mg orally twice daily and Disprin in an initial total dose of 3 g (administered in divided doses). The dose of salicylate was progressively increased, until by 3 May 1974 the total daily dose was 10 g. At this level the rheumatic fever process appeared to be under control, the patient's fever disappeared and the sedimentation rate began to fall.

Three weeks later (while still on 10 g salicylates a day) the patient suddenly developed a temperature of 39.5°C and complained of anorexia and nausea. A maculopapular diffuse skin rash was also noted. No change was detected in the cardiovascular system.
Blood Investigations

The sedimentation rate had again risen considerably, and the white cell count was 6,000/mm³, with a 10% eosinophilia. The serum complement was normal. The bilirubin was 2.1 mg/100 ml (conjugated bilirubin 1.9 mg), the serum glutamic oxaloacetic transaminase (SGOT) level was 700 Transac units and the alkaline phosphatase was 26 King-Armstrong units. The serum proteins were normal and the Paul Bunnell test was negative. The peripheral blood smear showed no atypical features except for the eosinophilia. Australia antigen was not detected in the blood.

A week later, on 5 May 1974, while he was still on salicylate 10 g daily, the SGOT rose to 1,050 Transac units while the bilirubin dropped to 1.4 mg/100 ml (conjugated 1.1 mg). The salicylates were stopped immediately and no other therapy given (Fig. 1).

Histology of Liver Biopsy

Four days later a liver biopsy was performed with a Menghini needle. The histology showed the features of a severe, active hepatitis. There was evidence of hepatocyte necrosis in the form of an occasional eosinophil body and areas of reticulin collapse, particularly in the region of the central veins. The hepatocytes showed fairly marked anisonucleosis and variation in size, with occasional mitotic figures. Foci of regeneration were also evident. A patchy but heavy infiltrate of lymphocytes and histiocytes was present within the lobule in these areas, together with a moderate number of eosinophils. Activation of Kupffer cells was also noted.

The portal tracts showed widening, with stellate fibrosis, and areas of disruption of the terminal hepatic plates, i.e. so-called piece-meal necrosis. A fairly heavy inflammatory infiltrate, including eosinophilia, was present in the portal areas, similar to that seen within the lobule. Cholestasis was not a feature, and haemosiderin pigment within Kupffer cells was not conspicuous (Figs 2 and 3).

Within 3 days of cessation of salicylate therapy the SGOT dropped to 346 Transac units and the bilirubin reverted to normal, as did the temperature. A further 14 days later the bilirubin and alkaline phosphatase levels were still normal, and the SGOT was 78 Transac units. The patient felt well, the anorexia had disappeared and he was asymptomatic. The sedimentation rate was 40 mm/hour.

At this stage, on 28 May 1974, salicylates were reintroduced in a total daily dose of 3 g. The next day the patient's temperature was raised and the white cell count rose to 13,000/mm³, with a 38% eosinophilia. The SGOT increased to 875 Transac units. The other liver function tests were within normal limits. The platelet count and
prothrombin index remained normal throughout the illness. The salicylate was withdrawn after 3 days and a week later all the liver function tests (including the SGOT) were normal.

Throughout the illness the patient received only the salicylate and phenoxymethyl penicillin, and no other drugs were administered.

DISCUSSION

An increase in the serum transaminases was first reported in children with rheumatic fever being treated with salicylates in doses of 0.6 - 1.0 g/6.8 kg body weight. Later reports showed an unequivocal correlation between serum transaminase levels and the blood levels of salicylate. There appears to be a threshold salicylate level of about 25 mg/100 ml—below this level the transaminases remained normal, above it a direct correlation with raised transaminases appeared. There was no evidence that much smaller doses of salicylate, such as are usually taken for minor ailments, have a serious effect on the liver. Once the salicylate level exceeded 30 mg/100 ml patients developed symptoms suggestive of hepatitis—anorexia, nausea and vomiting. A minority had a slightly raised bilirubin level as well.

The nature of the liver lesion is not entirely clear, but evidence at present suggests a direct toxic action, closely related to the serum level of the drug. Thus the liver lesion would seem to be dose-dependent, and a predictable injury. This should make the study of the problem amenable to scientific approach, not only in the experimental laboratory but in the clinical field, where large doses of salicylate are administered to patients with rheumatic fever, rheumatoid arthritis and lupus.

The histological changes reported include focal necrosis, inflammatory infiltration of the portal tracts, ballooning degeneration of hepatocytes, acidophilic body formation and the appearance of small acidophilic globules within the hepatocyte cytoplasm. One patient with lupus, who had been on salicylates for months, in addition showed early stellate fibrosis.

An interesting finding is that there has been an increase in the eosinophil count in all the patients on large doses of salicylate. Eosinophilia, especially eosinophils in the cellular infiltrate of the portal tracts, is commonly found in drug-induced cholestasis, suggesting an allergic reaction to the drug, e.g. chlorpromazine hepatitis. However, except in our patient, reports of salicylate-associated hepatitis have not mentioned eosinophils in the liver itself. Thus until now, an allergic hypersensitivity to salicylates as a factor in the pathogenesis of the hepatitis has not been put forward. Most workers so far have proposed a direct toxic action of salicylates, dose-dependent and closely related to the serum salicylate levels. Our patient's course indicates that the mechanism of the hepatitis may be more complex, and that both dose dependency and hypersensitivity play a part in the pathogenesis.

A very reassuring point, stressed in all reports and confirmed by our experience, is that there is a rapid and sustained fall in transaminase levels when salicylates are withdrawn. No definite evidence of chronic liver pathology secondary to salicylate therapy is at present available, and salicylate hepatotoxicity may be only a rare problem of high dose therapy in a few patients requiring long-term administration of salicylates. Further study of this aspect is to be undertaken.

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