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Letter to the Editor

Tryptophan in the Treatment of Carcinoid Crisis

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Summary. *A 56-year-old woman was admitted with carcinoid crisis and became comatose. Blood tryptophan at this stage was 5 μg/ml; after treatment with 3.4 g tryptophan daily her level of consciousness improved and blood tryptophan increased to 10 μg/ml. The carcinoid syndrome was not exacerbated by tryptophan. Tryptophan may have a supportive role in the management of carcinoid crisis.*

Introduction

Carcinoid crisis is a rare sequel of the carcinoid syndrome. It may occur spontaneously [5] or after chemotherapy [1, 14], and is characterized by hypotension, prolonged continuous flushing, confusion, and coma. We describe a patient in whom the crisis developed 2 weeks after laparotomy and whose coma improved with tryptophan.

Report

A 56-year-old white woman developed the carcinoid syndrome 2 years after radiotherapy for an orbital metastasis from an unknown primary site. She had a laparotomy which revealed multiple liver metastases and a 10 × 12 cm mass of fixed nodes around the ileocolic and superior mesenteric vessels, with a 1-cm polypoid tumour in the lumen of the terminal ileum. Ileotransverse colostomy was performed. Liver biopsy confirmed carcinoid tumour with a typical histological pattern and argyrophil granules. Review of the initial orbital tumour showed similar pathology.

Post-operatively she did well and was discharged 10 days later. She was readmitted 1 month after the operation with a 2-week history of severe flushing and episodes of fainting, confusion, and exacerbation of her diarrhoea. She had a continuous flush, hypotension (systolic blood pressure 90 mm Hg), and facial and upper limb oedema, and she was confused. She had hepatomegaly and her temperature was 37.5° C. She had two to three episodes daily of worsening of her flushing, during which she became blue and unconscious. Palpation of her abdomen exacerbated the continuous flush. She gradually became more drowsy until she only responded to deep pain.

She had a polymorphonuclear leucocytosis (total white cell count 17.8 × 10^3/mm^3) although blood and urine cultures were negative. Urine 5-hydroxyindolacetic acid (5HIAA) ranged from 104 to 319 mg/24 h (normal < 10 mg), plasma albumin was 28 g/l (normal 35–46 g/l), and alkaline phosphatase was 504 IU/l (normal less than 96 IU/l).

She was treated by adequate hydration [12] (urine output 2,800–4,370 ml/24 h) and with fresh frozen plasma and packed red cells to maintain her blood pressure. She was given Parentrovite (containing nicotinic acid and pyridoxine), gentamicin, and ticarcillin. The pyrexia did not respond to the antibiotics, which were stopped after 5 days. The pyrexia and leucocytosis were thought to be due to tumour necrosis. Antiserotinin and antikinin agents were tried (Fig. 1) but there was no response of her flushing, confusion, or hypotension to these agents.

Because she had an inoperable tumour, chemotherapy with 5-fluorouracil was tried (1 g/6 h on 3 successive days). The patient was comatose and at high risk of developing bronchopneumonia. She was given tryptophan on day 8 after her admission. It was administered via a nasogastric tube, 500 mg/6 h. Intravenous nutrition was also started, with 20% dextrose and Aminoplex 12 (1.4 g tryptophan/24 h). Within 24 h she was awake and able to co-operate with the nurses, although confused. Serial changes in blood tryptophan and urine 5HIAA are shown in Fig. 2. She developed gastrointestinal bleeding and bronchopneumonia 3 days before she died.

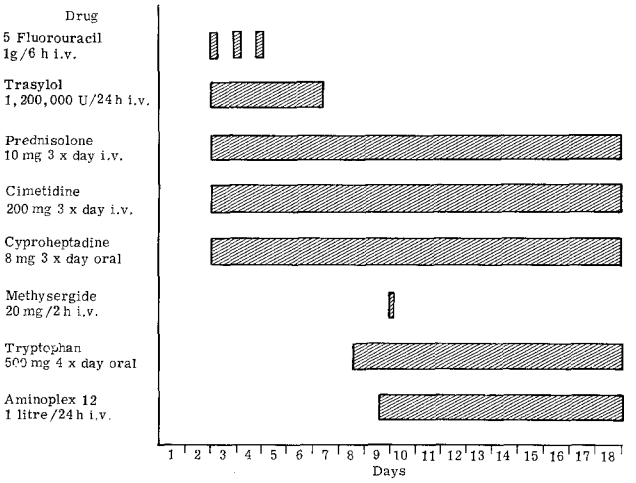

Fig. 1. Drugs used to treat carcinoid crisis. Days are days from admission to hospital

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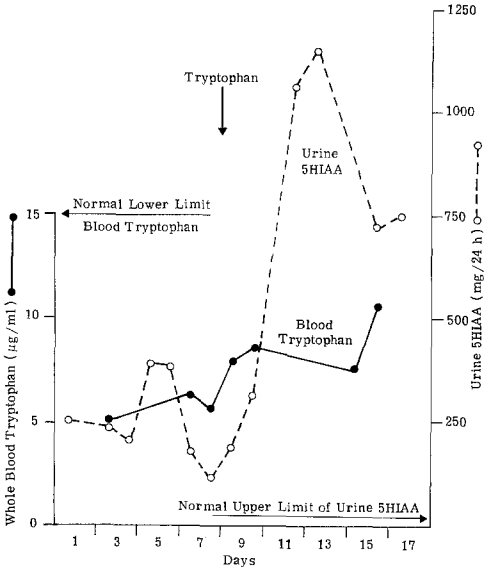

Fig. 2. Whole blood tryptophan and total urine 5HIAA before and during treatment with tryptophan, 2 g PO/day, 1.4 g IV daily. Tryptophan was started on the day indicated by the *vertical arrow* and continued until day 18

Post mortem showed metastases in the omentum, mesenteric, cervical and axillary lymph nodes, pancreas and ovaries. There was necrosis in the centres of the hepatic secondaries and mesenteric nodal mass.

Discussion

This patient with carcinoid crisis had a metabolic encephalopathy and very low blood tryptophan levels, both of which improved with tryptophan. One patient with carcinoid syndrome has been described [4], who became drowsy on a low-tryptophan diet containing the other essential amino acids. Another patient became comatose when her urine 5HIAA dropped from 40–60 mg/24 h to normal. Within a few hours of tryptophan administration (4 g IV and 7 g PO) she was fully alert [11]. She did not have severe carcinoid symptoms. The symptoms in these patients may be due to low cerebral 5-hydroxytryptamine (5HT, serotonin) secondary to a low plasma tryptophan concentration, the tryptophan being diverted to synthesis of 5HT peripherally by the carcinoid tumour.

Low cerebral 5HT may be implicated in depression [17], and high cerebral 5HT in animals is accompanied by hyperactivity [9]. Tryptophan hydroxylase is the rate-limiting enzyme in production of brain 5HT. The enzyme is not normally saturated by tryptophan, which is present at a concentration below the Km. Tryptophan levels can thus regulate 5HT synthesis [7]. In rats normal diurnal increases in plasma tryptophan increase brain 5HT.

Branched-chain amino acids compete with tryptophan for uptake into the brain on a common carrier [15]. Insulin, or carbohydrate feeding which stimulates insulin production, depresses branched-chain amino acid concentrations in plasma and can increase brain tryptophan and 5HT. A high-protein diet in rats, although leading to an increase in plasma tryptophan, did not increase brain tryptophan because of the concomitant increase in other amino acids competing for the same transport system [2].

Tryptophan is the only amino acid significantly bound to plasma proteins [15]. The Km for brain transport of tryptophan is similar to the binding affinity to albumin. Hence after protein and tryptophan feeding brain tryptophan correlated better with the ratio of total tryptophan to competing amino acids than with the ratio of free tryptophan to competing amino acids [15]. In the fasting state, free fatty acids can displace tryptophan from albumin and raise brain tryptophan [6]. Under conditions that raise free fatty acid levels brain tryptophan correlates better with free tryptophan [10] and there is usually no change or a fall in total plasma tryptophan.

Tryptophan is the least abundant amino acid in the free amino acid pool, and is very close to the amino-terminal end of the albumin molecule. Tryptophan supplementation of the diet of one patient with carcinoid tumour and severe hypoalbuminaemia was not performed for fear of exacerbating the symptoms of carcinoid syndrome [18]. Our case shows that even in carcinoid crisis tryptophan does not necessarily exacerbate the syndrome. The reason for this may be that flushing and hypotension are partly mediated by kinins [13]. The failure of response of the carcinoid crisis to 5HT blocking agents suggests that mediators other than 5HT were responsible for the syndrome in our patient, although 5HIAA urine levels were very high and tryptophan was probably diverted by the tumour into the 5HT pathway.

Parachlorophenylalanine [16] was considered in the treatment of this patient, but since it inhibits cerebral 5HT synthesis and can cause mental confusion it was not used.

Somatostatin, which can reverse hypotension, flushing, and diarrhoea [3, 8], was also considered (Dr R. Long, Hammersmith Hospital, personal communication), but since only release of the mediators is prevented some other effective treatment is also necessary. The patient had already had a laparotomy and was not suitable for embolization of the tumour. Severe rebound of symptoms has occurred on stopping somatostatin infusions [8].

Tryptophan deficiency can cause a metabolic encephalopathy in severe carcinoid syndrome, and this can be reversed with tryptophan without exacerbating the syndrome. The previous considerations suggest that IV nutrition with carbohydrates and sufficient amino acids for basal requirements should be given, together with tryptophan supplementation either PO or IV. Tryptophan may be useful in the supportive therapy of carcinoid crisis while other specific therapy is attempted.

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