

Inhalation of Racemic Epinephrine in Children with Asthma

Dose-Response Relation and Comparison with Salbutamol

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In this study the effects of nebulized racemic epinephrine (Micronephrine®) were investigated in children with asthma. The drug was inhaled by a compressor nebulizer with a plastic mask. In the first part of the study it is shown that nebulized Micronephrine has a dose-dependent bronchodilatory effect. In the second part the effect is compared with that of nebulized salbutamol in 10 children (7-16 years of age) with bronchial asthma. The highest dose used in the dose-response trials ($=0.9$ mg Micronephrine/kg body-weight) was compared with 0.15 mg salbutamol/kg body-weight, which is the dose commonly used in Sweden.

There was no significant difference between the drugs as regards increase of forced expiratory volume in 1 sec or duration of the increase.

There was a small but significant increase in systolic blood pressure, measured 5 min after the inhalation of Micronephrine but no significant change in diastolic pressure or heart rate. Four children complained of temporary sore throat after the inhalation.

Key words: asthma; children; racemic epinephrine.

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Treatment of acute asthma in children comprises inhalations of β_2 receptor agonists, e.g. terbutaline or salbutamol. The drugs are administered using compressor nebulizers or intermittent positive pressure ventilation. However, some acutely ill children do not respond satisfactorily to this treatment. One cause of insufficient response to specific β_2 agonists might be that the mucosal edema constitutes a greater part of the bronchial obstruction. A drug combining α and β_2 effects, e.g. racemic epinephrine, may be valuable in these children. Hitherto, inhalation of this drug in children has mainly concerned the treatment of croup and laryngotracheobronchitis (1, 3, 7, 11, 12, 13).

During the last 7 years racemic epinephrine inhalation has been used in our hospital for

treating adults and children. To evaluate our positive clinical impression we decided to investigate the effects of the drug in children. Thus, in the present study racemic epinephrine (2.25% Micronephrine), used as nebulized inhalation, was investigated in children with subacute asthma and with regard to (a) dose-response relation, (b) the bronchodilatory effect in comparison with that of a β_2 receptor agonist (salbutamol).

METHODS

Drugs

The racemic epinephrine (22.5 mg/ml) was diluted with sterile water to 2 ml in the first dose-response trial (A). In the second dose-

response trial (B) and in comparison with salbutamol the solution of racemic epinephrine was diluted to 4 ml. The salbutamol solution (Ventoline®, Glaxo Ltd, United Kingdom) in a concentration of 5 mg/ml was diluted to 4 ml. The dosage of salbutamol was 0.15 mg/kg body-weight, i.e. the dose commonly used in Sweden (2).

Equipment

Bronchial response was estimated using forced expiratory volume in 1 sec (FEV_1). FEV_1 was measured with an electronic spirometer (Monaghan M 403) in the younger children. In the older children Airflometer (AFM, Glaxo Ltd) was used. The AFM gives arbitrary units which were recalculated to FEV_1 according to a correlation equation ($r=0.99$) previously found in a study from our department (4). The same equipment was used during the whole investigation and in the way previously described (4). The predicted normal values correspond to the regression lines found in our previous study of healthy children (4).

PATIENTS AND PROCEDURE

Dose-response trial A

Five children, 7–15 years of age, with bronchial asthma joined this study. They were admitted to hospital because of acute asthma. The investigation was done about 2 days after admission. No medication was given 12 h before the investigation, which began in the morning. The children should have an initial FEV_1 less than -3 s.d. of predicted normal. Their initial FEV_1 -values in per cent of predicted normal were 41%–62% (mean 50%). The children inhaled Micronephrine in three increasing doses 0.25 ml = 5.6 mg, 0.50 ml = 11.25 mg and 1.0 ml = 22.5 mg at 30-min intervals. FEV_1 was measured before, 15 and 30 min after the inhalations.

Dose-response trial B

Two children, aged 7 and 11 years, with known bronchial asthma joined this study. They were investigated in the morning on 2 consecutive days about 2 days after admission due to acute asthma. They were expected to have milder obstruction than the children in trial A. The four initial FEV_1 -values in per cent of predicted normal were 54, 60, 70 and 74%.

The children inhaled Micronephrine in three increasing doses: 0.01 ml/kg body-weight = 0.225 mg/kg, 0.02 ml/kg and 0.04 ml/kg at 60-min intervals.

FEV_1 was measured before, 15, 30 and 60 min after the inhalation. In trial A and B the response was calculated as the change of FEV_1 in per cent of the FEV_1 obtained before the first inhalation.

Comparison between racemic epinephrine and salbutamol

Ten children with asthma were investigated. The ages were 7–16 years (mean: 12 years) and the heights were 127–181 cm (mean: 151 cm). Clinically, all were supposed to have a fairly stable bronchial obstruction and an initial FEV_1 under 70% of predicted normal. They were investigated on 2 consecutive days according to the randomized schedule shown in Fig. 1. Mean initial FEV_1 was 52% of predicted normal on both the 1st and 2nd day of the investigation. The ranges were 40–61% the first day and 34–68% the second day.

The response to the inhalations was calculated as the change of FEV_1 in per cent of the FEV_1 -value before each inhalation. The dose of racemic epinephrine was 0.04 ml/kg body-weight (0.9 mg/kg), i.e. the final dose used in the dose-response trial B.

For eight of the 10 children the difference between initial FEV_1 of the 1st day and that of the 2nd day did not exceed 15%. The results from these children were also analyzed in a special way, i.e. the response to the inhalations was calculated as the change of FEV_1 in per cent of predicted normal.

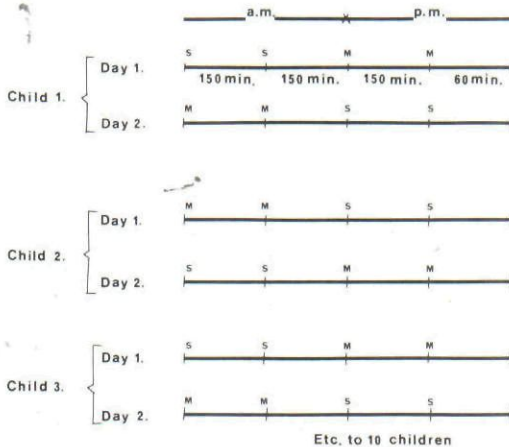


Fig. 1. Randomized schedule for the comparison of Micronephrine with salbutamol. M = inhalation of Micronephrine, S = inhalation of salbutamol. FEV₁ was estimated 5, 30, 60 and 150 min after each inhalation.

Heart rate and blood pressure (cuff method) were measured during the comparison between racemic epinephrine and salbutamol after every inhalation, i.e. four inhalations of both drugs for each of the children.

All children and their parents were informed about the investigation and gave their consent.

RESULTS

The dose-response relations are given in Fig. 2 and Table 1. Micronephrine shows a dose-dependent bronchodilatory effect. No systemic side effects were noted but two children had pale lips. One of the two patients complained of a sore throat after inhalation of the highest dose.

For the comparison with salbutamol the highest dose (0.9 mg/kg body-weight) of the dose-response investigation was chosen. The results of the comparison in all 10 children are presented in Fig. 3 and are given as the mean change of FEV₁ in per cent of the FEV₁-value before each inhalation. The differences between the drugs are not significant (Student's t-test).

In Fig. 4 the effects of the two drugs are compared in the eight children with stable

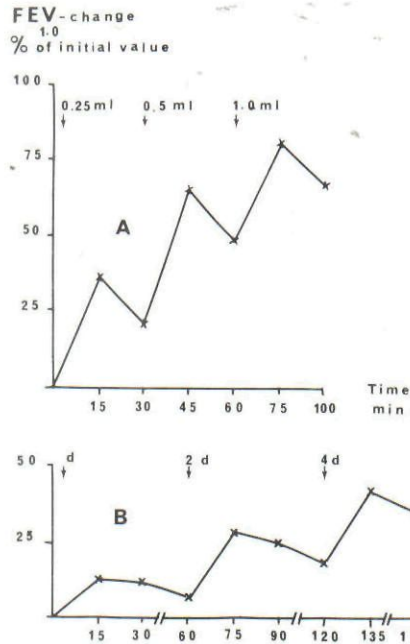


Fig. 2. Three different doses of inhaled Micronephrine (2.25%) and bronchial response estimated as FEV₁. A. Five children inhaled three doses: 0.25 ml, 0.5 ml and 1.0 ml at 30-min intervals. Mean change of FEV₁ is given in per cent of the FEV₁ before the first inhalation. FEV₁ was measured before the first inhalation, 15 and 30 min after each inhalation. B. Two children and two trials of each child. The three doses of Micronephrine were: d = 0.01 ml/kg body-weight, 2 d = 0.02 ml/kg and 4 d = 0.04 ml/kg. FEV₁ was estimated before inhalation, 15, 30 and 60 min after the inhalation. The changes of FEV₁ are expressed as in A.

bronchial obstruction (2 days difference of FEV₁ < 15%). Only the results of the a.m. investigations were calculated upon and shown. The changes of FEV₁ are expressed in per cent of predicted normal. To illustrate the large variation of the changes, not only the mean values are given but also the individual ones. Five of the eight children reached FEV₁-values within normal range already after the first inhalation of Micronephrine. The corresponding figure for salbutamol is four of the eight children. The effects of the two drugs do not differ significantly.

An evaluation of the side effects of Micronephrine and salbutamol showed no significant change as regards heart rate and

Table 1

Dose of inhaled racemic epinephrine (2.25%) and FEV₁-response (change of FEV₁ in per cent of initial FEV₁)

Trial	Dose	Time after inhalation (min)	FEV ₁ -change (%)	
			Mean	Range
A	0.25 ml	15	36	-5 - 94
		30	21	-16 - 84
	0.5 ml	15	65	21 - 121
		30	49	9 - 84
	1.0 ml	15	80	45 - 140
		30	66	23 - 103
B	0.01 ml/kg	15	13	2 - 24
		30	12	3 - 20
		60	6	0 - 14
	0.02 ml/kg	15	29	11 - 65
		30	25	6 - 62
		60	19	-18 - 44
	0.04 ml/kg	15	42	24 - 73
		30	35	17 - 73
		60	33	19 - 64

diastolic pressure. A small but significant ($0.01 \geq P > 0.001$) increase of mean systolic blood pressure (+7 mmHg) was registered 5 min after the inhalation of Micronephrine, whereas the changes registered after 30 min and 150 min were not significant.

Three children complained of sore throat after the inhalation of Micronephrine and the lips of two of these children became pale immediately after the inhalation.

DISCUSSION

As different doses of racemic epinephrine have been used in previous investigations of children, we started our study with dose-response trials. In these trials our doses were chosen with regard to the experiences gained in previous investigations (1, 3, 7, 11, 12, 13). Our dose (0.9 mg/kg body-weight) used for comparison with salbutamol corresponds on the whole with the highest doses used in these previous studies.

The drug was given by mask which implies

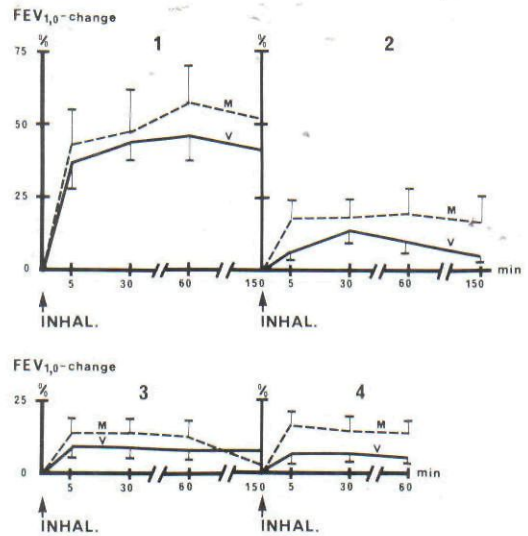


Fig. 3. Comparison between inhaled Micronephrine (M) and inhaled salbutamol (V) in 10 children. The four inhalations (1, 2, 3, 4) were randomized according to the schedule in Fig. 1. Mean values and standard errors of the means of the FEV₁-changes are shown. The change after each inhalation is expressed as the change in per cent of the FEV₁-value measured before each inhalation.

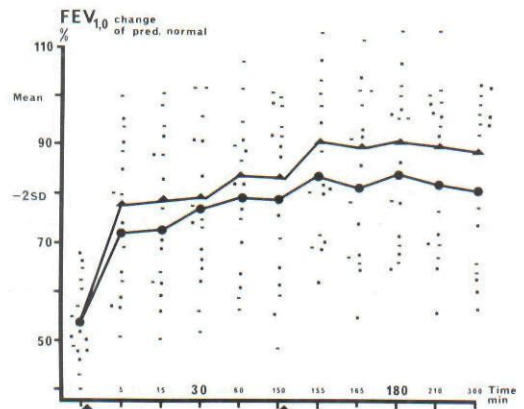


Fig. 4. Comparison between inhaled Micronephrine and inhaled salbutamol in eight children. Changes of FEV₁ in per cent of predicted normal are given for each child. Mean values of these changes are also shown. Only the values from the two inhalations (at 0 and 150 minutes) of the a.m.-investigations are included. The mean value of FEV₁ in healthy children and the lower normal limit (mean -2 s.d.) are also shown. ▲ = mean value after Micronephrine. ● = mean value after salbutamol. * = individual value after Micronephrine. • = individual value after salbutamol.

greater loss of the drug on its way to the bronchial tree than when given through a mouth tube or a tracheal tube. This must be considered when comparing the effects and side effects obtained in different studies.

In our investigation racemic epinephrine had as good bronchodilatory effect as salbutamol. The results of our dose-response trials gave us the impression that the *duration* of the bronchodilatory effect was rather short, in accordance with the short duration of the decongestant effect found in children with croup (12, 13). The results from the comparison with salbutamol show, however, that the duration of the bronchodilatation was the same for both drugs. It might be that the α -effect of racemic epinephrine, i.e. the decongestant effect, is of a shorter duration than the β_2 -effect, i.e. the effect on the bronchial muscle.

Fig. 4 shows convincingly the problem of the unavoidable individual variation when comparing effects of two potent drugs, and that a possible difference between the two drugs can only be evaluated with a larger material.

A comparison in younger children might show a better effect for racemic epinephrine than for salbutamol due to the α -effect on the mucosal edema, which can form a considerable part of the airway obstruction in infants and young children with wheezy bronchitis or asthma. Our clinical impression is in accordance with this hypothesis, but we have so far not been able to design a proper method or procedure for an evaluation in this age group, partly due to ethical difficulties. However, in a recent investigation of wheezy bronchitis in children under 18 months of age no significant effect was found either for an α -receptor stimulant or a β_2 -receptor agonist (9).

Inhalations of racemic epinephrine and not ordinary epinephrine are used because it is supposed to give the same bronchodilatory effect as ordinary epinephrine but less side effects (6). However, the advantage of racemic epinephrine over ordinary epinephrine has been criticized (5) and a dose-response comparison between these two drugs with

regard to bronchodilatory effect and side effects should be interesting.

Larsson & Svedmyr (8) have rightly emphasized the importance of a stable broncho-obstructive stage in patients selected for comparative drug studies. Such an ideal situation is very difficult to create in children. However, in Fig. 4 we have tried to take these circumstances into consideration, i.e. the degree of initial bronchial obstruction in each individual child differed less than 15% from the 1st day of investigation to the 2nd day. Furthermore, the changes of FEV_1 after the inhalations were calculated in per cent of the predicted normal values in order to avoid false exaggerations of the percentual changes in the children with very low initial FEV_1 . Such an exaggeration is easily obtained with a calculation of the change in per cent of a very low initial FEV_1 . This way of presentation has one more advantage—the importance of the change related to the absolute limit of a change, i.e. normality, is shown.

Our predicted normal values are those obtained in studies made in our own department and with the same equipment, which further supports this method of calculation and presentation.

The local side effects obtained in some children after inhalation of racemic epinephrine are probably due to the α -effect of the drug and were of minor importance except in one boy who received one of the highest doses. He thought the soreness of his throat was so unpleasant that he refused to join any further investigations.

There was a significant rise of systolic blood pressure immediately after the inhalation of Micronephrine but the rise was small. Such an increase of systolic blood pressure was also found in healthy adults (10).

We conclude that nebulized racemic epinephrine gives a good bronchodilatory effect in children with bronchial asthma and that the side effects seem small. Our dose, 0.9 mg/kg body-weight, might be too high for routine use, particularly in older children. We do not know whether racemic epinephrine has

any advantage over β_2 -agonists, but further studies are worthwhile, especially in infants and young children.

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