

## Plasma 11-Hydroxycorticoid Levels after Carbenoxolone Sodium

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**S**ummary: A definite rise in plasma 11-hydroxycorticoid levels has been shown in eight patients with duodenal ulcer following the oral administration of carbenoxolone sodium. A similar rise was seen in one patient with sarcoidosis whose pituitary A.C.T.H. secretion had been acutely suppressed with dexamethasone. No such rise, however, was seen in three patients suffering from adrenal insufficiency. It is suggested that carbenoxolone acts directly on the adrenal cortex, causing an increased production of corticosteroids.

### Introduction

Carbenoxolone sodium (Biogastrone) is synthesized from glycyrrhizic acid, which is one of the many constituents of liquorice root. Apart from its apparent healing effect on the gastric mucosa, this compound, like crude liquorice preparations, has other pharmacological actions which resemble those of certain adrenocortical hormones. In rats it has an anti-inflammatory action which is about one-third that of cortisol (hydrocortisone) when given by subcutaneous injection, though, unlike cortisol, it is ineffective in rats when given by mouth. This effect persists in hypophysectomized animals but is greatly reduced when both adrenal glands are removed (Khan and Sullivan, 1968).

This anti-inflammatory action of carbenoxolone has not been investigated in man, but a significant proportion of patients treated with this drug have developed salt retention, a rise in blood pressure, hypokalaemia, and occasionally severe potassium depletion (Doll *et al.*, 1962; Doll *et al.*, 1965; Horwich and Galloway, 1965; Turpie and Thomson, 1965; Hausmann and Tarnoky, 1966; Mohamed *et al.*, 1966; Forshaw, 1969). These side-effects have also been reported with crude liquorice preparations, and resemble those produced by an excess of adrenal mineralocorticoids such as is seen in Conn's syndrome.

Possibly these pharmacological actions of carbenoxolone are due to direct stimulation of corticosteroid production by the adrenal cortex, but evidence to support this hypothesis is lacking. In particular, a number of workers have shown that aldosterone secretion is normal or reduced in patients given liquorice or its derivatives (Baron *et al.*, 1969). It has, therefore, been suggested that these results are consistent only with the hypothesis that the mineralocorticoid effect of carbenoxolone is due to its possessing intrinsic aldosterone-like properties. This theory, however, fails to take into account the observations of Borst *et al.* (1953), who concluded that the favourable effects of liquorice on salt loss in Addison's disease were seen only in those patients who still had some functioning adrenal tissue left, and those of Elmadjian *et al.* (1956), who found that the mineralocorticoid-like action of monoammonium glycyrrhizinate, observed in intact subjects, was absent in two adrenalectomized patients. The work reported here provides evidence that the administration by mouth of carbenoxolone sodium produces a rise in the unconjugated plasma 11-hydroxycorticoid levels, raising once again the question of its mode of action.

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### Methods

All the tests were carried out in the morning, and a single dose of 100 mg. of carbenoxolone sodium was given orally to the subjects between 10.30 and 11.30, with the exception of one man who was given only 50 mg. The tablets were given with 20-30 ml. of water. Patients had breakfasted normally at 7.30. Venous blood samples of 5-6 ml. were taken from the antecubital fossa by means of an indwelling cannula. Two control samples were taken at intervals of one hour before the dose of carbenoxolone, and further samples were taken over the subsequent two and a half hours.

Plasma 11-hydroxycorticoids (11-OHCS) were estimated by the fluorimetric method previously described, 2 ml. of plasma being used for each estimation (Mattingly, 1962). The presence of carbenoxolone sodium in the plasma in concentrations up to 10 mg./100 ml. does not interfere with the measurement of 11-OHCS by this technique. The synthetic analogues of cortisol do not fluoresce if this method is used, so that endogenous corticosteroid production can be studied during the administration of these compounds.

### Subjects

The subjects, six men and six women, were all inpatients at the time of study and were resting in bed throughout its duration. The nature and purpose of the investigation was explained to each patient before inclusion in the series. Their ages ranged from 25 to 62 years, and in all but four instances they were suffering from duodenal ulcers. The four exceptions are described below.

*Case 1.*—A woman of 43 had Addison's disease. On admission her morning plasma 11-OHCS level was only 3.9  $\mu\text{g./100 ml.}$ , and there was no rise in plasma or urinary corticosteroid levels when she was given 1 mg. of intramuscular tetracosactrin depot each morning for three days. During this period she was also given prednisolone 2.5 mg. and fludrocortisone 0.2 mg. daily by mouth, and next day she was again given these steroids five hours before the carbenoxolone was administered.

*Case 2.*—A man of 58 with a pituitary tumour, was found to have had hypopituitarism two years ago. His morning plasma 11-OHCS level was only 0.4  $\mu\text{g./100 ml.}$ , and he had a negligible adrenal response to exogenous A.C.T.H. Since that time he had been maintained on oral cortisol and thyroxine, and on the day of the test was given a single dose of 30 mg. of cortisol by mouth five and a half hours before the carbenoxolone was administered.

*Case 3.*—A man of 57 had Addison's disease. His initial morning plasma 11-OHCS level was 8  $\mu\text{g./100 ml.}$ , which is just within the normal morning range, but there was no rise in plasma or urinary steroid levels after three days on tetracosactrin depot in a dose of 1 mg. intramuscularly each morning. During the tests he was maintained on oral prednisolone 5 mg. twice daily and fludrocortisone 0.1 mg. by mouth daily.

*Case 4.*—A woman of 48 with sarcoidosis, was about to be started on corticosteroid therapy. She was given 2 mg. of dexamethasone by mouth at 11.30 on the night before the administration of carbenoxolone, and a further oral dose of 2 mg. at 6 a.m. next day in order to ensure acute suppression of pituitary A.C.T.H. secretion during the test.



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## Human Fascioliasis in Shropshire

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**S**ummary: Five patients with fascioliasis presented with malaise, pruritus, and pain in the right hypochondrium. Eosinophilia, increase in serum gamma globulin, and pyrexia were other features. Four patients treated with oral bithionol recovered completely and it is suggested that this is an effective form of therapy. The double diffusion precipitin test, being speedy and simple, was used as a screening procedure for diagnosis. The source of infection was wild watercress growing in a farm ditch.

### Introduction

The aim of this paper is to describe an outbreak of fascioliasis in humans during which we assessed the response to bithionol (Actamer) and used the double diffusion precipitin reaction as a screening test.

### The Outbreak

#### Clinical Description

*Case 1.*—A housewife aged 22 years was admitted to hospital on 20 December 1968. She complained of attacks of severe pain in the right hypochondrium for three months, loss of appetite, rigors, and weight loss. She had a fever of 39.4°C. and an enlarged tender liver. Her haemoglobin was 11.6 g./100 ml. and the total leucocyte count was 12,000/cu.mm., of which 6,480 were eosinophils. The erythrocyte sedimentation rate was 33 mm. in the first hour (Wintrobe), the serum aspartate transaminase was 28 units, and the serum alkaline phosphatase was 28 King-Armstrong units/100 ml. The serum albumin was 3.4 g./100 ml. and the globulin 4.5 g./100 ml.; paper electrophoresis revealed an increase of alpha-2 globulin and a diffuse increase of gammaglobulin. The Wassermann cardioliipin reaction was positive, but the *Trepomena pallidum* immobilization test and Reiter protein complement fixation test were negative. A needle liver biopsy demonstrated focal granulomata with small areas of necrosis

heavily infiltrated by eosinophils. Ova of *Fasciola hepatica* were found in the stools. The fasciola complement fixation test was positive 1/80. The double diffusion precipitin test was also positive. The hydatid complement fixation test and Casoni skin test were negative.

This patient was a member of an isolated farming community. The other members of the community were examined; there was neither clinical nor laboratory evidence of infection in 10 of these. The remaining four are described below.

*Cases 2-5* consisted of two men aged 58 and 49 and two females aged 45 and 14 years. All had pain in the right hypochondrium, malaise, and pruritus, and in three the liver was enlarged and tender. Eosinophilia between 2,880-6,000 per cu.mm. was present in all. Ova were found in the stools of one patient. The complement fixation test was positive between 1/20 and 1/80 in three. The double diffusion test was positive in all.

#### Treatment and follow-up details

*Case 1.*—This patient was treated in hospital with emetine hydrochloride 60 mg. daily, the 10-day course being interrupted for 48 hours because of atrial ectopic beats. Within a week there was definite symptomatic improvement and ova were no longer found in the stools. After three months she relapsed with abdominal pain for a few days; her erythrocyte sedimentation rate was 40 mm. in the first hour and the eosinophil count was 1,300 per cu.mm. After eight months she was well and had a normal eosinophil count, but precipitin and complement fixation tests were still positive. The Wassermann reaction was negative and the serum alkaline phosphatase normal.

*Case 2.*—This man was treated with bithionol, 1 g. three times daily orally on alternate days. A few hours after the first dose he had very severe pain in the right hypochondrium and treatment was stopped. Within 10 days of restarting he was symptom-free and ova were not present in his stools. Severe nausea limited the total dosage to 22.5 g., but he recovered completely in six weeks. After eight months he was well, had a normal eosinophil count, but was positive serologically.

*Cases 3-5.*—Two received 45 g. of bithionol, but the dose for the girl aged 14 was limited to 22.5 g. All returned to normal health but experienced nausea and vomiting on the drug. The eosinophil counts returned to normal but the serological reactions remained unchanged after eight months.

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