Hepatocellular Damage with Ethacrynic Acid

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Ethacrynic acid is a potent diuretic agent and has been particularly useful in cases of fluid retention refractory to other diuretic agents (Datey *et al.*, 1967). This is a new drug, and all its toxic effects are still not known. Some side-effects and toxic effects have been well documented. Toxic effects such as cholestatic jaundice, agranulocytosis, and thrombocytopenia have been reported in one patient each (Merck Sharp and Dohme, 1964). A toxic effect not reported so far is presented in this communication.

Case Report

A man aged 25 with rheumatic heart disease (mitral stenosis and aortic stenosis with incompetence), subacute bacterial endocarditis, and gross congestive cardiac failure was admitted to the K.E.M. Hospital, Bombay, on 24 August 1966. He was given the appropriate antibiotic therapy, a low-salt diet, digitalis, and ethacrynic acid. In the first eight days the diuretic response was good and he lost 8 lb. (3.6 kg.) (with 50 mg. of ethacrynic acid daily). However, his urinary output subsequently decreased and an additional dose of 50 mg. of ethacrynic acid was given on alternate days. Various

FIG. 1.—Changes in S.G.O.T., S.G.P.T., and serum bilirubin during the course of therapy with ethacrynic acid.

tests, including serum electrolytes, liver function, blood urea nitrogen, etc., were carried out periodically to detect the toxic effects of this drug. Two weeks after starting the therapy mild jaundice was noticed (Fig. 1), and, as we were not certain of its aetiology, the drug was continued and the tests were repeated every four days. When two consecutive tests showed deterioration (Fig. 1), ethacrynic acid was omitted and all other treatment was continued. Though the drug was omitted, the jaundice increased for about a week and then began to recede. It cleared in another two weeks. During this period, when ethacrynic acid was omitted, other diuretics were used. However, they were relatively ineffective. As the condition

of the patient deteriorated, ethacrynic acid had to be restarted in a dose of 50 mg. daily. Subsequently the dose had to be increased to 200 mg. daily to get the desired diuretic response. During the next seven weeks hypokalaemia and hypochloreaemia often appeared but were corrected by appropriate measures. Seven weeks after restarting this drug mild jaundice developed and the serum transaminase levels were high (Fig. 1). Hence the drug was again discontinued. The jaundice regressed, and six days later, though the serum bilirubin was 1.5 mg./100 ml., the serum transaminase levels had become normal.

As the cardiac status of the patient deteriorated and there was fluid retention (the weight gain was 2 kg.) during this period, and as other diuretics proved ineffective, ethacrynic acid was restarted, 50 mg. initially. In the next seven days he was given 50 to 150 mg. of ethacrynic acid daily. Jaundice again developed and this time mental changes were also present. The drug was immediately discontinued. Both jaundice and mental changes progressed gradually. In the beginning there was hypersomnia, reduction of spontaneous movements, a fixed stare, and apathy. Intermittent changes included childishness, irritability, and loss of concern for his disease. Speech became slow and slurred, the voice monotonous and often faint. The characteristic "flapping tremors" were observed for a short time, a few hours before coma supervened. He was treated appropriately for hepatic coma, and after three days he came out of coma but still had mental confusion and hypersomnia. No further improvement occurred for the next four days, the serum bilirubin remaining at 4.25 mg./100 ml. and serum aspartate aminotransferase (S.G.O.T.) and serum alanine aminotransferase (S.G.P.T.) 108 and 94 units respectively (Fig. 1). The patient died the next day in congestive cardiac failure.

Post Mortem Examination

The body was emaciated and poorly built. There was an icteric tinge on the skin and in the conjunctiva. The heart was enlarged and showed changes of rheumatic mitral and aortic valve stenosis, with evidence of healed bacterial endocarditis. There was a small healed infarct in the cortex of the left kidney in addition to chronic venous congestion. The lungs and the spleen showed chronic venous congestion. The cut surface of the liver had the typical

FIG. 2.—Photomicrograph showing area of focal necrosis. ($\times 400$.)

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nutmeg appearance of chronic passive congestion. There was a small patch of necrosis, yellowish in colour, in the right lobe. This was rather friable. The gall bladder and biliary tract were normal.

Histology.—The liver showed changes of chronic venous congestion in most of the liver lobules and consisted of dilated central veins and dilated and congested sinusoids. A few cells around the dilated central veins showed changes of necrosis. The periportal connective tissue was slightly increased. In addition to this, in many areas the parenchymatous cells showed evidence of focal necrosis irregular in distribution (Fig. 2), and quite different from that seen in chronic venous congestion. These areas of necrosis morphologically resembled those produced by carbon tetrachloride injury in experimental animals. The necrosed cells showed pyknotic nuclei and indistinct cell walls. The cytoplasm showed hydropic degeneration and in places the presence of amorphous eosinophilic material. A few vacuoles could be seen in some cells. Kupffer cells were prominent and contained increased pigment. The bile ducts showed a moderate degree of proliferation. However, no stagnation of bile could be seen.

Discussion

Jaundice due to drugs is usually hepatocellular or cholestatic and rarely haemolytic. The clinical and biochemical differentiation of the various types is well known.

Ethacrynic acid has been reported to produce cholestatic jaundice in one patient (Merck Sharp and Dohme, 1964); however, to the best of our knowledge there are no reports of hepatocellular damage due to it. Experimentally, it has been proved that this drug is stored in the liver and secreted in the bile (Beyer *et al.*, 1965). The highest concentration of ^{14}C ethacrynic acid, after one week of its intravenous administration, was found in the liver, though this was only 2% of the dose, less than 3% being present in all the other organs (Merck Sharp and Dohme, 1964). We feel that in our patient this may account for the increase in jaundice for some days, even after the drug was withdrawn.

In our case the rise in S.G.O.T., S.G.P.T., and serum bilirubin and positive flocculation tests clearly indicates that the jaundice was hepatocellular in nature. The hepatocellular damage was probably due to ethacrynic acid, because on the first two occasions the jaundice developed when the drug was administered and regressed when it was discontinued. On the third occasion, however, after restarting the drug the patient developed hepatic coma and increasing jaundice. He recovered from the coma with appropriate measures, though the jaundice persisted. The irregular distribution of focal necrosis in the liver, quite different from that seen in chronic venous congestion, which shows centrilobular focal necrosis and resembling morphologically that produced by carbon tetrachloride in experimental animals, is in favour of its being due to the drug and not to acute or chronic heart failure. This correlates well with the clinical observations. As the drug is stored in the liver it is not surprising that hepatocellular damage was produced. Hence caution is required in the administration of this potent drug.

Summary

Ethacrynic acid is a new diuretic agent. Some of its side-effects and toxic effects are well documented, while others have been reported but rarely. A new toxic effect, hepatocellular damage, is reported in this communication.

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Preliminary Communications

Sugar Consumption in Acne Vulgaris and Seborrhoeic Dermatitis

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There is little concrete evidence that diet plays a part in the aetiology of disorders of the skin, except in nutritional deficiency diseases such as pellagra and kwashiorkor. Nevertheless, many authorities implicate diet—dietary excess rather than dietary deficiency—as an aetiological agent, notably in acne vulgaris and, to a less extent, in seborrhoeic dermatitis. Consequently, changes in diet are frequently recommended as part of the treatment of these diseases. Of 10 recent textbooks, diet is mentioned in 9 in connexion with the cause or treatment of acne, and in 6 in connexion with seborrhoeic dermatitis. In neither disease are the authors unanimous; most frequently mentioned, however, is an excessive intake of fat or of carbohydrate, or of both. In addition chocolate is several times specifically mentioned in connexion with acne.

There are three criteria by which one tests the hypothesis that a dietary component is implicated in the causation of a disease (Yudkin, 1953). Firstly, there should be evidence that the diet of persons with the disease differs significantly from that of persons without the disease. Secondly, the symptoms and signs should be those that are known to be, or at least are

plausibly suspected of being, caused by dietary imbalance. Thirdly, correction of the dietary imbalance should result in correction of the signs and symptoms.

In this paper we bring evidence of the first sort: that patients with seborrhoeic dermatitis consume significantly more sugar (sucrose) than persons without the disease. We believe that this is the first demonstration of a dietary difference in such patients. We have also shown that there is no such difference in patients with acne.

If the excessive amounts of a dietary constituent are thought to be a possible cause of disease, there are several reasons—evolutionary, historical, and metabolic—why sugar should be regarded as a likely candidate (Yudkin, 1963). It happens, too, than in practice it is more feasible to assess sugar intake than the intake of any other dietary constituent (Yudkin and Roddy, 1966). For these reasons, we measured the sugar intake of patients and control subjects with a short questionnaire that could be completed in 10–15 minutes by each of the subjects (see Appendix by J. Yudkin below).

The patients were referred to one of us at the skin clinics held at two hospitals. Seborrhoeic dermatitis was diagnosed when the patient presented with severe scaling of the scalp, together either with itchy scaly patches of the sternal or interscapular region or about the eyelids or nasolabial folds, or with intertrigo of the axillae, groins, or retroauricular areas, or with both types of lesions. All the patients had had previous