had disappeared not only in the group treated with the sulphonamide-pyrimethamine combination but also in the group given sulphonamide alone; in the third group the asexual parasite rate was 26%, with densities approximately those in "untreated" infections.

These results indicate that in combating pyrimethamine-resistant malaria, not only is sulphorthodimethoxine apparently successful in combination with pyrimethamine but it is equally effective when used alone. Details of this and subsequent drug trials will be published in due course.

Comment

This example of the schizonticidal action of a long-acting sulphonamide against pyrimethamine-resistant forms of *P. falciparum* should encourage further investigations into the antimalarial action of sulphonamides, at least in the suppressive field. For treatment of the acute attack of malaria preliminary tests suggest that the action of sulphorthodimethoxine is too slow.

Summary

A preliminary field trial to test the potentiative effect of giving sulphonamide with pyrimethamine against pyrimethamine-resistant falciparum malaria was carried out among African schoolchildren in north-east Tanganyika, where drug-resistance was known to be present.

A surprising finding was that the sulphonamide used, the long-acting sulphorthodimethoxine (Fanasil), was equally effective as a schizonticide in weekly doses of 500 mg. *per se* as when given with weekly 25-mg. doses of pyrimethamine.

I should like to thank Dr. J. Garrod, of Roche Products Ltd., for information and advice on sulphorthodimethoxine, and to the firm for supplies of the drug.

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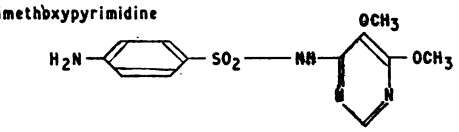
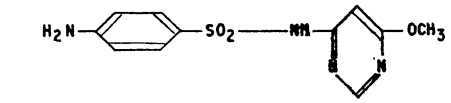
Footnotes

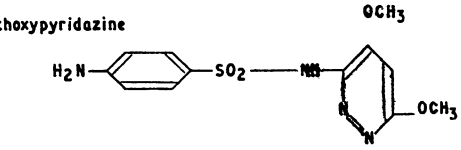
1. 4-sulphanilamido-5, 6-dimethoxypyrimidine (Fanasil)



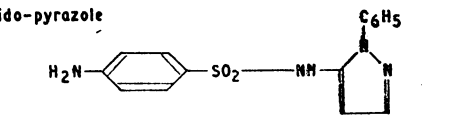
2. 4-sulphanilamido-2, 6-dimethoxypyrimidine (Madribon)



3. 3-sulphanilamido-6-methoxypyridazine (Lederkyn, Midicel)



4. 1-phenyl-5-sulphanilamido-pyrazole (Orisul)



Medical Memoranda

Carcinoid Syndrome Due to Carcinoid Tumour of the Ovary

Brit. med. J., 1964, **2**, 1440–1441

Carcinoid tissue in an ovarian teratoma was first described in 1939 (Stewart *et al.*). The association of the carcinoid syndrome with ovarian teratomas, though well recognized, must be rare. Since the first case, described by Sauer *et al.* (1958), only three reports have appeared in the literature (Thorson *et al.*, 1958; Torvik, 1960; Kephart *et al.*, 1960).

The importance of recognizing this association lies in the fact that surgical removal of the ovarian teratoma has, in these cases, resulted in complete arrest of the syndrome.

Before this association was recognized extensive hepatic secondaries had been considered necessary for the development of the carcinoid syndrome. The 5-hydroxytryptamine (5-HT) secreted by the primary intestinal tumour is thought to be inactivated by monoamine oxidase in the liver. In the same way other substances produced by the tumour, which may be more important for the development of the syndrome, may also be inactivated by the liver. Hepatic metastases, apart from providing an increase in the mass of secreting tumour, are drained more directly into the caval system, and therefore avoid this "trap" (Thorson, 1958). Similarly, the venous drainage of the ovary is into the inferior vena cava, which accounts for the development of the syndrome in the absence of hepatic metastases in the above cases.

The following case is a further example of an ovarian tumour associated with the carcinoid syndrome. Of additional interest was the finding of terminal uraemia.

Case Report

A woman of 73 was admitted to hospital in January 1963 with a history of severe diarrhoea and abdominal pain for three years, and oedema, ascites, and blood loss per rectum for the past three months. She died 24 hours after admission.

For the previous nine months she had experienced flushing attacks after meals. Her face and neck would become purple, the colour fading after about 15 minutes. Frequent attacks of colicky abdominal pain often coincided with the flushes.

On examination she was in a stupor and grossly anaemic. She was in severe congestive cardiac failure with atrial fibrillation and generalized oedema; her blood-pressure was 90/70 mm. Hg. A loud systolic murmur was heard, maximal at the left sternal edge. The chest was clear; the abdomen was distended with ascites. On rectal examination there was watery, dark red stool; on vaginal examination a fixed mass was felt in the pouch of Douglas.

The results of investigations carried out before death were as follows: haemoglobin 7.2 g./100 ml., with an M.C.H.C. of 30%.

The red cells showed slight hypochromia. The white-cell count was 4,300/c.mm. with a normal differential. Blood urea was 484 mg./100 ml., serum sodium 140 mEq/l., potassium 4.5 mEq/l., and chloride 100 mEq/l.

At necropsy 2,400 ml. of ascitic fluid were found. Opaque, thick fibrous tissue covered the peritoneum of the small gut, and there were areas of "sugar-icing" thickening of the parietal peritoneum.

A spherical firm grey tumour, 6 cm. in diameter, replaced the left ovary, its capsule showing a few streaks of fibrosis but no "sugar-icing."

The whole of the gastro-intestinal tract was opened and inspected but contained no neoplasm. The rectum and lower sigmoid colon showed haemorrhagic inflammation of the mucosa.

There was no evidence of metastases in the liver. The kidneys were slightly enlarged but showed cloudy swelling only.

The heart weighed 340 g. The epicardium over the right atrium showed slight fibrous thickening. Both the pulmonary and tricuspid valves were considerably stenosed with thickening of the cusps; fibrosis affected the endocardium of the ventricle in parts, and of the right atrium almost entirely. The valves of the left side of the heart were normal.

Sections of the ovarian tumour were characteristic of carcinoid, showing small cubical cells with variable cytoplasm staining pale or deeper pink in eosin. The acid diazo reaction with *p*-nitroaniline was negative (Pearse, 1960). The stroma of the tumour was cellular or hyaline collagenous fibrous tissue.

Histology of the heart valves and walls of atrium and ventricle showed delicate fibrous connective tissue overlying the endocardial elastica (Cosh *et al.*, 1959).

Sections of the kidney showed the convoluted tubules to be dilated and to contain occasional crystalline deposits (probably urate). There was extensive albuminous degeneration of the tubular epithelium with small areas of necrosis, and elsewhere there was evidence of tubular epithelial regeneration. The nature of these changes was obscure.

The presence of 5-HT was demonstrated by two-way paper chromatography of tumour extracts, using *iso*-propanol ammonia followed by butanol-acetic acid (Jepson, 1960). 5-HT was the only indole detected. The amount of 5-HT in the tumours was estimated according to the method of Udenfriend *et al.* (1958). One gramme of tissue yielded 35 μg. of 5-HT. This is a minimum value, as the tumour could not be completely dispersed and, moreover, had been stored at −20° C. for five weeks before processing.

Comment

Most of the ovarian carcinoids so far reported have been clearly teratomatous. Often the carcinoid tissue is adjacent to intestinal or respiratory tissue (Stewart *et al.*, 1939; Thorson *et al.*, 1958), supporting the suggestion that all sites for carcinoid development are derived from embryonic gut (Williams and Sandler, 1963).

In this case thorough examination of the tumour failed to reveal other types of teratomatous tissue. However, a careful search of the entire gut revealed no other primary tumour, and it is therefore assumed that this is a teratoma with one-sided development.

Haemorrhagic proctitis in a uraemic patient would account for the anaemia, but the cause of the uraemia is less obvious. In spite of probable anuria for the last three days, a blood-urea level of 484 mg./100 ml. suggests that some degree of renal failure was present previously. In addition, mercurial diuretics given before admission to hospital had failed to produce any diuresis.

Erspamer in 1954 suggested an antidiuretic role for 5-HT; and he demonstrated such an effect in rats. Other workers (Page and Glendening, 1955; del Greco *et al.*, 1956) reported similar results, and produced renal cortical necrosis in rats, using large doses of intravenous 5-HT.

Several cases of carcinoid syndrome have been reported with either oliguria during attacks or evidence of decreased renal blood flow (del Greco *et al.*, 1956; Page, 1957; Smith *et al.*, 1957; Thorson, 1958). Nevertheless, it appears that renal function is affected in only a small proportion of cases of carcinoid syndrome.

It now seems unlikely that 5-HT is responsible for many features of the syndrome such as flushing and diarrhoea (Robertson *et al.*, 1962; Oates *et al.*, 1964); but perhaps occasionally it is produced in sufficient quantities to disturb renal function.

Our thanks are due to Dr. G. P. Baker for his permission to publish details of this case, and for his advice.

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