Haematemesis during oral aminophylline treatment

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Summary

Two cases of gastrointestinal bleeding in patients being treated with continuous-release aminophylline tablets are reported.

Introduction

Theophylline and its derivatives are given orally to relieve the dyspnoea of obstructive airways disease and left ventricular failure. Their use has been limited by nausea and vomiting, side effects thought to be related to high concentrations of theophylline in plasma (Jenne *et al.*, 1972) and not to local gastrointestinal irritation. Oral formulations which will produce plasma theophylline levels reliably within the therapeutic range have therefore been sought. The authors treated a series of in-patients, expected to benefit from a theophylline derivative, with a continuous-release aminophylline tablet (Boroda *et al.*, 1973). Gastrointestinal bleeding which could not be explained readily on other grounds occurred in 2 patients.

Case 1

An 81-year-old man (weight 48.3 kg) with ischaemic heart disease and cerebrovascular disease was admitted with left ventricular failure and mental confusion. He had mild renal impairment (serum creatinine 141 $\mu\text{mol/l}$), normal liver function, and no history of gastrointestinal disease. Oral sustained-release aminophylline was introduced one month after admission in an attempt to alleviate persistent severe Cheyne-Stokes respiration. His other treatment (bumetanide, ampicillin, ferrous sulphate) was not altered. Aminophylline was started at 225 mg 12-hourly, increasing to 450 mg 12-hourly after 4 days. He had transient nausea, and vomited once, during the second day of treatment, but showed no evidence of toxicity thereafter. On the ninth

day of treatment he vomited blood without warning. Despite blood transfusion his condition deteriorated, and he died 6 hr after the haematemesis. Post-mortem examination showed both chronic and acute duodenal ulceration, with evidence of haemorrhage from the acute ulcer. Plasma theophylline concentration measured on the seventh day of treatment, but not available until after death, was 50 $\mu\text{g/ml}$.

Case 2

A 63-year-old man (weight 66.0 kg) with complicated diabetes mellitus, hypertension and peripheral vascular disease was admitted for treatment of deteriorating right and left heart failure. Serum creatinine was elevated (210 $\mu\text{g/l}$), liver function tests were normal, and there was no history of gastrointestinal disease. Orthopnoea and paroxysmal nocturnal dyspnoea persisted after 6 days of treatment with digoxin, frusemide, spironolactone, insulin and amoxycillin, and oral continuous-release aminophylline was started at 225 mg 12-hourly. Eight hours after the third dose of aminophylline he had a haematemesis (estimated volume 1200 ml). Endoscopy showed that the source of bleeding was oesophagitis involving the lower third of the oesophagus. Mucosal appearances suggestive of oesophageal varices were also noted, and the duodenum was not examined. Aminophylline was stopped, he was transfused with 2 units of blood, and there was no further bleeding. The plasma theophylline concentration 12 hr after the final dose of aminophylline was 9.1 $\mu\text{g/ml}$.

Discussion

Although the first patient had a chronic duodenal ulcer and the second possibly had oesophageal varices, the bleeding did not originate from these lesions but from acute ulceration of the duodenum and lower oesophagus respectively. Both patients were seriously ill, but their clinical state was stable

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when aminophylline was started, and in these circumstances gastrointestinal haemorrhage is relatively uncommon. This raised the possibility that aminophylline may have caused the gastrointestinal ulceration and bleeding. The association has not been reported in adults to the authors' knowledge, but similar episodes in 4 children (Pearson, 1964; Meyler, 1966; Meyler and Herxheimer, 1968) strengthen the possibility of a causal relationship. It may be relevant that high doses of caffeine, which is also a methylated xanthine, increase gastric acid output and cause duodenal ulceration in some animal species (Goodman and Gilman, 1975).

In one large study (Jenne *et al.*, 1972) gastrointestinal side effects of aminophylline occurred only with plasma theophylline concentrations higher than 13 µg/ml, and generally with concentrations above 20 µg/ml. In the first case described in this paper the plasma theophylline concentration (50 µg/ml) was clearly in the toxic range. In the second patient the trough plasma concentration was 9.1 µg/ml, and with this formulation (Boroda *et al.*, 1973) it seems unlikely that the peak concentration exceeded 13 µg/ml. If aminophylline did cause the oesophagitis in this patient, this suggests either that it had a local irritative action, or that systemic toxic effects may occur occasionally with plasma theophylline concentrations below 13 µg/ml. The first case history illustrates the advisability of monitoring plasma theophylline levels when prescribing theophylline derivatives. Nausea and vomiting while taking aminophylline 450 mg daily were so transient that they were not recognized as symptoms of possible toxicity. The patient was otherwise entirely

asymptomatic despite a dangerously high plasma theophylline concentration until the haematemesis supervened. The reason for the very high plasma level in this case is not known but a very long theophylline half-life (28 hr) in a 71-year-old man without liver dysfunction has been reported previously (Jacobs and Senior, 1974). This indicates the need for caution in adjusting oral aminophylline dosage in the elderly, particularly where there is concurrent physical illness, and suggests the need for further study of theophylline kinetics in the elderly.

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