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Grand mal seizure induced by oral theophylline

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Matthay, R. A., Matthay, M. A., and Weinberger, M. M. (1976). *Thorax*, 31, 470–471. **Grand mal seizure induced by oral theophylline.** A grand mal convulsion occurred in a patient with decompensated cor pulmonale. Although only modest doses of oral theophylline were being administered at the time of the convulsion the serum theophylline level was markedly raised and the theophylline clearance was very low. After treatment for cor pulmonale theophylline clearance improved; however, with the subsequent onset of fever and pneumonia the clearance decreased again, illustrating the potential lability of theophylline clearance.

Grand mal convulsions due to excessive serum theophylline concentrations from intravenous aminophylline have been reported recently (Zwillich *et al.*, 1975). The purpose of this report is to describe the occurrence of a theophylline-induced convulsion in a patient receiving oral aminophylline and to illustrate the potential lability of theophylline clearance.

CASE REPORT

A 65-year-old man with severe chronic airways obstruction and cor pulmonale was admitted to the medical intensive care unit on 11 April 1975 for evaluation and treatment of atrial flutter. The patient had been receiving 200 mg aminophylline (170 mg theophylline) orally four times daily for several months. Blood pressure was 170/110 mmHg, pulse 140/min and regular, respirations 28/min, temperature 37.5°C, and weight 70 kg. There were inspiratory and expiratory wheezes in both lungs, jugular venous engorgement to the angle of the jaw, the liver was 13 cm below the costal margin and there was oedema of the legs. The rest of the physical examination was normal. Haematocrit, WBC count, serum creatinine, blood urea nitrogen, and electrolytes were normal. Bilirubin (total/direct) was 9/2 $\mu\text{mol/l}$ (0.5/0.1 g/dl), SGOT 31 IU/l (normal less than 20), alkaline phosphatase 39 IU/l (normal less than 60).

Arterial blood gases breathing 2 litres of oxygen were pH 7.44, Pco_2 5.2 kPa (39 mmHg), Po_2 6.9 kPa (52 mmHg). The chest radiograph showed hyperinflated lungs without cardiomegaly or increased vascular markings. Atrial flutter with 2:1 block and a ventricular rate of 140/min were present on the electrocardiogram.

On admission the aminophylline was increased to 200 mg orally every four hours. Twenty-four hours after admission the rhythm spontaneously converted to sinus tachycardia with a rate of 120 per minute and wheezing was decreased. However, 48 hours after admission and 3½ hours after the patient had received aminophylline (200 mg) a grand mal convulsion occurred. No dysrhythmia was present on the cardiac monitor, and arterial blood gases drawn one hour before the convulsion, while the patient was breathing 2 litres of oxygen per minute, were pH 7.52, Pco_2 5.5 kPa (41 mmHg), Po_2 7.7 kPa (58 mmHg). An electrocardiogram showed sinus tachycardia with a rate of 100 and no other changes. Spinal fluid analysis, brain scan, and electroencephalogram were all within normal limits. However, a serum theophylline level obtained immediately after the convulsion was 64 $\mu\text{g/ml}$. The patient recovered from the convulsion and the cor pulmonale subsequently improved with loss of oedema, decrease in liver size, and return to normal of the jugular venous pulse after bed rest and diuretic therapy.

TABLE
RELATIONSHIP BETWEEN THEOPHYLLINE CLEARANCE AND CLINICAL STATUS

Date	Theophylline Dose (mg/hr)	C _{ss} (μg/ml)	Cl (ml/kg/min)	Clinical Status
13 Apr. '75	42.5 ¹	64 ²	0.16	Decompensated cor pulmonale; seizure Compensated cor pulmonale Compensated cor pulmonale Febrile for 36 hours with pneumonia; no change in cardiovascular status from 25 Apr. 1975
23 Apr. '75	17 ³	7.3	0.55	
25 Apr. '75	42.5 ³	18.4	0.55	
28 Apr. '75	42.5 ³	> 33.5 ⁴	< 0.30	

C_{ss} = steady-state concentration; Cl = theophylline clearance (normal 1.2 ml/kg/per minute).

¹170 mg oral theophylline every four hours.

²Value obtained immediately after convulsion assumed to be approximately steady state.

³Constant intravenous infusion.

⁴Intravenous infusion stopped during acute rise from previous C_{ss} of 18.4 μg/ml.

DISCUSSION

When the convulsion occurred, this patient's serum theophylline level was over three times the upper limit of the accepted therapeutic range of 10 to 20 μg/ml (Jenne *et al.*, 1972; Weinberger and Riegelman, 1974). However, the oral aminophylline dose averaged only 0.61 mg/kg per hour, which was below the recently recommended average intravenous dose for adults (0.72 mg/kg per hour) (Mitenko and Ogilvie, 1973). The clearance rate for theophylline was determined after clinical improvement by administering a constant intravenous infusion of theophylline (as aminophylline —85% theophylline) and by dividing the dose given by the steady-state serum concentration attained. Assuming that 64 μg/ml represents a steady state at the time of the convulsion, the theophylline clearance on admission (0.16 mg/kg per minute) was very low (Table) compared with previously reported mean clearance values of 1.2 ml/kg per minute (Jenne *et al.*, 1972; Mitenko and Ogilvie, 1973). At this time the patient was in a decompensated state with signs of right heart failure. After treatment for the cardiac failure, theophylline clearance increased to 0.64 ml/kg per minute and was stable for at least three days. A febrile episode due to pneumonia was associated with a decreased clearance of theophylline only a few days later when there was no evidence of cardiac failure (Table).

This case demonstrates that oral agents containing theophylline can be as hazardous as intravenously administered preparations in patients with impaired clearance secondary to decompensated cor pulmonale. Serum theophylline levels should be monitored in these patients. When this is not possible the oral or intravenous dose of

theophylline-containing preparations should be reduced. Fever, which has been shown to reduce the metabolic degradation rate of other drugs, may also be associated with a decreased theophylline clearance (Elin, Vesell, and Wolff, 1975). In the present case, fever developed with pneumonia two weeks after the convulsion and was associated with a decreased theophylline clearance (Table), illustrating the potential lability of theophylline clearance.

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