

## Nebulized or intravenous beta<sub>2</sub> adrenoceptor agonist therapy in acute asthma?

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Nebulized salbutamol has been known to be an effective treatment of asthma for almost two decades [1] and nebulized bronchodilator therapy has now become first-line treatment of severe acute asthma in the Emergency Departments of most British hospitals [2]. This treatment was recommended as the most effective in 1972 [3], but after the advent of intravenous salbutamol and terbutaline the choice of administering these drugs in severe acute asthma by aerosol or by the intravenous route was considered to be contentious [4], because of conflicting results of clinical trials in which the efficacy of these two routes of administration had been compared. In mild asthma it has been reported that salbutamol was more effective when inhaled than when given intravenously [5], but in the report of a study of 10 patients with severe acute asthma it was concluded that sympathomimetics should be given intravenously if the response to nebulized therapy was poor [6]. Unfortunately, in this study all 10 patients were given aerosol before intravenous salbutamol instead of being allocated at random to the two forms of treatment, and the validity of the conclusions is, therefore, open to question. Recently it was concluded that intravenous salbutamol is more effective than nebulized salbutamol in severe acute asthma, but may have unacceptable cardiovascular effects [7]. However, the design of this study has been harshly criticized on a number of counts, including patient selection and the doses of salbutamol chosen for intravenous and aerosol administration [8].

Evidence for superiority of the intravenous route of administration of beta<sub>2</sub> adrenoceptor agonists is sparse and based mainly upon poorly designed studies. The case for nebulized salbutamol is much stronger. In a double-blind, parallel group study of 16 patients with severe asthma, nebulized salbutamol was considered to be superior to intravenous treatment because it produced fewer unwanted cardiovascular effects, but efficacy of the two routes of administration was similar [9]. The same conclusion was reached after a double-blind, cross-over study of 22 episodes of life-threatening asthma in which all patients received intravenous and nebulized salbutamol, the treatment order being randomized [10].

The multicentre study organized by the Swedish Society of Chest Medicine [11] provides definitive evidence of the superiority of the inhaled route of salbu-

tamol administration in the treatment of episodes of acute asthma. In this open, parallel group study of 176 patients two doses of nebulized salbutamol (0.15 mg·kg<sup>-1</sup>) given 30 min apart were compared with one dose of intravenous salbutamol (0.5 µg·kg<sup>-1</sup>) given over a period of 10 min. The results of this large study clearly show a better effect in terms of peak expiratory flow (PEF) improvement, which was apparent even after the first nebulized treatment. However, unlike previous reports, nebulized therapy was associated with more subjective side-effects of tremor and palpitations than intravenous treatment. The nebulized route of administration was found to produce higher plasma levels of salbutamol at 55 and 90 min after the start of the trial. This can, in part, be explained by the time at which the blood samples were taken; 15 and 35 min after the second inhaled dose of salbutamol, compared with 45 and 80 min after intravenous administration. Nevertheless, this does show that nebulized salbutamol is associated with significant systemic drug absorption, which may be responsible for some bronchodilator activity. However, it is also possible that recirculation within the lungs *via* the bronchial and/or pulmonary circulations also occurs, which might explain the surprising efficacy of the inhaled route of administration in patients with intense bronchial inflammatory oedema and mucous plugging.

The clear demonstration of greater efficacy of inhaled compared with intravenous salbutamol in this Swedish study [11] is in contrast to the findings reported in previous studies comparing nebulized and intravenous salbutamol in severe acute asthma [9, 10]. One explanation for this could be the larger number of patients included in the Swedish multicentre study, but this seems unlikely. Another explanation could be that the Swedish patients had less severe asthma than those in the British studies, since it is known that the inhaled route achieves better and more prolonged bronchodilatation in patients who do not have very severe asthma [5].

Irrespective of the explanation there is now firm evidence that nebulized salbutamol in a dose of 0.15 mg·kg<sup>-1</sup> is more effective than the same drug given intravenously in a dose of 5 µg·kg<sup>-1</sup>. The recommendation of the Swedish physicians is that nebulized salbutamol should be used as first-line treatment for severe asthma, a view already widely held in Britain [2]. No doubt the arguments will continue about the possibility that a continuous intravenous infusion of

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salbutamol could be more effective than repeated doses of nebulized salbutamol. However, it is known that continuous infusion of salbutamol carries the risk of considerable unwanted cardiovascular effects [7], and protagonists of inhaled therapy could argue that continuous nebulization of low dose salbutamol could be more effective than intermittent high dose aerosol treatment.

The evidence now available allows a recommendation to be made that nebulized salbutamol or terbutaline should be the first-line treatment for all patients with severe acute asthma. Accurate calculations of doses on a body weight basis are not necessary, since the amount of drug inhaled by individual patients will vary considerably depending upon the type of nebulizer used, the flow rate of driving gas (preferably oxygen) and the volume of drug solution in the nebulizer chamber. Salbutamol 5–10 mg or terbutaline 10–20 mg are suitable initial doses for adults, but it should be appreciated that additional treatments, when necessary, have to be given early since all the beneficial effects of the first nebulized treatment can be anticipated to have been achieved within 15 min [12]. Beta<sub>2</sub> adrenoreceptor agonists should be nebulized in oxygen since patients with acute severe asthma are hypoxaemic and treatment has the potential of increasing hypoxaemia. Simple jet nebulizers are, however, as effective as intermittent positive-pressure breathing machines [13].

The beneficial role of the combination of nebulized beta-adrenoreceptor agonists and ipratropium bromide in the treatment of severe acute asthma appears to have been established [14–16]. The multicentre study from Sweden [11] casts doubt about the frequently used additional therapy of theophylline, since it is suggested that there are no clinically important additional effects to high dose inhaled beta<sub>2</sub> adrenoreceptor agonist therapy afforded by the concurrent use of intravenous theophylline. The evidence provided to support this reappraisal of the hallowed use of intravenous theophylline in the treatment of patients with severe asthma is less convincing than the data generated to recommend nebulized, in preference to intravenous, salbutamol. Perhaps the next important clinical question to be answered is, what is the role of theophylline treatment in patients with life-threatening asthma? It may be that this will only be achieved by the organization of a large national or international multicentre study of the treatment of patients with life-threatening severe acute asthma. This has been shown to be possible by the members of the Swedish

Society of Chest Medicine and for this they must be congratulated.

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