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Theophylline Intoxication Following Viloxazine Induced Decrease in Clearance

J. P. Laaban[1], J. P. Dupeyron[2], M. Lafay[1], M. Sofeir[2], J. Rochemaure[1], and P. Fabiani[2]

[1] Department of Pneumology and Intensive Care and [2] Department of Toxicology, Hôtel-Dieu, Paris, France

Summary. A case is reported of theophylline intoxication due to a dramatic decrease in theophylline clearance following concomitant administration of viloxazine.

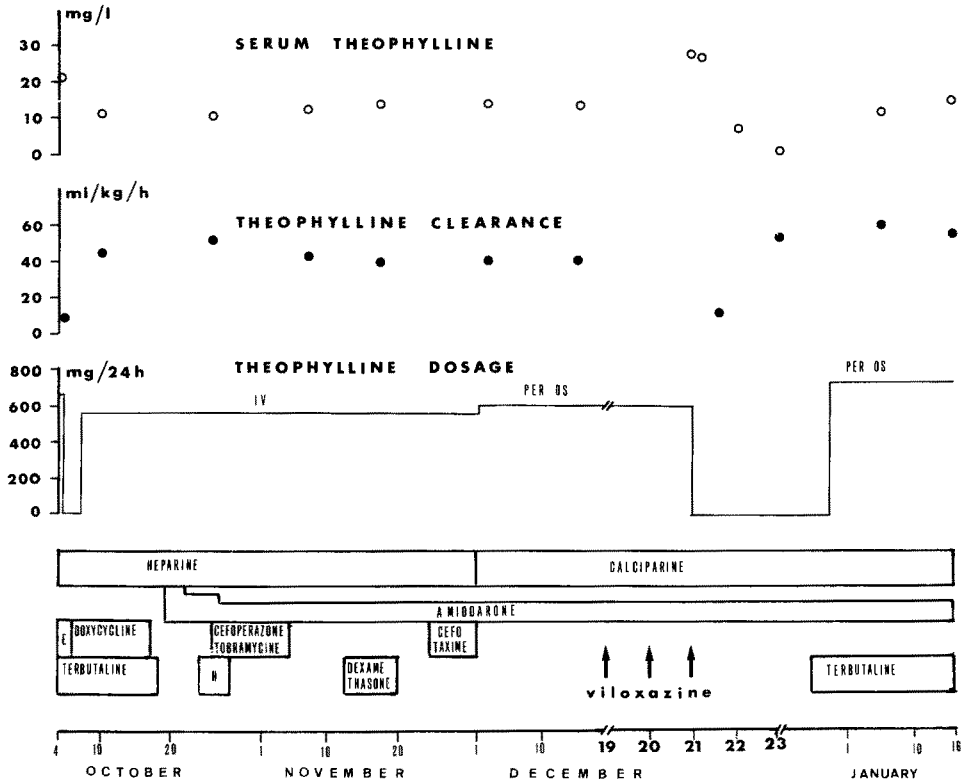
Key words: theophylline, viloxazine; clearance, drug interaction

Several drugs are known to decrease clearance of theophylline, e.g. erythromicin, cimetidine and troleandomycin [1]. This report describes a case of theophylline intoxication following a dramatic decrease in theophylline clearance, possibly induced by the concomitant administration of the antidepressant viloxazine (Vivalan, ICI), [2].

Case Report

A 73 year-old woman with severe chronic airways disease was admitted to the Intensive Care Unit on 4th October 1984 for acute respiratory failure. Physical examination showed: pulse rate 140 beats/min, respiration 36/min, blood pressure 130/80 mmHg, temperature 38 °C, cyanosis, jugular venous distension, hepatomegaly, oedema of the legs and expiratory wheezes in both lungs. The remainder of the physical examination was normal. Arterial blood gas analysis showed PaO_2 31 mmHg, $PaCO_2$ 73 mmHg, pH 7.31 and CO_2 36 mEq/l while she was breathing 1 l/min O_2. Haematocrit, WBC count, serum creatinine, blood urea nitrogen, electrolytes and liver function tests were normal. The chest radiograph showed hyperinflated lungs and moderate cardiomegaly. The patient was immediately intubated and was placed on a volume respirator (CPU_1 Atm, Medishield). She was given terbutaline, erythromicin, heparin and a continuous infusion of theophylline 0.56 mg/kg/h. The infusion had soon to be stopped because the serum theophylline level was 20.8 mg/l after 12 hours. The total body clearance CL was 3.9 ml/kg/h estimated by the method of Chiou et al. [3]. Three days later, theophylline 0.48 mg/kg/h was recommenced. The steady-state concentration was 10.7 mg/l, with a CL of 45.3 ml/kg/h, calculated by dividing the zero-order infusion rate by the steady-state plasma level [4]. The increase in CL was thought to be due to improvement in right ventricular failure. Tracheostomy was performed on the 12th November 1984. The patient's course was marked by several episods of bronchospasm relieved by terbutaline and corticosteroids, supraventricular tachycardia well controlled with amiodarone, and bronchial superinfection with *Pseudomonas aeruginosa* treated with cefoperazone and tobramycin. The main problem was that the patient could not be weaned off ventilatory support. During this period, CL was remarkably stable, ranging from 38 to 42 ml/kg/h, whilst the patient received oral theophylline (Euphylline, Valpan, Fr) 300 mg bd. in a sustained release form.

On 21st December 1984, a grand mal convulsion occured. Spinal fluid analysis and brain scan were within normal limits. The ECG showed atrial tachycardia with a rapid ventricular rate (170 beats/min). The serum theophylline concentration immediately after the convulsion was 28 mg/l. Treatment was stopped and the serum theophylline level fell to 27 and 17 mg/l after 7 and 26 h, respectively. Its calculated half-life and clearance were 29 h and 12.8 ml/kg/h. At that time, the patient had no sign of right ventricular failure. During the previous three weeks, she had been given only amiodarone and subcutaneous heparin.



- Heparin 40 mg/day i.v.
- Calciparin 7500 UI/day s.c.
- Amiodarone 450 mg/day, then 400 mg/day i.v., and then 200 mg/day p.o.
- Erythromycin (E) 2 g/day i.v.
- Doxycycline 200 mg/day i.v.
- Cefoperazone 4 g/day i.v.
- Tobramycin 150 mg/day i.v.
- Cefotaxime 3 g/day i.v.
- Terbutaline 2 mg/day i.v.
  then 3.75 mg/day p.o.
- Hydrocortisone hemisuccinate (H)
  300 mg/day i.v.

• Dexamethasone i.v.	12/11 48 mg	13/11 48 mg	14/11 24 mg	15/11 12 mg	16/11 4 mg
• Viloxazine p.o.	19/12 200 mg	20/12 200 mg	21/12 200 mg		

Fig. 1. Time course of serum theophylline concentrations and its total body clearance before, during and after viloxazine administration Drug administration

Two days before the convulsion, she had been started on viloxazine 200 mg/day for a depressive state. Viloxazine was stopped immediately after the convulsion. The serum theophylline was 1 mg/l 52 h after cessation both of viloxazine and theophylline. At that time the half-life of the latter was 6.5 h and its clearance was 53.4 ml/kg/h. The patient recovered from the convulsion. One week later, oral theophylline was restarted and CL was stable at steady state (58.2 and 60.6 ml/kg/h). The patient was finally weaned off the ventilator and left hospital on 16th January 1985.

Comment

We consider that the dramatic decrease in theophylline clearance observed in the patient was caused by viloxazine. There had been no other change in medication in the three weeks prior to the convulsion, and her clinical state was unchanged during that period. At the time of the convulsion, there was no obvious explanation for the decrease in the clearance of theophylline; right cardiac failure, fever and pneumonia were not present, and liver function tests were

normal. To rule out analytical interference by viloxazine with the theophylline assay (HPLC; mean coefficient of variation $< 5\%$), theophylline concentrations were also determined by an immuno-enzymatic method (Emit) which gave similar values.

The decrease in the clearance of theophylline during concomitant administration of viloxazine could be due to competitive antagonism, as both are metabolized by the hepatic microsomal mixed-function oxidase system [2], and the rapid increase in clearance after stopping viloxazine could be due to the short half-life of the latter drug.

The present case only suggests that viloxazine may decrease theophylline clearance and further studies are required to confirm the occurrence and nature of the theophylline - viloxazine interaction.

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Dr. J. P. Laaban
Service de Pneumologie et Réanimation
1, Place du Parvis Notre-Dame
F-75181 Paris Cédex 04
France