current color Doppler technology will be of sufficient sensitivity to detect the high velocity jet across the neck of the false aneurysm.

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Enhancement of Theophylline Clearance by Intravenous Albuterol*

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Co-administration of intravenous albuterol and theophylline resulted in increased theophylline clearance in a child with severe asthma. This required a threefold increase in theophylline dosage to maintain therapeutic serum theophylline concentrations. The possible effect of intravenous albuterol on theophylline metabolism was further supported by a 50 percent decrease in theophylline clearance upon discontinuation of albuterol and a second increase in its clearance when albuterol was readministered. To the best of our knowledge, this is the first documentation of enhanced theophylline clearance by albuterol.

Theophylline has a relatively low therapeutic index, i.e., a narrow therapeutic-toxic serum concentration range, and since both its bronchodilatory efficacy and toxicity are related to its serum concentrations, it is important to recognize factors which might influence theophylline levels. Drug interaction has been reported between theophylline and erythromycin, cimetidine, phenobarbital, propranolol, isoproterenol, and terbutaline. Both isoproterenol and terbutaline have recently been shown to increase theophylline clearance in asthmatic children. Albuterol is another β-agonist extensively used in the management of acute asthma in conjunction with theophylline. We report a child who received continuous intravenous theophylline for the treatment of status asthmaticus and whose theophylline clearance was increased by intravenous administration of albuterol.

METHODS

Theophylline blood concentrations were determined by the enzyme immunoassay method (Emit, Syva). Theophylline clearance (T/cl) in L/kg/hr was calculated from the equation.

\[ T/cl = \frac{R/C}{0.10} \]

where R is the infusion rate of theophylline (mg/kg/hr) and C is the concomitant theophylline concentration (µg/ml).

CASE REPORT

A 19-month-old boy was admitted to our ward with severe asthma. On admission, the child was alert and weighing 12 kg (60th percentile), in mild respiratory distress, with a respiratory rate of 30 breaths per minute, substernal retractions, prolonged expiration, and diffuse expiratory wheezes. Physical examination was otherwise normal. His blood count, liver enzymes, blood urea nitrogen and creatinine values were all within normal limits, and his chest x-ray film revealed no infiltrates. He was treated with continuous intravenous hydrocortisone (1 mg/kg/hr) and theophylline (0.9 mg/kg/hr) in conjunction with albuterol (2.5 mg in 2 ml) by nebulizer at four-hour intervals. Mild clinical improvement was observed after three days. However, during the next two days, the child's condition deteriorated. Arterial blood gas values showed increasing hypoxia (Po2, 33 mm Hg) and hypercarbia (PCO2, 47 mm Hg). Theophylline infusion rate was increased to 1.2 mg/kg/hr; and the child was put in a humidity tent with oxygen. However, his condition did not improve, and intravenous isoproterenol was added. Theophylline levels prior to initiation of isoproterenol therapy ranged between 6.8 and 12 µg/ml with a mean clearance of 0.10 (range 0.08 to 0.13) L/kg/hr. Theophylline clearance (T/cl) values are represented in Figure 1. Since the theophylline serum concentration during isoproterenol infusion was only 0.6 µg/ml, with a T/cl of 0.18 L/kg/hr, the theophylline infusion rate was increased to 1.5 mg/kg/hr. However, there was no clinical improvement in the child's condition, and isoproterenol was substituted with intravenous albuterol given at a rate of 5 µg/kg/hr. During this period, further increments in the theophylline infusion rate up to 3 mg/kg/hr were required, in order to achieve therapeutic theophylline levels. The T/cl remained high, reaching a peak of 0.24 L/kg/hr. Due to technical reasons, albuterol infusion was withheld for 12 hours.

FIGURE 1. Theophylline clearance (L/kg/hr) in a 19-month-old asthmatic boy during intravenous isoproterenol and albuterol therapy.
(Fig 1), during which time, T/cl declined markedly. Following the reinstitution of albuterol, T/cl again increased up to 0.21 L/kg/h. Since the child's condition deteriorated with progressive hypoxia and hypercarbia, mechanical ventilation was instituted. During the next few hours, there was progressive improvement, allowing discontinuation of albuterol therapy. The T/cl, measured a few hours later again, showed values of 0.13 and 0.10 L/kg/h, similar to those measured before the initiation of isoproterenol therapy.

**DISCUSSION**

In this report, we describe an asthmatic child who had marked variations in theophylline clearance, in association with co-administration of isoproterenol and albuterol. The T/cl values measured in our patient at times when no sympathomimetics were delivered resembled those previously reported in children of this age.\(^5\) It has been shown that intravenous infusion of isoproterenol increased T/cl in six asthmatic children treated for status asthmaticus.\(^1\) The T/cl in our patient during simultaneous infusion of theophylline and isoproterenol was higher than before institution of the latter. Since isoproterenol has a very short half-life,\(^6\) it is reasonable to assume that several hours after its discontinuation, no further circulating isoproterenol was present. Therefore, the increased T/cl observed during the intravenous albuterol therapy suggests a possible role for albuterol to this effect. Furthermore, the unplanned break in albuterol infusion was associated with a decrease in T/cl which supports this assumption. Indeed, reproducibility of the effect was demonstrated later, when during the second period of albuterol infusion, the T/cl increased by approximately 60 percent, whereas discontinuation of albuterol at the end of the treatment resulted in a reduction of the clearance.

The possible role of hydrocortisone in increasing T/cl in our patient is unlikely. Hydrocortisone was given at a constant rate throughout the whole course—before, during and after the treatment with albuterol. Additionally, hydrocortisone does not seem to cause significant alteration in T/cl.\(^5\)

The mechanism of increased theophylline clearance by albuterol is unclear. Theophylline is eliminated from the body mainly through biotransformation by microsomal oxidative hepatic enzymes. A possible explanation for the enhancement of T/cl by albuterol may involve either induction of hepatic enzymes or an increase in hepatic blood flow secondary to the vasodilatory effect of albuterol. Since it usually takes 24 to 72 hours for significant enzyme induction to occur, this mechanism is less likely to explain the prompt changes in T/cl observed in our patient while receiving albuterol. Increased hepatic blood flow can account for some enhancement of T/cl; however, since theophylline has a low hepatic extraction ratio,\(^6\) the magnitude of this effect may be limited.

Our report, in addition to those of others, indicates that all three β-sympathomimetic agents—albuterol, isoproterenol and terbutaline-enhance T/cl. By contrast, β-blocker agents, such as propranolol, decrease T/cl.\(^6\) Since co-administration of albuterol and theophylline is frequent in the management of acute asthma, a possible effect of albuterol on theophylline metabolism may bear important consequences for dosage adjustments in theophylline therapy. Further studies are required to evaluate this interaction, and especially, to determine whether giving albuterol by metered dose or nebulization has any effect.

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