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Nasal administration of albuterol: an alternative route of delivery

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Abstract

The use of metered-dose inhalers for the delivery of albuterol, a β_2-selective adrenergic agonist, is associated with drawbacks, especially in children and the elderly. This investigation was designed to assess the effectiveness of albuterol delivered intranasally and to compare this delivery route with intratracheal and intravenous delivery. Three parameters of pulmonary function (peak maximal expiratory flow, maximal expiratory flow at 50% vital capacity, and total lung capacity) in anaesthetized, artificially ventilated guinea pigs were used to determine the degree of protection produced by albuterol against bronchoconstrictor responses provoked by acetylcholine. The heart rate was also measured. Although intranasal albuterol induced a slower protective action during the very initial phase of absorption, the drug was shown to be equally effective when administered either intranasally or intratracheally. In contrast, despite a significant effect initially in the case of intravenous albuterol, its ability to influence pulmonary function faded rather rapidly. No statistically significant differences in heart rate could be detected among the different treatment groups. In conclusion, intranasal albuterol may offer an alternative to metered-dose inhalers for the treatment of acute bronchospasm and for prevention of exercise-induced asthma, especially for children and the elderly.

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Introduction

Appropriate use of metered-dose inhalers (MDIs) is essential to ensure therapeutic efficacy in asthmatics. However, children and the elderly experience difficulty in coordinating deep inhalation and activation of the MDI (Anon 1991). Such difficulty is most apparent during severely acute asthma bouts. As a result, multiple doses may be required to affect relief from bronchospasm and such a situation could possibly result in an overdose of the intended drug.

Albuterol is a β_2-selective adrenergic agonist commonly administered by metered-dose inhalation. It is one of the most effective drugs available for the treatment of acute bronchospasm and for prevention of exercise-induced asthma (Anon 1993). Although it is available in oral dosage forms, it is less effective and has a slower onset of action orally than by inhalation. In severely dyspneic patients, albuterol has been administered intravenously (Ahrens & Smith 1984).

Previous investigations have shown that many drugs of varied chemical structures and pharmacological activities are readily absorbed from the nasal cavities in animals and humans (Hussain 1998). The resulting blood profiles were frequently similar to those observed following intravenous injection. If it is assumed that the pharmacological effect of albuterol after oral or intravenous administration is related to blood concentration, then the drug might also be effective intranasally. Consequently, it could be possible to formulate nasal dosage forms (drops, sprays or gels) containing albuterol or other β_2-selective adrenergic agonists that are easier to use and more economical than MDIs.

The maximal dose of albuterol that can be safely delivered by MDI and simultaneously provide an optimum therapeutic activity is still unclear (Spector & Gomez 1977; Nelson et al 1983). It has furthermore been suggested that the cardiovascular and metabolic side effects that are observed in some patients are associated with the inhalation of increased doses of albuterol (Kung et al 1987).

The present study was designed to investigate the dependence of the route of administration on the level of protection produced by albuterol against bronchoconstriction induced by acetylcholine. Several indices to detect changes in pulmonary function were determined in guinea pigs.

Materials and Methods

Male Hartley guinea pigs (approx. 350 g) were anaesthetized with intraperitoneal injection of 30–50 mg kg^{-1} of pentobarbital sodium (50 mg mL^{-1}). After attainment of surgical anaesthesia, the trachea and right external jugular vein were cannulated for mechanical ventilation and intravenous drug administration, respectively. The animals were placed in a Plexiglas plethysmograph, paralysed with gallamine triethiodide (4 mg kg^{-1}, IV), and mechanically ventilated (tidal volume, 6 mL air kg^{-1}; frequency, 60 breaths min^{-1}).

Thirty-three animals were randomly divided into a control group and three treatment groups: intravenous, intratracheal and intranasal. In the control group (n = 8), physiological saline was administered intranasally (0.1 mL) and intratracheally (1 mL kg^{-1}). For the intravenous treatment (n = 8), albuterol (salbutamol, racemic; Sigma-Aldrich, Saint Louis, MO, USA) in saline (100 μg mL^{-1}) was administered via the jugular vein (100 μg kg^{-1}). The same dose was delivered intratracheally to the animals (n = 8) in the third group. In the last group (n = 9), albuterol was administered (100 μg kg^{-1}) by instilling 0.1 mL of drug solution (350 μg mL^{-1}) into the nasal cavity. In experiments in which the treatment was administered intranasally, the oesophagus was ligated as close to the pharynx as possible in order to retain the solution in the nasal cavity and prevent gastrointestinal absorption of albuterol. Furthermore, the nasopalatine tract was blocked with a cyanoacrylate sealant (Super Glue 3; Woodhill Permatex, Cleveland, OH, USA).

Airway function tests were performed before treatment with albuterol (baseline) and at several appropriate time intervals following administration of the drug. In order to determine the effectiveness of albuterol as a bronchodilator, acetylcholine (10 μg) was injected intravenously to induce bronchoconstriction in the guinea pigs within 1 min before different physiological functions were measured at 5, 20, 35, 50 and 65 min after albuterol administration. The maximal expiratory flow-volume (MEFV) manoeuvre was performed in accordance with a previously reported method (Lai 1988). The basic principle of this test is that the maximal expiratory flow rate is a function of airway dimension in the presence of fixed pressure gradient from alveoli to the airway opening. In other words, a high maximal expiratory flow can be obtained under conditions of a large airway dimension (bronchial relaxation); alternatively, a low maximal expiratory flow results in the presence of bronchial constriction. Following each MEFV manoeuvre, the functional residual capacity was determined by a neon dilution method.

The heart rate was measured via the determination of cardiac electrical activity monitored with platinum electrodes implanted subcutaneously in two limbs (Model E2B; Grass Instruments, Quincy, MA, USA).

In order to eliminate individual differences between animals, percentages of baseline values (before drug treatment was initiated) were used to determine the acetylcholine-induced change at each time interval in each of the control and treatment groups. Data are presented as means ± s.e. Analysis of variance was used to establish differences among groups, while differences between any two groups were determined using Duncan's test. Differences were considered significant at $P < 0.05$. All studies were conducted in accordance with the Principles of Laboratory Animal Care (NIH publication no. 85-23, revised in 1985), and were approved by the Department of Laboratory Animal Research at the University of Kentucky.

Results

The bodyweight and baseline respiratory parameters of the guinea pigs in the four groups are listed in Table 1. The groups were deemed comparable as no significant difference could be detected in any of the listed attributes between any two groups.

Albuterol administered intranasally, intravenously or intratracheally at a dose of 100 μg kg^{-1} inhibited the acetylcholine-induced bronchoconstrictor responses ($P < 0.01$ or < 0.05); however, the extent of the inhibitory effect varied with the route of administration (Figure 1). The peak maximal expiratory flow is the highest flow rate as determined from the MEFV curve. Although intranasally

Table 1 Bodyweight and respiratory parameters during baseline period in four groups of guinea pigs

	n	Body weight (g)	Total lung capacity (mL)	Peak maximal expiratory flow rate (mL s^{-1})	Maximal expiratory flow rate at 50% vital capacity (mL s^{-1})	Heart rate (beats min^{-1})
Control	8	364 ± 7	11.8 ± 0.5	170 ± 4	77.6 ± 6.1	288 ± 8
Intravenous	8	351 ± 10	12.2 ± 0.6	161 ± 9	72.5 ± 5.3	289 ± 12
Intratracheal	8	348 ± 8	12.1 ± 0.5	170 ± 3	75.9 ± 5.1	285 ± 7
Intranasal	9	346 ± 8	11.7 ± 0.4	166 ± 3	72.3 ± 3.5	292 ± 9

Data are presented as mean ± s.e. There were no significant differences between any two groups ($P > 0.05$).

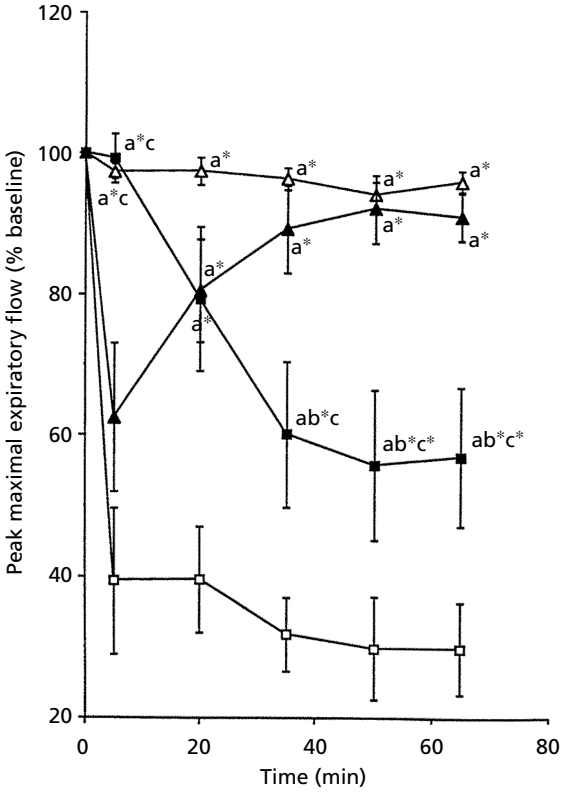

Figure 1 Inhibition by intravenous, intratracheal and intranasal albuterol of acetylcholine-induced bronchoconstriction in anaesthetized guinea pigs. The effect of albuterol is expressed as a percentage of the baseline (before any drug treatment) value of the peak maximal expiratory flow in four groups of guinea pigs: control (□, n = 8), intravenous (■, n = 8), intratracheal (△, n = 8) and intranasal (▲, n = 9). Data are presented as mean ± s.e. a, b or c indicate $P < 0.05$, a*, b* or c* indicate $P < 0.01$; a: compared with control; b: compared with intratracheal; and c: compared with intranasal.

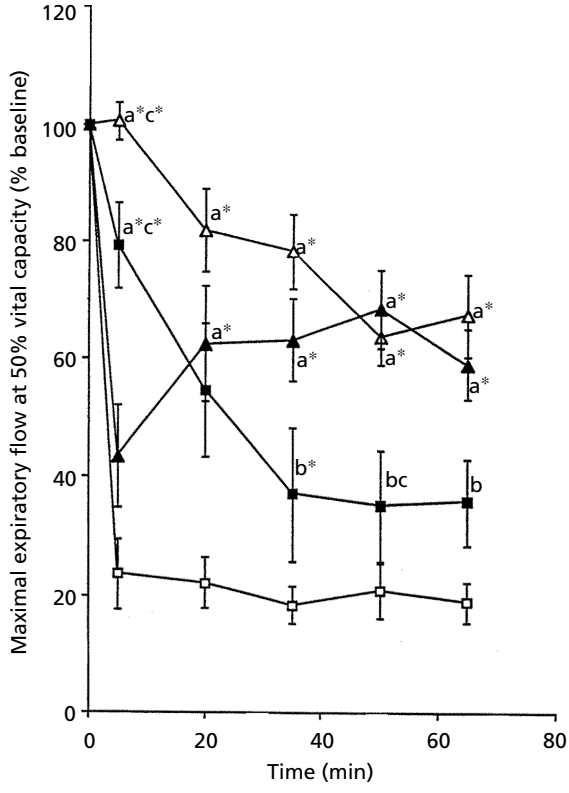

Figure 2 Inhibition by intravenous, intratracheal and intranasal albuterol of acetylcholine-induced bronchoconstriction in anaesthetized guinea pigs. The effect of albuterol is expressed as a percentage of the baseline (before any drug treatment) value of the maximal expiratory flow at 50% vital capacity in four groups of guinea pigs: control (□, n = 8), intravenous (■, n = 8), intratracheal (△, n = 8) and intranasal (▲, n = 9). Data are presented as mean ± s.e. a, b or c indicate $P < 0.05$, a*, b* or c* indicate $P < 0.01$; a: compared with control; b: compared with intratracheal; and c: compared with intranasal.

administered albuterol exhibited a slow onset of inhibitory action, significant inhibition was achieved after 20 min ($P < 0.01$). On the other hand, intratracheal albuterol resulted in eliminating bronchoconstriction totally ($P < 0.01$) at each time interval. The pattern of inhibitory action of intravenously delivered albuterol was distinctly different from that observed with either the intranasally or intratracheally administered drug. It was very effective initially, causing immediate inhibition ($P < 0.01$), but its action faded significantly after a few minutes. After approximately 30 min, the effect of both intranasal and intratracheal albuterol on peak maximal expiratory flow was significantly greater than the effect observed with intravenous albuterol ($P < 0.01$), that is less constriction in the airways.

The effect of albuterol using another index of pulmonary function, the maximal expiratory flow at 50% vital capacity, is shown in Figure 2. Although the pattern of inhibitory action of albuterol as reflected by this index differed slightly from the one obtained using the peak maximal expiratory flow, the drug was equally effective intranasally and intratracheally after 20 min. Also, albuterol was found to be more effective both intranasally and intratracheally than intravenously. When delivered intravenously, it afforded protection against the bronchoconstriction induced by acetylcholine only for the first 20 min, after which there was no significant difference compared with the control group.

Figure 3 shows the changes in total lung capacity affected by albuterol. These changes are overall similar to those shown in Figure 1, that is intranasally administered albuterol is as effective as intratracheal after 20 min of administration. When administered intravenously, the effect of the drug decreased very rapidly after the first 5 min.

The effect of albuterol on heart rate is shown in Figure 4. After 5 min of administration, the increase in heart rate induced by intravenous albuterol was much greater than the increase observed in the other groups. However, this tachycardiac effect decreased rapidly afterwards. Figure 4 shows that the level of tachycardia produced by intranasally administered albuterol remains practically constant following the initial 5 min. No statistically significant differences

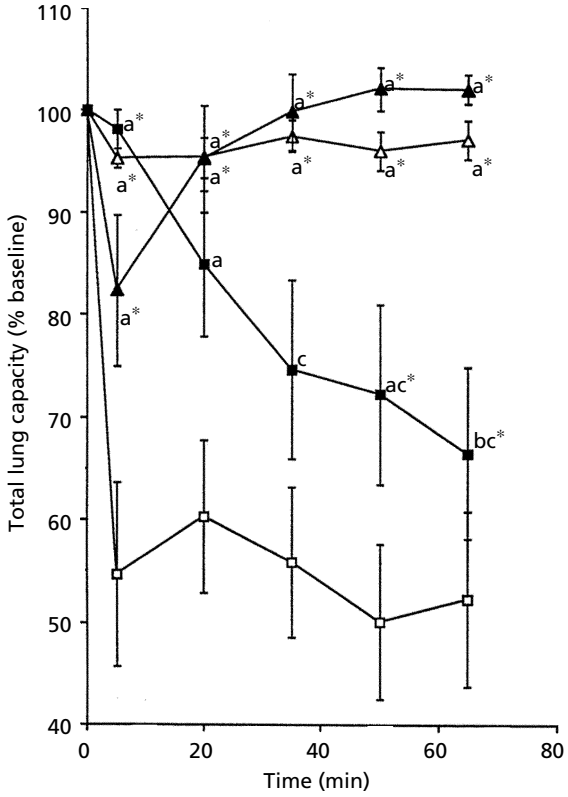

Figure 3 Inhibition by intravenous, intratracheal and intranasal albuterol of acetylcholine-induced bronchoconstriction in anaesthetized guinea pigs. The effect of albuterol is expressed as percentage of the baseline (before any drug treatment) value of total lung capacity in four groups of guinea pigs: control (□, n = 8), intravenous (■, n = 8), intratracheal (△, n = 8) and intranasal (▲, n = 9). Data are presented as mean ± s.e. a, b or c indicate $P < 0.05$, a*, b* or c* indicate $P < 0.01$; a: compared with control; b: compared with intratracheal; and c: compared with intranasal.

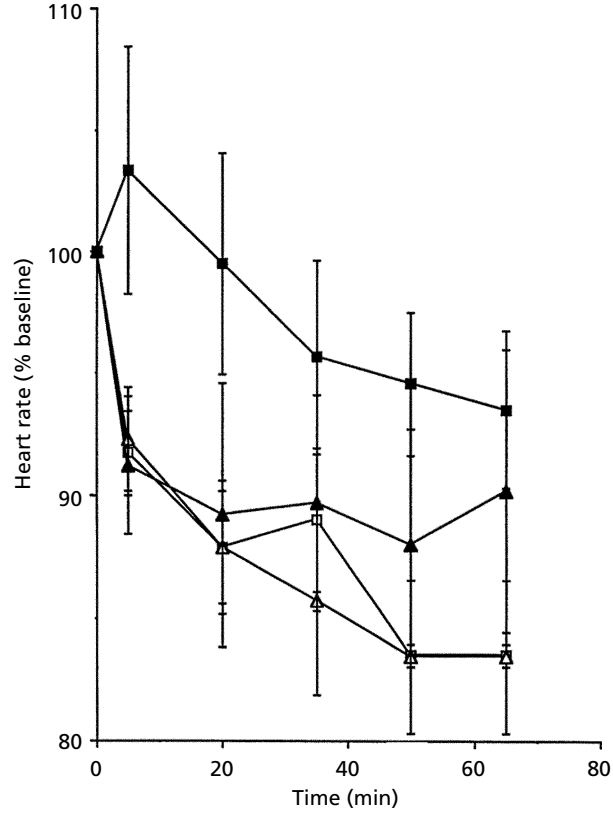

Figure 4 Inhibition by intravenous, intratracheal and intranasal albuterol of acetylcholine-induced bronchoconstriction in anaesthetized guinea pigs. The effect of albuterol is expressed as percentage of the baseline (before any drug treatment) value of heart rate in four groups of guinea pigs: control (□, n = 8), intravenous (■, n = 8), intratracheal (△, n = 8) and intranasal (▲, n = 9). Data are presented as mean ± s.e. a, b or c indicate $P < 0.05$, a*, b* or c* indicate $P < 0.01$; a: compared with control; b: compared with intratracheal; and c: compared with intranasal.

in heart rate could be detected among the different treatment groups ($P > 0.05$).

Discussion

It is generally thought that induced β_2-selective adrenergic agonists are the most effective agents used prophylactically for the prevention of exercise-induced asthma or for treatment of acute bronchospasm (Anon 1993). However, MDIs have several serious drawbacks. (i) Less than 10–20% of the dose is delivered to the site(s) of action in the lungs (Gerrity 1990), while most of the dose is lost in the oral cavity and pharynx (Newman et al 1981a, b). (ii) The patient must be trained to coordinate actuation of the MDI with deep inhalation. Children and the elderly do not easily master such coordination (Anon 1991). Appropriate use and cleaning of the devices are viewed as essential components in childhood asthma management (Childhood Asthma Management Program Research Group 1998). (iii) MDIs tend to be bulky, expensive and inconvenient to use.

In contrast, intranasal dosage forms, such as drops, sprays and gels are much less expensive to manufacture and they deliver the drug very rapidly to the systemic circulation, with a 95% or better bioavailability for small drug molecules such as albuterol. Furthermore, effective self-administration of such products requires little or no training for all patient populations. One may conclude, in view of these advantages, that intranasally administered β_2-agonists might be expected to elicit more reproducible clinical responses and hence be more efficacious on a dose-for-dose basis than when these drugs are administered by MDI.

In a previous investigation, we contrasted the efficacy of intranasal and intravenous albuterol in protecting guinea pigs against bronchoconstriction provoked by vagal nerve stimulation (Hussain et al 1992). It was found that although the intravenous albuterol induced a faster protective effect than the intranasally administered drug, within 16 min intranasal albuterol produced a level of protection equivalent to that observed with the intravenous route. The present study compared the efficacy of

albuterol administered intravenously, intratracheally and intranasally in protecting guinea pigs against bronchospasm induced by acetylcholine. Overall and irrespective of the route of administration, albuterol inhibited the bronchoconstrictor responses ($P < 0.05$), although not to the same extent. Except for the very initial phase of absorption, the drug was shown to be equally effective when administered either intranasally or intratracheally in alleviating bronchoconstriction using three indexes of pulmonary function: peak maximal expiratory flow, maximal expiratory flow at 50% vital capacity and total lung capacity. On the other hand, in the case of intravenous albuterol, despite a significant initial effect, its ability to influence pulmonary function faded rather rapidly. It should be pointed out that the intranasal head-to-head comparison with the intratracheal route reflects a comparison with drug directly delivered to the airways. MDIs, although they deliver via the same route, are considerably less efficient.

Figures 1–3 show that the extent of the recovery of pulmonary function in response to albuterol administration was not only dependent on the route of administration of the drug, but also on the index used in assessing such function. Despite this quantitative variation in recovery among indexes, the overall patterns of temporal change in the three indexes were basically similar. The similarity in percent change among the pulmonary function indexes in response to drugs affecting airway spasms was also observed by other investigators (Lin & Lai 1998). The fact that irrespective of the route of administration albuterol had no effect on the heart rate at the dose used in this study is not surprising. Albuterol is known to be much more active on the bronchial smooth muscle compared with the cardiac muscle (Martin et al 1971). The same behaviour was observed recently with a similar drug, fenoterol, which was administered to asthmatic patients by inhalation, infusion and nasal instillation (Hochhaus et al 1992). In general, with the relatively β_2-selective adrenergic agonists, when effective bronchodilation doses of the drug are taken, the cardiovascular effects are limited.

In conclusion, the present study suggests that albuterol is effective in providing bronchoprotection when delivered intranasally to guinea pigs. This route of administration may be useful in patient populations who experience difficulty with MDIs.

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