Clinical and biochemical effects of parachlorophenylalanine in a patient with the carcinoid syndrome

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Summary

The clinical and biochemical features of a patient with flushing and severe diarrhoea due to the carcinoid syndrome are described. The patient had a paradoxical response to the tryptophan hydroxylase inhibitor parachlorophenylalanine with complete abolition of flushing and no effect on the diarrhoea. Treatment with this drug was limited by adverse effects.

Introduction

Diarrhoea and skin flushing are characteristic features of the carcinoid syndrome. The diarrhoea is thought to be caused mainly by 5-hydroxytryptamine (5-HT) (Grahame-Smith, 1972) whereas the possible causes of the flushing attacks include bradykinin (Oates et al., 1964), prostaglandins (Sandler, Karim and Williams, 1968; Kaplan et al., 1973) 5-HT (Page and McCubbin, 1953) and noradrenaline and adrenaline (Schneckloth et al., 1957). The tryptophan 5-hydroxylase inhibitor parachlorophenylalanine (PCPA) has been shown to alleviate carcinoid diarrhoea and concurrently lower the urinary excretion of 5-hydroxyindole acetic acid (5-HIAA) (Engelman, Lovenberg and Sjoerdsmia, 1967) but is reported to be of little or no value in the treatment of carcinoid flushing (Grahame-Smith, 1972; Marks, 1979).

We report the clinical and biochemical features of a case in which a patient with the carcinoid syndrome was treated with PCPA and had an anomalous response with abolition of flushing attacks but no lessening of diarrhoea.

Case report

The patient, a male aged 42 years, gave a 2-year history of diarrhoea (3-6 attacks per day), periodic abdominal swelling accompanied by borborygmi and colicky central abdominal pain and a weight loss of 13 kg. He was having 4-5 flushing attacks each day involving the face, neck and upper chest which were induced by emotional factors but not by alcohol. He gave no history of asthma.

On clinical examination there was generalized wasting and a persistent violaceous facial flush. In the abdomen an enlarged liver with an irregular edge was palpable and there was an orange sized mass in the right iliac fossa. There were no cardiac murmurs and no abnormalities were found in the respiratory system.

Investigations

Haemoglobin concentration was 13·3 g/dl, white cell count 5·4 x 10⁶/litre with a normal differential, platelets 190 x 10⁶/litre and ESR 35 mm/h. Serum electrolytes, urea, albumin, bilirubin, and transaminase concentrations were normal. The serum gamma glutamyl-transpeptidase concentration was elevated at 52 i.u./litre (normal under 22 i.u./litre) and the serum alkaline phosphatase at 115 i.u./litre (normal range 25–103 i.u./litre). The prothrombin time was normal and there was no evidence of malabsorption. The urinary 5-HIAA excretion rate (Udenfriend, Weissbach and Brodie, 1958) was considerably elevated at between 113 and 198 mg/24 hr (normal value less than 10 mg/24 hr). The fasting plasma tryptophan concentration (Denckla and Dewey, 1967) was low, between 7·4 and 10·0 µg/ml (normal
range 14–20 μg/ml). Urinary tryptophan excretion (Denckla and Dewey, 1967) was also low, being between 1·3 and 1·7 mg/24 hr (normal around 4 mg/24 hr). A barium enema showed a filling defect in the caecum and an isotopic liver scan demonstrated multiple filling defects consistent with secondary deposits in both lobes of the liver. An echocardiogram was normal.

**Treatment and response**

The diagnosis of carcinoid syndrome having been established, the patient underwent laparotomy during which the intestinal tumour was resected and all accessible hepatic secondary deposits removed. Postoperative recovery was uneventful. The patient continued taking codeine phosphate in doses of up to 120 mg three times daily and methysergide 1 mg three times daily and for a year after the operation the diarrhoea and flushing attacks occurred once or twice a day. Subsequently both became more frequent, the diarrhoea being at times explosive and associated with a more severe colic than previously.

In an attempt to control the diarrhoea PCPA was started at a dose of 250 mg twice daily and increased over the course of 7 days to a total daily dose of 3·5 g (see Fig. 1). The codeine phosphate was stopped, but the methysergide continued. By the sixth day of treatment PCPA had abolished the flushing attacks but had no effect on the frequency or intensity of the diarrhoea. PCPA was stopped after 13 days of treatment because the patient developed profound depression and painful but not weak limb muscles. The serum muscle enzyme concentrations were not elevated. Both these complications resolved within a few days of stopping the drug by which time flushing had recurred at its pre-treatment frequency.

The mean urinary excretion rate of 5-HIAA (mg/24 hr ± s.d.) was decreased by PCPA treatment from a pre-treatment value of 164 ± 36 to 72 ± 28; \( P<0.001 \) (see Fig. 1). By the ninth day after stopping PCPA the urinary 5-HIAA excretion rate had risen to

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**Fig. 1.** The effect of PCPA (parachlorophenylalanine) on plasma tryptophan concentration, the urinary excretion rates of tryptophan and 5HIAA (5-hydroxyindole acetic acid) and the frequency of attacks of diarrhoea (■) and flushing (□).
198 mg/24 hr. A comparison of mean fasting plasma tryptophan concentrations (µg/ml ± s.d.) and mean urinary excretion rates (mg/24 hr ± s.d.) before and during PCPA treatment showed no significant differences: 8.2 ± 4.2 v. 8.9 ± 1.9 and 1.5 ± 0.2 v. 1.6 ± 0.4 respectively.

Discussion

In patients with the carcinoid syndrome it has been reported that flushing may occur independently of any increase in 5-HIAA urinary excretion rate (Davis and Rosenberg, 1961; Smith et al., 1964), and that PCPA, whilst an effective treatment for carcinoid diarrhoea, does not lessen the flushing attacks (Grahame-Smith, 1972; Marks, 1979). The patient reported here had abolition of flushing attacks and a marked lowering of the 5-HIAA urinary excretion rate whilst taking PCPA. It is possible that the patient was biochemically unusual with 5-HT causing flushing attacks but not diarrhoea or that vasoactive polypeptides other than 5-HT were responsible for causing this man's symptoms. The synthesis of bradykinin or prostaglandins, both of which have been implicated in causing carcinoid flushing (Oates et al., 1964; Sandler et al., 1968; Kaplan et al., 1973) may have been impaired by PCPA, although such effects have not been reported.

All five of the carcinoid patients reported by Engelman et al. (1967) had less diarrhoea when treated with PCPA but only one had less flushing. Three of the 5 developed psychiatric changes which included depression, hallucinations, confusion and anxiety. Our patient's depression began abruptly 9 days after starting PCPA and resolved quickly when the drug was stopped. PCPA crosses the blood-brain barrier (Lehmann, 1972) and may therefore have inhibited brain 5-HT synthesis. Such an effect might be expected to precipitate a mood change (van Praag, 1976).

Muscle pains have been reported previously in association with the use of PCPA in patients with migraine (Sicuteri, Anselmi and Del Bianco, 1973). The cause of the pains is unknown but Sicuteri et al., (1973) suggested it may be related in part to depletion of 5-HT from the central nervous system.

Low serum tryptophan concentrations in patients with the carcinoid syndrome were described by Lehmann (1972). The fasting plasma tryptophan concentration and 24 hr urinary tryptophan excretion rate in our patient were both lower than found in normal but younger healthy controls (Green, et al. 1980). We have observed this in other patients with the carcinoid syndrome (unpublished observations) and these findings may be due to increased tryptophan utilisation by the tumour mass.

We do not know why our patient responded to PCPA in the way observed but this may have reflected the heterogeneous nature of the disease. PCPA may be of benefit to some patients with the carcinoid syndrome but its use may be limited by its adverse effects.

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References


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