The effect of salbutamol on airways following maximal response to theophylline

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It has been claimed that the combination of theophylline and β_2-agonists has additive effects in obstructive airways disease (Campbell, Middleton, MacKenzie, Shetter, McHardy & Kay, 1976; Wolfe, Tashkin, Calvarese & Simmons, 1978), but these claims are based on studies which used standard doses without allowing for the well-known differences between individuals in theophylline clearance and without making sure the response to the first drug was the maximum available (R_{max}) before adding the second. This study assesses the value of adding salbutamol to R_{max} from theophylline.

Six men aged 53–72 years, with moderate to severe chronic bronchitis were studied. FEV_1 values ranged from 0.3–1.4 l. Preliminary single dose studies were necessary to determine individual pharmacokinetic profiles. 500 mg aminophylline (≡ 450 mg theophylline) was given i.v. over 10 min and relevant pharmacokinetic parameters were estimated from nonlinear least squares fitting of the post infusion curves. Theophylline concentrations were measured by HPLC.

Individual dose response curves were then obtained by assessing pulmonary function during 4 or 5 incremental steady state (SS) infusions over the plasma concentration range 5–25 μg/ml. Loading dose and SS infusion rates were calculated from the previously determined pharmacokinetic parameters. To avoid exaggerated peak levels when changing from one SS to another, each loading dose was given over 20 min followed immediately by a 40 min SS infusion using a Tekmar pump. Plasma concentrations were measured twice at each SS allowing infusion rates to be adjusted if necessary.

Ventilatory function was assessed during the control pre-infusion period and twice during each SS infusion. Each assessment consisted of recording PFR, FEV_1, and FVC seven times at one min intervals.

Salbutamol (400 μg) was administered by pressurised aerosol when one or more of the following endpoints was reached.

1. No significant difference in three successive sets of ventilatory function measurements as judged by the Student's *t*-test.
2. A plasma theophylline level of 25 μg/ml.
3. Symptoms suggesting theophylline toxicity.

Ventilatory function was measured again at 30 min and at 1 h after salbutamol administration while the theophylline level was maintained at the final SS.

Three patients achieved R_{max} to theophylline between 15–20 μg/ml, 50% R_{max} having been attained by approximately 10 μg/ml. Each showed a further significant improvement with salbutamol. One patient failed to achieve R_{max} by 25 μg/ml and again showed a significant improvement with salbutamol. Two patients, who were relatively poor responders, achieved R_{max} between 5–10 μg/ml. One improved further with salbutamol; the other showed no improvement.

This study emphasises that patients with chronic bronchitis may show important differences in responses to theophylline and salbutamol. Additive effects have been demonstrated but it is clear that some patients may not achieve a *useful* response to theophylline until concentrations are at the upper end of the accepted therapeutic range.

References

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