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Systemic absorption of adrenaline after aerosol, eye-drop and subcutaneous administration to healthy volunteers

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Adrenaline is the drug of choice for management of the anaphylactic reaction. The objective of this study was to compare systemic absorption of adrenaline after administration by different routes to healthy volunteers. Ten puffs (1.5 mg as adrenaline base) with 10–15 s intervals between them followed 2 h later by 20 puffs (3 mg) of adrenaline from a pressurized aerosol (Medihaler-Epi, 3M Riker, 14.0 mg/ml adrenaline acid tartrate) were sprayed into the cheek pouch or inhaled through the mouth or the nostrils. Adrenaline was also administered to the eyes by giving 2 drops (1 mg) of Isopto-Epinal (Alcon, 10 mg × ml^{-1}). Finally, 0.5 ml (0.5 mg) of adrenaline was given subcutaneously in the upper arm of the same individuals. The systemic absorption was determined by measuring plasma adrenaline levels and effects on blood pressure, heart rate and finger tremor before and 5, 15, 30, 60, 90, and 120 min after adrenaline administration. Adrenaline given as eye-drops did not have any significant effect on these parameters. Subcutaneously administered adrenaline caused within 5 min a significant increase of plasma adrenaline level (from 1.0 ± 0.2 to a peak of 6.5 ± 1.2 nM) which gradually decreased during 2 h. This mode of adrenaline administration increased the systolic blood pressure by a maximum of 11 ± 3.5 mmHg, heart rate by 9 ± 2.2 beats × min^{-1}, tremor ratio by 4 ± 0.6 and reduced the diastolic blood pressure by 18 ± 4.7 mmHg. The cardiovascular effects were approximately maximum 15 min after administration and lasted almost 90 min. After 10 inhalations through the mouth no significant effects were seen, whereas after 20 inhalations the plasma adrenaline level increased significantly (from 1.1 ± 0.2 to a peak of 2.4 ± 0.6 nM). The effects on blood pressure, heart rate and finger tremor ratio were more short-lived than those caused by subcutaneously administered adrenaline. The effects of nasal inhalation of adrenaline were similar but more long-lasting when compared to oral inhalation. *Conclusion.* Inhaled adrenaline gives rapid systemic absorption but this is less pronounced and more short-lasting than with subcutaneous adrenaline. Apart from being easier for the patient to use, the inhaled route of adrenaline administration also appears to be cardiovascularly safe within a wide dose range. It is therefore suggested that patients known to be hypersensitive should be equipped with Medihaler Adrenaline for emergencies as a complement to subcutaneous adrenaline. Further, the recommended dose of this inhaler in the treatment of acute upper airway hyperreactive conditions should be increased to 10–20 inhalations, which can be repeated if necessary.

Key words: adrenaline; anaphylactic reaction; cardiovascular; inhalation and systemic absorption.

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CLINICAL ASPECTS

Subcutaneous adrenaline, which is widely used in the treatment of anaphylaxis, gives rapid systemic absorption which is more pronounced and longer-lasting than that achieved by inhalation from a pressurised inhaler. However, adrenaline is easy to self-administer from an inhaler, provides direct contact with the airways and gives rapid systemic absorption. Inhaled adrenaline also appears to be cardiovascularly safe within a wide dose range. Consequently, Medihaler Adrenaline may be therapeutically valuable both as a first aid and in the subsequent treatment of uvula-larynx oedema, pseudocroup, in patients having hypersensitivity reaction combined with bronchospasm-mucosal oedema and also in prodromal status of anaphylactic reaction. A dose of 10–20 puffs in the acute situation is recommended, and can be repeated if necessary.

A severe anaphylactic reaction can appear within minutes after an insect sting or bite. 100 fatal cases caused by insects underwent autopsy and the result was presented as follows: 69% of the deaths were considered secondary to respiratory failure (airway obstruction) and the rest due to cardiovascular failure, e.g. anaphylactic shock (1). Similar results were reported by Mosbech (7) who examined deaths resulting from bee and wasp stings in Denmark 1960–1980.

Patients known to react to insect stings and other allergens with an anaphylactic reaction are usually equipped with adrenaline and glucocorticoids for acute use when necessary. Adrenaline can be given subcutaneously as an injection or inhaled from an aerosol. Knowledge of the plasma adrenaline levels obtained by these two routes of administration is at present very limited. In a recent study by Heilborn et al. (4) the plasma concentration of adrenaline in healthy volunteers was assayed after subcutaneous administration and after 10 and 20 inhalations of aerosol adrenaline (Adrenaline Medihaler, 3M Riker). The systemic absorption after subcutaneous administration was found to be slow and variable between individuals. The peak concentration was not reached before 40–120 min in 5/8 volunteers. Thus subcutaneous injection of adrenaline was not considered to be the appropriate treatment for a threatening anaphylactic reaction. In contrast, inhalation of aerosol adrenaline caused a faster increase in the plasma adrenaline level without causing marked cardiovascular effects at any of the doses studied. Four healthy volunteers, however, experienced nausea and epigastric pain 2 h after 20 inhalations of aerosol adrenaline. These adverse effects were reported at a time when the plasma levels of adrenaline were normal and no cardiovascular effects could be seen. It has been shown that when pressurized aerosol inhalers are used, about 80% of the inhaled dose is swallowed (8). In the study referred to aerosol adrenaline was given on an empty stomach and it is possible that the epigastric pain was secondary to a late local vasoconstriction within the duodenum, since adrenaline is protected from oxidation by the acidic gastric environment.

Despite the fact that asthmatics are used to the technique of inhalation, they may have difficulties in inhaling efficiently. A non-asthmatic unused to inhalers, e.g. a person with a threatening anaphylactic reaction, is likely to use inhalers less effectively. It was therefore of interest to compare the systemic absorption of adrenaline after various methods of aerosol administration with that of eyedrop and subcutaneous administration. It was also of interest to see whether epigastric pain could be avoided by pretreatment with antacids and charcoal.

MATERIAL AND METHODS

Eight normal healthy volunteers (7 males, 1 female, age 20–50, weight 55–85 kg) who gave informed consent were studied. The protocol was approved by the Local Ethics Committee at the Gothenburg University. Before the volunteers were allowed to take part in the study, they were medically examined and excluded if signs of cardiovascular disease or ECG abnormalities were found.

The healthy volunteers were told to omit

breakfast on each experimental day. On arrival at the laboratory, an intravenous cannula was inserted into a left forearm vein for blood sampling. After the cannulation the person was allowed to rest at least half an hour before baseline heart rate, blood pressure, ECG and finger tremor were recorded. In addition, a venous blood sample was drawn for analysis of the basal plasma adrenaline level. After that each volunteer received one of six treatments in a randomized crossover design and on separate days:

1. Ten inhalations of aerosol adrenaline (Adrenaline Medihaler, 3M Riker, 14.0 mg × ml^{-1} adrenaline acid tartrate, approx. 0.15 mg adrenaline base per puff) with an interval of about 15 s between inhalations. Before the experiment full instruction was given in inhaler technique. The aerosol was inhaled by slow breathing in from near residual lung volume to total lung capacity and breathholding for 5–10 s. One venous blood sample (5 ml) for adrenaline assay was drawn 5, 15, 30, 60, 90 and 120 min after the end of adrenaline administration. The subject then received 20 inhalations of adrenaline and the same blood sample schedule was followed. Heart rate, blood pressure and finger tremor were recorded after 15, 30, 60, 90 and 120 min.

2. The same experimental schedule as shown in (1) was followed, but before the first inhalation the subject was given an antacid mixture (10 ml of Novaluzid, Hässle), and a charcoal suspension (1 g of Carbomix; Medica). Immediately after the last inhalation the mouth and pharynx were thoroughly rinsed with water.

3. The same experimental schedule as shown in (1) but the subject was told to spray the aerosol adrenaline into the nostrils and then make a nasal inhalation.

4. The same experimental schedule as shown in (1) but the subject was told to spray the aerosol adrenaline into the cheek pouches without concomitant inhalation.

5. The same experimental schedule as shown in (1) but instead of the aerosol the subject received 0.5 ml 1/1000 adrenaline (0.5 mg) subcutaneously below the deltoid muscle in the opposite arm from which the blood samples were taken.

6. The same experimental schedule as shown in (1) but instead of the inhalation the subject was given one drop of adrenaline solution (Isopto-Epinal 1 %, 10 mg/ml, in total approx. 1 mg) in each eye.

In an additional series of experiments subcutaneous administration of adrenaline was made in the upper arm and in the thighs of four subjects. The venous blood samples (5 ml) were collected on ice in test tubes containing EDTA (10 nM final concentration). After centrifugation the plasma was removed and stored at -80°C until analysed for endogenous adrenaline by performance cation exchange liquid chromatography with electrochemical detection (5). At the time of the adrenaline assay the minimal level of detection of the method in our hands was 0.7 ± 0.2 nM.

The results are presented as means ± SEM. Statistical evaluation was made with Student's paired t test (two-tailed) and a probability $P < 0.05$ was considered statistically significant.

RESULTS

Effects on plasma adrenaline concentration

Subcutaneous administration of adrenaline (0.5 mg) significantly increased the baseline plasma adrenaline level from 0.97 ± 0.19 to 6.48 ± 1.24 nM (at 5 min, $n = 7$, $P < 0.01$, Fig. 1A). A significant increase in plasma adrenaline concentration after subcutaneous administration was still seen 90 min after the administration.

Ten inhalations of aerosol adrenaline through the mouth (approx. 1.5 mg) did not affect the baseline plasma adrenaline concentration (1.35 ± 0.23 nM, $n = 7$) of the subjects. Twenty inhalations of aerosol adrenaline (3 mg) tended to increase the plasma adrenaline level 5 min after the end of administration (from 1.16 ± 0.19 to 2.36 ± 0.59 nM, $P = 0.069$, Fig. 1B). Similar results were obtained if the subject had taken antacid and charcoal immediately before the inhalation. Five minutes after 20 inhalations of aerosol adrenaline the plasma adrenaline concentration increased from (0.92 ± 0.21 to 2.17 ± 0.42 nM, $n = 8$, $P < 0.05$, Fig. 1C).

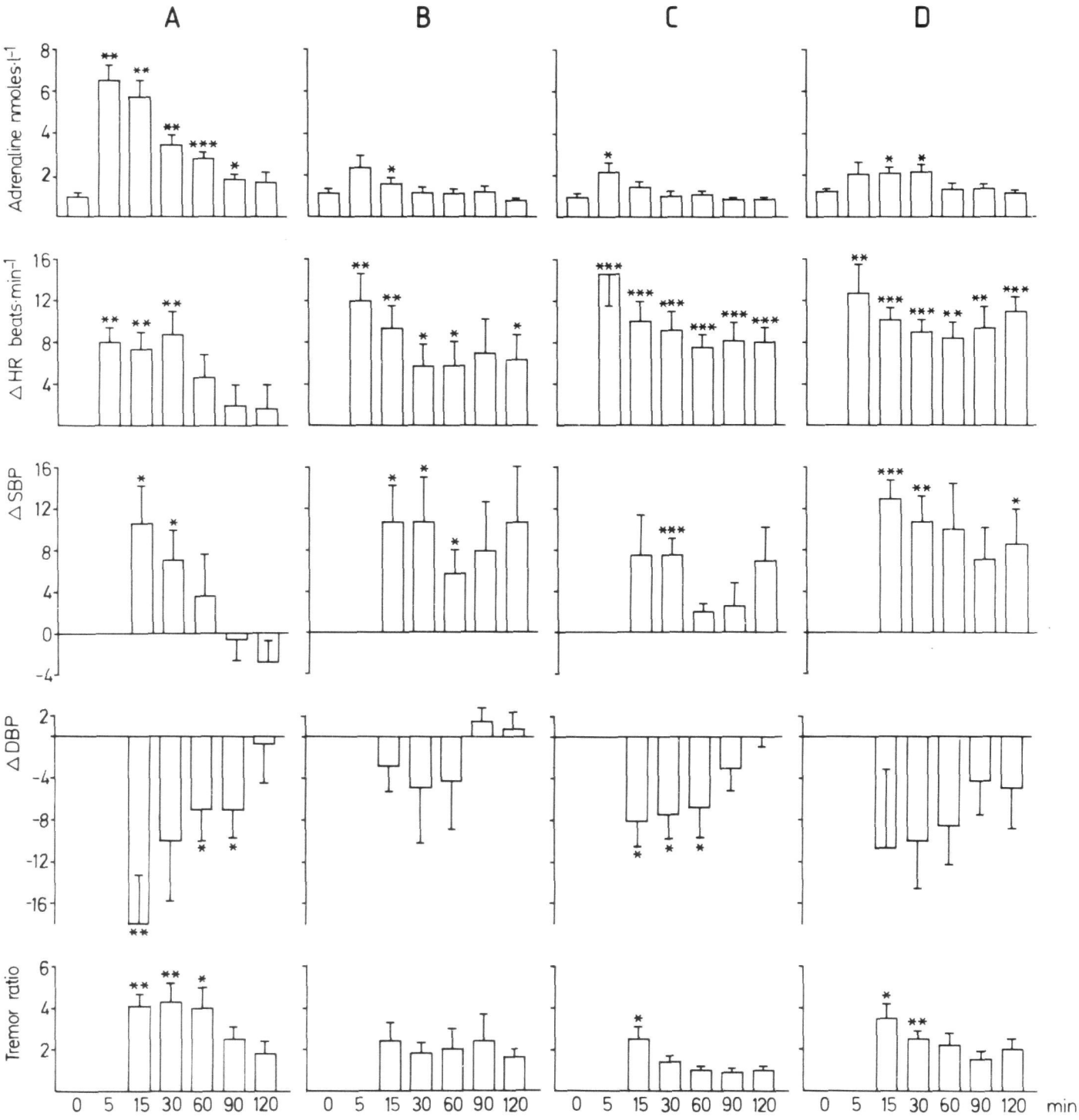

Fig. 1A, B, C, D. Effects on plasma adrenaline concentration (nmol/l^{-1}), heart rate (HR, beats × min^{-1}), systolic blood pressure (SBP, mmHg), diastolic blood pressure (DBP, mmHg) and tremor ratio before (0) and 5, 15, 30, 60, 90 and 120 min after administration of adrenaline by different routes: A) subcutaneous injection (0.5 mg); B) oral inhalations (20; 3 mg); C) oral inhalations after pretreatment with antacid mixture and charcoal suspension (20; 3mg); D) nasal inhalations (20; 3 mg). Data are given as means ± SEM; * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$, compared to baseline values before (0) administration of adrenaline.

Ten inhalations of aerosol adrenaline through the nostrils significantly increased the plasma adrenaline level 15 and 30 min after the end of administration (from 1.08 ± 0.26 to a maximum of 1.82 ± 0.22 nM at 30 min, $n = 7$, $P < 0.05$). The plasma adrenaline concentration (at 15 min) after 20 inhalations of aerosol adrenaline was 2.10 ± 0.30 nM ($n = 7$, $P < 0.05$, Fig. 1D).

In the additional series of experiments, in one

of the four subjects who received a subcutaneous injection in the thigh the systemic systemic absorption of adrenaline was delayed for at least 30 min. The other subjects followed the same pattern of systemic absorption as already described, e.g. maximum plasma adrenaline concentration was obtained within 15 min.

Adrenaline administration in the form of an aerosol adrenaline sprayed into the cheek pouches or given as eyedrops did not have any significant effect on the plasma adrenaline level or any of the other parameters studied.

Effects on heart rate

A significant increase by about 9 beats/min was seen after subcutaneous administration of adrenaline (Fig. 1A).

Ten inhalations of adrenaline aerosol (independently of route of administration) did not cause any significant effect on the heart rate. Twenty inhalations of adrenaline aerosol, however, caused a significant heart rate increase in each experimental group (Fig. 1B-D).

Effects on systolic blood pressure

After subcutaneous injection of adrenaline (0.5 mg) the systolic blood pressure increased from 120.0 ± 4.2 to 130.7 ± 4.8 mmHg (10.7 ± 3.5 mmHg, $n = 7$, $P < 0.05$, Fig. 1A).

Aerosol adrenaline increased the systolic blood pressure significantly (Fig. 1B-D) only after the high dose (20 inhalations, approx. 3 mg).

Effects on diastolic blood pressure

Fig. 1A-D shows changes in response to adrenaline administration. No significant effects were observed after 10 inhalations of aerosol adrenaline, whereas the diastolic blood pressure tended to be reduced after 20 inhalations. Fifteen minutes after subcutaneous administration of adrenaline the diastolic blood pressure was reduced from 67.1 ± 2.4 to 49.3 ± 5.6 mmHg (17.9 ± 4.3 mmHg, $n = 7$, $P < 0.01$).

Effects on finger tremor

Fig. 1A-D shows the effect of adrenaline on tremor ratio after different routes of administration. Significant effects on tremor ratio were observed only after subcutaneous administration and after 20 inhalations of aerosol adrenaline via the nostrils.

Side effects

Independently of route of administration adrenaline did not cause any gastric pain or other serious side effects. However, the subjects occasionally experienced unpleasant side effects like tremor and palpitation.

DISCUSSION

The baseline plasma adrenaline concentrations of the subjects in the present study were shown to be somewhat higher than those reported by Hjemdahl et al. (5). This discrepancy could partly be due to the lower detection limit of the plasma adrenaline assay used in the present study (0.7 nM) and partly be a consequence of more stressed subjects under our experimental conditions.

Plasma adrenaline concentration was only increased significantly by 10 inhalations of aerosol adrenaline, when administration was made via the nostrils. Independently of route of administration however, 20 inhalations of aerosol adrenaline (3 mg) caused about a two-fold increase of the plasma adrenaline level, which was maximal in the blood samples collected 5 min after the end of administration. When inhaled via the nostrils, the increase in plasma adrenaline concentration was more long-lasting compared with that of oral inhalation of adrenaline.

There was no marked difference on the observed parameters when aerosol adrenaline was administered alone or in combination with antacid mixture and charcoal suspension. Thus, the main systemic absorption of aerosol adrenaline appears to take place in the respiratory epithelium. However, the plasma adrenaline concentrations obtained in the present study

after inhalation of adrenaline from a pressurized inhaler were only 1/3 of those reported in another study with a similar design and corresponding doses (4). The reason for this discrepancy is difficult to understand, especially since the subjects of both studies were given full instruction in inhaler technique. In another recent study 30 inhalations of adrenaline were taken in an almost identical manner as in the present experiments (9). The maximal plasma adrenaline concentration obtained 1 min after 30 inhalations was 4.86 ± 2.5 nM, which is in accordance with the results of the present study. Systemic absorption of adrenaline when sprayed into the cheek pouches or when given as eyedrops appears to be minimal, since neither of these routes of administration had any effect on the plasma adrenaline concentration.

In the present study and in the study by Warren et al. (9) subcutaneous administration of adrenaline in the upper arm causes an immediate increase of plasma adrenaline concentration, with the maximal peak level in the blood samples collected 5 min after administration. In contrast to these findings the increase of plasma adrenaline level was delayed (40–120 min) when adrenaline was given subcutaneously in the thigh (4). The reason for this discrepancy could be because the systemic absorption of adrenaline is dependent on the site of the subcutaneous injection. The preliminary comparison of the plasma adrenaline concentrations obtained after subcutaneous injections of adrenaline in the upper arm and in the thigh lends some support to this hypothesis, since an increase of plasma adrenaline concentration in one subject was first observed 60 min after subcutaneous injection of adrenaline in the thigh. In the present study the subjects were told to avoid breakfast on the experimental day so that adrenaline was always administered on an empty stomach. In spite of this, none of the subjects experienced such side effects as gastric pain or nausea.

In all experimental groups there was a close correlation between the changes in plasma adrenaline concentration and the effects on all other studied parameters. Thus a significant increase in plasma adrenaline concentration was accompanied by an increase in heart rate, systolic blood pressure and tremor ratio, whereas the diastolic blood pressure was decreased. One interesting exception was the increase in heart rate, which tended to remain long after the plasma adrenaline level had returned back to baseline level. Similar observations have been made after adrenaline infusions to humans (2). The reason for the prolonged effect on heart rate by adrenaline administration has been suggested to be a consequence of neuronal uptake of adrenaline, whereby adrenaline is protected against degradation. Adrenaline is then released as a co-transmitter to noradrenaline and is capable of stimulating prejunctional facilitatory β-adrenoceptors, which leads to an increase of NA release per impulse and heart rate (3).

Judging from the effect on the studied parameters, subcutaneous injection of adrenaline in the upper arm appears to be the best method for achieving good systemic absorption. The present study, however, indicates that adrenaline is also rapidly absorbed by the inhaled route. After 20 inhalations of aerosol adrenaline, no serious adverse effects were seen, and the plasma adrenaline concentrations obtained, as well as the cardiovascular effects observed, were less marked than those elicited after subcutaneous adrenaline. Subcutaneous adrenaline is widely used in the emergency room for treatment of acute anaphylactic reactions. The data available at present do not allow the conclusion that this way of administration is superior to inhalations of aerosolised adrenaline. In favour of the inhaled route is the fact that the greatest danger of anaphylactic reactions arises from the accompanying bronchospasm and laryngeal oedema. The inhaled route has the advantage of providing direct contact between adrenaline and the laryngeal and bronchial mucosa. This property might be more therapeutically important than high systemic plasma adrenaline concentrations for the treatment of acute asthma and anaphylactic reactions. Further studies, however, are required in order to elucidate this hypothesis.

Two other factors in favour of the inhaled route of administration are that aerosol adrena-

line is easy to self-administer and that the risk of serious side effects appears to be negligible even when used in several multiples of the presently recommended dose. Aerosol adrenaline may therefore be of good therapeutic value as complementary treatment and as first aid in patients with a hypersensitivity reaction combined with bronchospasm-mucosal oedema, and also in the prodromal stage of an anaphylactic reaction. The recommended dose for this indication should be increased to 10-20 puffs consecutively, and repeated if necessary at intervals until medical help is obtained. These recommendations are based on studies performed in adults. With reference to a clinical study on asthmatic children (7-16 years) who were treated with racemic adrenaline given by continuous nebulization up to 22.5 mg, the above recommendations are most probably valid for children in this age group (6). Clinical experience also supports the conclusion that children tolerate adrenaline better than adults. However, dose recommendations for dose-aerosol adrenaline in children need to be confirmed in future studies.

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