PERFORATION OF GALL-BLADDER DURING PREDNISONE TREATMENT

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During the past few years cases have been reported of gastro-intestinal ulceration, sometimes accompanied by massive haemorrhage or perforation, in patients receiving steroid therapy. A marked rise in the incidence of such cases, due to the increasing use of these drugs, is apparent. The recognition of the complications arising in these cases therefore merits careful consideration. The following case is of interest, as no similar occurrence of perforation of the gall-bladder during steroid therapy has been reported previously.

Case History

A man aged 45 had suffered from rheumatoid arthritis for 11 years, and during the last three years had developed psoriasis with severe polyarthritis. Salicylates, rest, and physiotherapy failed to give any relief, and in 1953 he was treated with corticotrophin, 40 units daily, and in the next years with cortisone, 100 mg. daily, which produced a satisfactory remission of both the arthritis and the psoriasis for a period. After four months, however, he developed severe fluid retention, which was not controlled by sodium restriction; so in September, 1955, he was given prednisone acetate 30 mg. daily, which is five times more potent than normal cortisone; there was symptomatic improvement, although the anaemia was not corrected and the E.S.R. remained raised. The dose was gradually reduced to 15 mg. daily, and in March, 1956, he discontinued treatment on his own initiative, which resulted in his urgent admission to hospital on July 10 with a severe exacerbation of both arthritis and psoriasis. In August he first complained of nausea and vomiting, which occurred before and after meals, and also of abdominal pain. There was no diarrhoea, colic, or jaundice, but he had lost 14 lb. (6.4 kg.) in weight in the previous eight months.

The arthritis and psoriasis responded to 20 mg. of prednisone daily, but the dyspeptic symptoms persisted. There was no abdominal tenderness. Traces of occult blood were present intermittently in the stools, and a barium-meal examination on August 9 showed an inconstant deformity in the prepyloric region but no ulcer crater. A diagnosis of acute prepyloric ulceration with pylorospasm was made and a full medical regime instituted. Therapeutic response was not good and there was an exacerbation of the arthritis and psoriasis, probably due to vomiting, which prevented adequate absorption of prednisone.

In the early hours of September 28 he developed acute epigastric pain radiating to the right iliac fossa, and there was marked abdominal tenderness, slight rigidity, with normal bowel sounds and liver dullness intact. The temperature was 100.2° F. (37.9° C.) and the pulse 95, and a straight x-ray film of the abdomen showed no subdiaphragmatic gas or fluid collection. These symptoms slowly improved, but in view of the severity of his arthritis and the inadequate oral absorption of prednisone it was decided to change to intramuscular cortisone, 100 mg. daily, and corticotrophin, 20 units, in addition.

Thirty-six hours after the first attack he had a recurrence of acute abdominal pain radiating down to the right iliac fossa, persistent and progressive in severity. Rigidity developed and bowel sounds were absent. A diagnosis of gastro-intestinal perforation with peritonitis was made and an emergency laparotomy was performed.

Operation.—On September 29 a right paramedian incision was made. The liver was found to be enlarged to three and a half fingerbreadths below the costal margin. The stomach and first part of the duodenum were normal. On raising the duodenum thick dark fluid was found in the Rutherford Morison pouch, and there was a perforation, about 2 by 2.5 mm., in the postero-lateral wall of the gall-bladder. The gall-bladder was enlarged and had a thickened wall; on palpation no stones could be felt. Cholecystectomy was performed and the abdominal cavity was drained by a stab drainage. Fifteen minutes after the beginning of the operation the patient's blood pressure fell to 90/50; hydrocortisone administration was begun immediately, and after 10 minutes the blood pressure rose to 120/80 and was maintained at this level. During the operation he received 1 pint (570 ml.) of blood and 15 mg. of hydrocortisone in 5% dextrose.

Post-operative Progress

The immediate post-operative period was covered by intravenous hydrocortisone, which was gradually reduced and withdrawn after 36 hours, when a total of 240 mg. had been given. Corticotrophin was then given. The patient was icteric in the immediate post-operative period, and in the absence of evidence of blood destruction or incompatibility, as shown by a negative modified indirect Coombs test, this was thought to be obstructive in origin: it cleared within five days.

For the first 24 hours after operation the patient was oliguric, but after this there was polyuria and proteinuria with granular casts. No proteinuria was detected after the tenth day. The blood urea was raised (95 mg. per 100 ml.), and it was thought that amyloid involvement of the kidney was a possible underlying cause, in spite of proteinuria before operation; this was subsequently proved. Bowel sounds returned on the sixth day. The wound healed by first intention and the sutures were removed on the fourteenth day. The patient was then transferred to the medical ward, where treatment was continued to stabilize his rheumatoid arthritis, and 12 weeks later he was discharged in a fit condition.

Pathological Report

The gall-bladder measured 2 cm. × 5 cm. Its outer surface was red and covered by a film of fibrin up to 2 mm. in thickness. The inner surface showed a red but largely intact mucosa, though there were localized deposits of fibrin, including one at the site of the perforation. The wall varied

Low-power view of a section of the thickest part of the wall, showing abscesses and Rokitsansky-Aschoff sinuses.

from 1 to 10 mm. in thickness, and in the thicker parts pockets of pus could be seen in the substance of the wall. Microscopically the lining epithelium was mostly intact. The lamina propria was oedematous and infiltrated by inflammatory cells comprising polymorphonuclears, macrophages, plasma cells, lymphocytes, and eosinophils. There were also collections of red cells. The muscularis was intact. The perimuscular connective-tissue layer was greatly thickened and was the seat of a severe purulent inflammation. This layer contained numerous large Rokitsansky-Aschoff sinuses distended with pus, and in addition there were abscesses free in the wall (see Fig.). This layer was much more severely

inflamed than the mucosa, and the cell reaction was largely polymorphonuclear. The outer surface showed peritonitis of apparently some days' duration. An occasional Gram-positive coccus was seen. Special staining revealed amyloid deposits in small vessels and in the basement membrane.

Discussion

The diagnosis of peritonitis was based on the sudden onset of upper abdominal pain radiating to the right iliac fossa and acute abdominal tenderness, followed later by rigidity and absence of bowel sounds. In retrospect, the episode three days previously was one of perforation with local peritonitis, and this was supported by histological examination. Before operation the gall-bladder was not suspected as the seat of disease, and it is probable that a reflex pylorospasm was responsible for the symptom-complex.

The significance of the relationship of onset of dyspepsia to the starting of treatment with prednisone is difficult to assess. It is known that peptic ulceration occurs more frequently with prednisone than with cortisone, but cholecystitis has not yet been described as a complication of either of these drugs. Because of deterioration in the general condition associated with persistent vomiting, prednisone was replaced by intramuscular cortisone. The stress associated with surgical trauma was covered by intravenous hydrocortisone.

Corticotrophin has been found to bring the temperature and pulse rate to normal levels within 12–36 hours after its administration (Beck *et al.*, 1950). It also causes a decrease of the leucocytes during the first few hours, with lymphopenia and eosinopenia. In the reported cases of patients undergoing treatment with corticotrophin and cortisone we found that the physical signs of all underlying diseases were obscured and there was a delay in diagnosis due to the reduction of inflammatory response caused by these drugs.

When an operation is contemplated on a patient undergoing treatment with corticotrophin and cortisone, care must be taken to ensure that large doses of cortisone are given immediately before and after the operation, because there is a possibility that, without taking this precaution, the patient may develop post-operative adrenal cortical insufficiency due to stress (Salassa *et al.*, 1953). As cortisone was withdrawn, adrenal stimulation with intramuscular corticotrophin was maintained. Adequate dosage of corticosteroids must be ensured, otherwise clinical features of adrenal cortical insufficiency develop quickly, the most important being restlessness, nausea, vomiting, weakness, hypotension, and coma. In treating the adrenal cortical deficiency state, intravenous hydrocortisone—the quickest therapeutic agent—gives an almost immediate response; oral cortisone acts in four to six hours, and intramuscular cortisone more slowly.

Because the severity of the post-operative renal failure was more marked than could be accounted for by the transient oliguria, the possibility of amyloidosis was considered and a special staining technique confirmed this in the specimen removed. Two months later the congo-red retention test (Unger *et al.*, 1948) was shown to be positive, 90% of the dye being retained after one hour.

In life the overall incidence of amyloid in rheumatoid arthritis is 4% (Fearnley and Lackner, 1955) and should be suspected in any patient with persistent and prolonged activity of the arthritis who has proteinuria, hepatomegaly, or splenomegaly.

Summary

A case of perforation of the gall-bladder in a patient with rheumatoid arthritis treated with prednisone is described. Histological examination of the gall-bladder revealed amyloidosis. The clinical features of the illness and its management are discussed.

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Medical Memoranda

Treatment of Acute Primidone Poisoning with Bemegride and Amiphenazole

Since its introduction as an anticonvulsant in 1950 primidone ("mysoline") has shown itself to be a valuable drug, particularly in grand mal. For this reason it has come to be used extensively; but, in spite of this, only one fatal case of acute poisoning with the drug has been reported—no doubt, among other things, owing to its relatively low toxicity. Up to the present it appears that only four cases of serious acute poisoning with the drug have been reported. Three of these cases were suicide attempts by adults, and one was a 4½-year-old child, in whom the poisoning was due to lack of supervision. Among the three cases of attempted suicide the amount of primidone taken by the first reported case (Arnold and Ceranke-Höfermayer, 1953) was 30 g. (120 tablets). This produced unconsciousness for 12 hours, followed by sleepiness for another two days. In another case, reported by Sciarra *et al.* (1954), a dose of 6.5 g. (25 tablets) only produced a deep sleep lasting four to five hours. In the third case, which was quoted by Morley and Wynne (1957), a dose of about 20–30 g. (80–120 tablets) led to death in the course of 12 to 24 hours. In the fourth case, reported by Morley and Wynne (1957), a 4½-year-old boy had taken about 12.5 g. (50 tablets), which caused loss of consciousness lasting about 36 hours.

In the case described below, a 57-year-old man had taken about 25 g. (100 tablets) of primidone in an attempt at suicide; this put him into a state of drowsiness, which passed into unconsciousness after about 36 hours. This lasted about 12 hours, after which unconsciousness was terminated by means of treatment with bemegride ("megimide," "malysol") and amiphenazole ("daptazole," "fenamizol"), which was obviously effective. About 40 minutes after the beginning of treatment the patient was quite lucid.

We have been unable to find in the literature a single case of primidone poisoning treated with these drugs. But, since they have a good antidotal effect against barbiturates, these drugs should obviously be tried. This is because primidone and phenobarbitone are closely related in chemical constitution, although they differ substantially in toxicity. Primidone can be regarded as a reduction product of phenobarbitone, one oxygen atom in the pyrimidine ring of the molecule being replaced by two hydrogen atoms linked to the same carbon atom.

CASE REPORT

A 57-year-old man with symptomatic epilepsy of some years' standing had for the past six months been put on primidone in a dosage of 2–3 tablets a day. His attacks had been controlled by that treatment. Earlier he had been suffering from mental depression, and had attempted suicide in August, 1956. For some time before admission he had again been depressed and had uttered threats of suicide. According to his own statement, in the evening of November 19 he took 100 0.25-g. primidone tablets with intent to kill himself. He was admitted to hospital on the following day, and brought with him an empty jar which had contained 100 primidone tablets dated November 19, 1956. He was admitted in a dazed condition, with slurred speech. He confirmed that he had attempted suicide with primidone.