

## Osmolality changes in nebulizer solutions

M.H. Schöni\*, R. Kraemer\*\*

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**ABSTRACT:** Paradoxical effects (bronchoconstriction instead of bronchodilatation) have been reported after inhalation of beta<sub>2</sub>-mimetics in asthmatic children, and it has been suggested that this was due to osmolality and pH changes of the nebulizer solution. We tested commercially available nebulizer solutions and found osmolality changes after 5, 10 and 15 min of nebulization. Osmolality was measured in the nebulizer chamber and the airstream of two types of jet nebulizers. When normal saline was nebulized a filling volume time dependent increase of osmolality in the nebulizer chamber, from 282±7 mmol·kg<sup>-1</sup> to 432±18 mmol·kg<sup>-1</sup> resulted. Salbutamol ready made solution, and terbutaline respules were isotonic, whereas fenoterol, disodium cromoglycate (DSCG), beclomethasone dipropionate (BDP) and salbutamol (respirator solution 0.5%) were hypotonic (60–100 mmol·kg<sup>-1</sup>). When a mixture of sodium chloride (NaCl) and the drug solution (salbutamol, terbutaline, fenoterol) was nebulized for 10–15 min, the osmolality in the nebulizer cup increased to 420–500 mmol·kg<sup>-1</sup>. However, mixtures of the same beta<sub>2</sub>-agonists with DSCG or with BDP remained hypo-osmolar. The same osmolality changes were present in the airstream. This study shows that after 10–15 min of nebulization osmotic changes occur in the nebulizer cup and airstream and that these changes differ according to the drug mixtures and the amount of the solution in the nebulizer chamber.

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Inhalation of antiasthmatic drugs is an important form of treatment for children and adults with bronchial asthma. Various aerosol devices are currently used: metered dose inhalers, drug powder inhalers and nebulizers in which solutions are aerosolized by compressed air or ultrasound. The choice of device depends on the kind of drug, on the practicability of handling the delivery device and also on age of the patient. In children the ability to use inhalers and the efficacy and side effects of aerolized drugs are difficult to determine. Controversies exist as to whether inhalational devices are able to deliver sufficient amounts of drugs to the bronchial tree [1, 2].

It has been demonstrated that oral beta<sub>2</sub>-agonists are effective in more than 80% of infants aged 2–22 months of age, if changes in pulmonary hyperinflation are evaluated with concomitant changes in airway resistance [3, 4]. In addition, during inhalation of beta<sub>2</sub>-agonists, side effects have been observed in infants, with bronchoconstriction occurring instead of bronchodilatation [2]. It has been suggested that such a paradoxical reaction might be due to changes in the osmolality or acidity in the nebulized solutions. Therefore, we determined baseline osmolality levels in a variety of nebulizer solutions and followed osmolality in the filling cup and airstream during nebulization from two jet-type nebulizers, which are commonly used for home treatment. Our aim was to discover whether osmolality changes occur in different

brands of beta<sub>2</sub>-agonists, whether these changes are also present in the airstream, and whether there were factors during nebulization upon which these changes might depend.

### Methods

Osmolality in the filling cup of two jet type nebulizers, newly supplied by the manufacturer (Hospitak cup with Novair air driven compressor, flow 9 l·min<sup>-1</sup>; Pari Inhalerboy with its original inhalation set, flow 12 l·min<sup>-1</sup>, open vent) was determined using the micro-osmolality method as described previously [5]. In short, 8 µl of fluid are taken by a small filter paper (ø 8 mm) which was either dipped into the fluid of the filling cup or held in the airstream of the nebulizers outlet. The outlet was redesigned to taper off conically and to cover only the surface of the filter paper. Using a micro-osmometer (Wescor, Utah, USA) osmolality was determined in this device by the vapour pressure method and results were obtained in a digital outprint within 30 s. At the start of a nebulizing period, 5, 10 and 15 min later osmolality was determined in at least triplicate sets and the mean±SEM values were analysed in an osmolality time plot. To study the dependence of osmolality on the filling volume, 1–5 ml of a drug carrier solution of sodium

chloride (NaCl) was tested. When self prepared mixtures were tested, two starting volumes in the filling cup were processed, either 2 or 4 ml, to test the effect of volume on osmolality changes. In other experiments (with ready made solutions and disodium cromoglycate (DSCG)) the original volumes from the commercially available vials were used.

The following solutions were tested: normal 0.9% physiological saline, pure  $\beta_2$ -agonist solutions as they are marked (salbutamol 0.5%, fenoterol 0.5%, terbutaline 1.0%) dilutions of these drugs in 2 or 4 ml of saline, fixed commercially available mixtures (salbutamol ready made solution, bricanyl respules), DSCG or beclomethasone dipropionate (BDP). The latter two were tested alone or in combination with  $\beta_2$ -agonists. In all experiments the Novair air compressor and the Hospitak nebulizer were used. In two sets of experiments the results of the Novair were compared to those from the Pari.

Results are given in  $\text{mmol}\cdot\text{kg}^{-1}$  (mean $\pm$ SEM); statistical analysis was performed by Student's t-test and a  $p<0.05$  was accepted as significant.

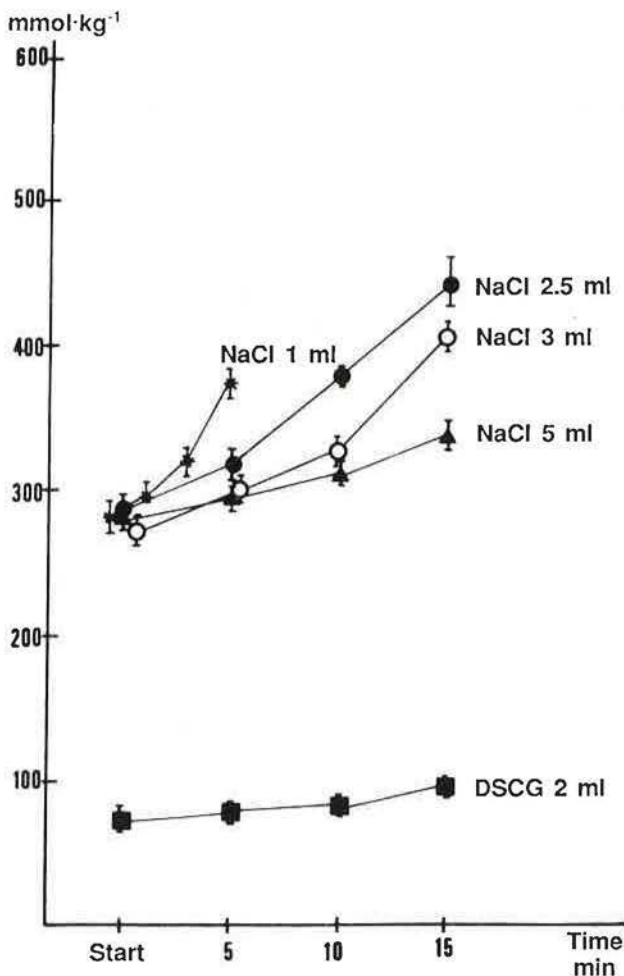


Fig. 1. – Osmolality-time relationship for different starting volumes in the filling cup. Time denotes minutes after start of permanent nebulization (Novair, Hospitak jet-nebulizer flow  $9\text{ l}\cdot\text{min}^{-1}$ ). NaCl: sodium chloride; DSCG: disodium cromoglycate.

## Results

### Relationship between filling volume and osmolality of the drug carrier solutions in the filling cup (NaCl and DSCG)

When different starting volumes of 0.9% NaCl or 2 ml of DSCG in the nebulizer cup were nebulized a filling-volume dependent increase of osmolality was observed as it is shown in figure 1. The higher the initial filling volume of NaCl, the lower were the osmolality values after 15 min of nebulization. For volumes smaller than 2 ml osmolality was not determined after 10 min since almost all of the fluid was aerolized after that time. With a starting volume of 2 ml, 150  $\mu\text{l}$  remains in the cup after 15 min of nebulization.

NaCl, dependent on the initial volume, increased its osmolality significantly from  $282\pm 7\text{ mmol}\cdot\text{kg}^{-1}$  up to  $432\pm 18\text{ mmol}\cdot\text{kg}^{-1}$ . The differences between the osmolality levels which were reached after 15 min of nebulization starting from 1 ml, 2.5 ml, 3 ml and 5.0 ml filling volume were statistically significant ( $p<0.01$ ).

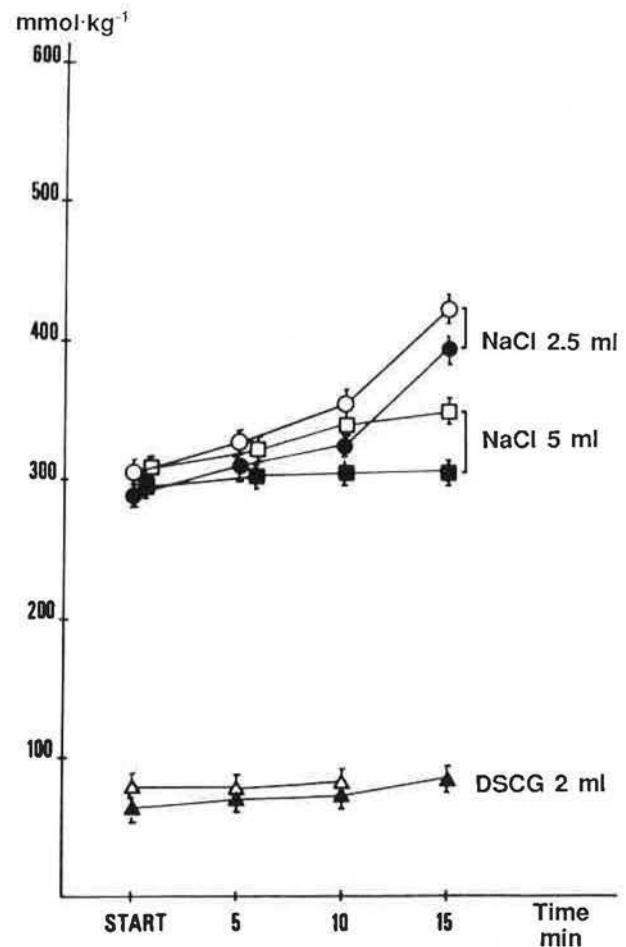


Fig. 2. – Comparison of osmolality measured in the airstream and the filling cup with two starting volumes for saline and for DSCG. Time axis and abbreviations as in figure 1. (Novair, Hospitak jet-nebulizer flow  $9\text{ l}\cdot\text{min}^{-1}$ ). Open symbols (○, △, □), airstream; closed symbols (●, ■, ▲), cup.

However, DSCG from the marketed vials was always hypo-osmolar ( $75 \pm 3 \text{ mmol} \cdot \text{kg}^{-1}$ ) and osmolality rose only slightly to  $96 \pm 8 \text{ mmol} \cdot \text{kg}^{-1}$  within 15 min.

In summary, these experiments showed that osmolality in the cup at the start of nebulization are independent of volume and that osmolality rose in a fashion which was inversely related to the starting volume.

*Relationship between filling volume of the cup and osmolality in the airstream (NaCl and DSCG)*

In figure 2, the comparison of osmolality in the filling cup and the airstream is depicted, showing that airstream osmolality parallels the values in the filling cup. In the airstream the values were significantly higher than in the filling cup ( $p < 0.01$ ) when 5 ml of NaCl was nebulized for 10 or 15 min. The differences were less in smaller starting volumes and were insignificant with DSCG.

In the case of nebulized DSCG no value was measured at 15 min since not enough aerosol was present in the airstream for osmolality determination despite a small amount of residual fluid in the cup.

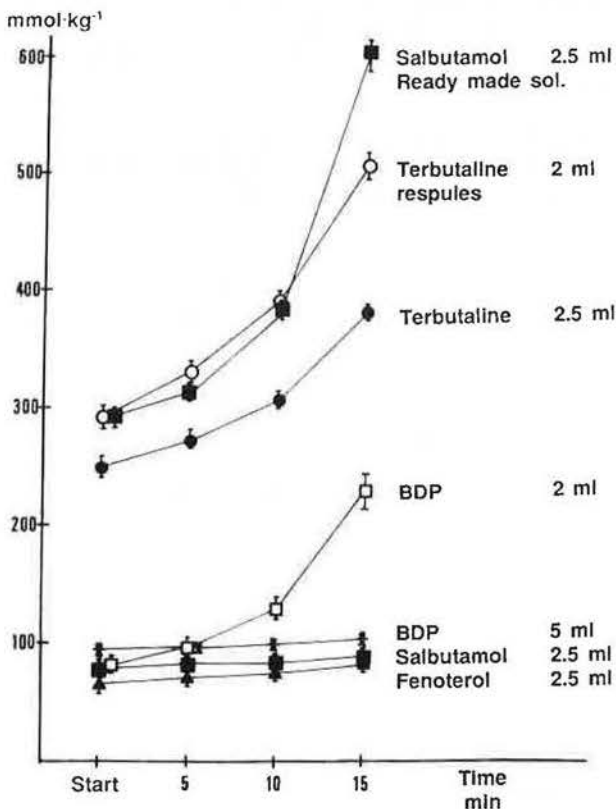


Fig. 3. - Baseline values and osmolality changes in the cup of native, pure drug solutions as they are marketed either as ready to use solutions (salbutamol ready made solution, terbutaline respules, BDP) or as solution for mixing with a carrier (terbutaline, salbutamol, fenoterol) (Novair, Hospitak jet-nebulizer flow  $9 \text{ l} \cdot \text{min}^{-1}$ ). BDP: beclomethasone dipropionate.

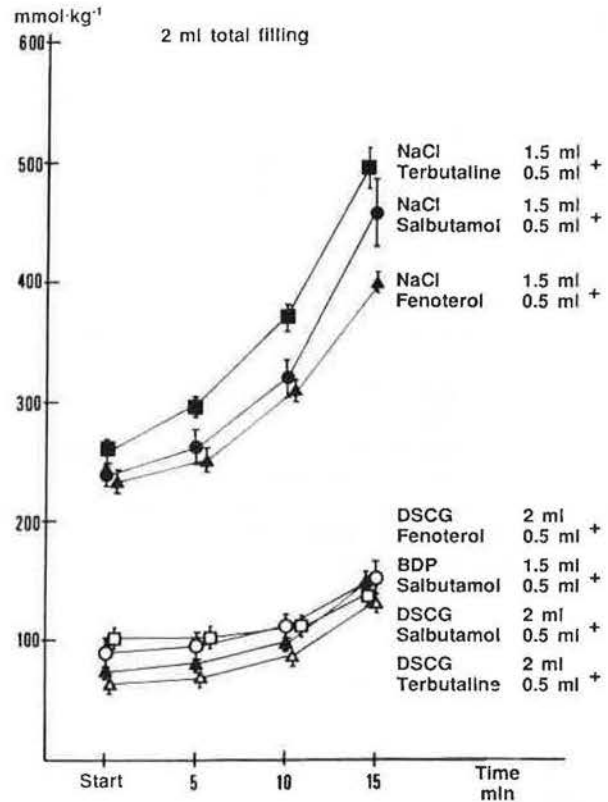


Fig. 4. - Osmolality changes in the cup for self-made mixtures of  $\beta_2$ -agonists with saline or with DSCG or BDP; cup filling volume is 2 ml. (Novair, Hospitak jet-nebuliser flow  $9 \text{ l} \cdot \text{min}^{-1}$ ). BDP: beclomethasone dipropionate.

*Osmolality changes of commercially available ready made solutions and of native drugs: determinations in the cup*

Figure 3 shows the baseline osmolality and changes in native drug solutions as they were taken from the marketed vials and tested undiluted. From the  $\beta_2$ -agonists, salbutamol "ready made solution", terbutaline "respules" and terbutaline 1.0% were isotonic at the start and dramatically increased their osmolality values to ranges from  $386 \pm 2.5 \text{ mmol} \cdot \text{kg}^{-1}$  for terbutaline up to  $624 \pm 34 \text{ mmol} \cdot \text{kg}^{-1}$  for "ready made solution" of salbutamol. Two other brands of  $\beta_2$ -agonists (salbutamol 0.5% and fenoterol 0.5%) were initially hypotonic ( $81 \pm 9 \text{ mmol} \cdot \text{kg}^{-1}$  and  $87 \pm 6 \text{ mmol} \cdot \text{kg}^{-1}$  respectively) and the osmolality did not change with nebulization. BDP, which is a dispersion of small BDP particles in a carrier solution, was initially also hypo-osmolar. BDP time dependent increase of osmolality was seen only when the starting volume was 2 ml (rose to  $243 \pm 23 \text{ mmol} \cdot \text{kg}^{-1}$ ) but not with the 5 ml starting volume.

*Relationship between filling volume of the cup and osmolality of self made drug carrier solutions*

In figures 4 and 5 the results of self made mixtures as they are usually prepared at home by the patients are shown for two starting volumes, 2 ml (fig. 4) and 4 ml

(fig. 5), respectively. In the former 1.5 ml of saline was mixed with 0.5 ml of a  $\beta_2$ -agonist solution (salbutamol 0.5%, fenoterol 0.5%, terbutaline 1.0%). In the latter, 3 ml of saline was mixed with 1 ml of  $\beta_2$ -agonist solution to assure comparable concentrations in the cup. It can be seen from figure 4 that with the 2 ml starting volume all NaCl- $\beta_2$ -agonist mixtures became hyperosmolar with increasing nebulization time, whereas this effect was partially prevented by the higher starting volume (fig. 5). However, when osmolality was measured continuously in the filling cup with the 4 ml starting volume the same increase of osmolality occurred after 20 min. As shown in figure 5, osmolality levels after 10 min of nebulization, which is a reasonable time for treatment, were in the range of 274–322  $\text{mmol}\cdot\text{kg}^{-1}$  for the saline  $\beta_2$ -agonist mixtures which represents an approximate rise of only 100  $\text{mmol}\cdot\text{kg}^{-1}$  from the start of the nebulization period. When  $\beta_2$ -agonists were mixed with DSCG or BDP, hypo-osmolar solutions resulted in little increase after nebulization.

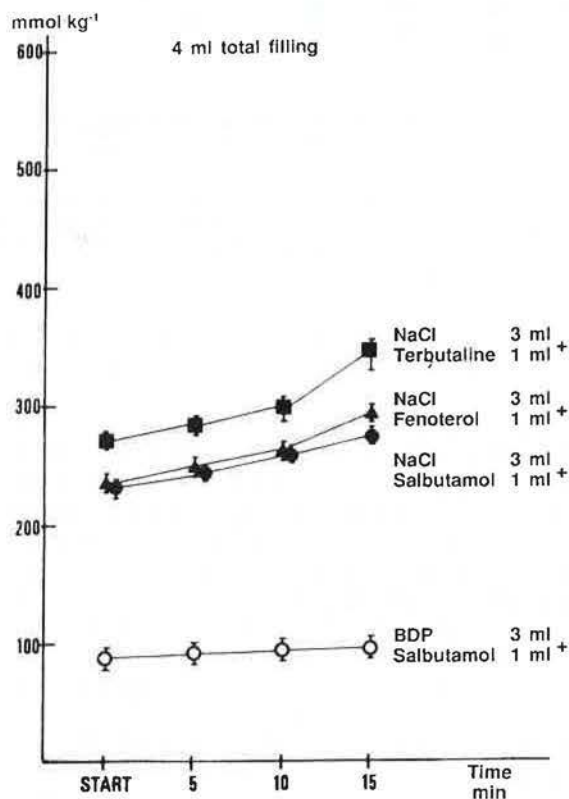


Fig. 5. – As in figure 4 but a cup filling volume of 4 ml. (Novair, Hospitak jet-nebulizer flow 9  $\text{l}\cdot\text{min}^{-1}$ ). Abbreviations as in figure 1–4.

#### Relationship between filling volume and osmolality in the airstream of self made drug carrier solutions

Table 1 gives the osmolality values in NaCl  $\beta_2$ -agonist mixtures measured in the cup and in the airstream. The only statistical difference between airstream and cup osmolality at 15 min was for the salbutamol 1 ml and NaCl 3 ml mixture.

Table 1. – Comparison of osmolality in the cup and in the airstream of self-made NaCl  $\beta_2$ -agonist mixtures. ("Novair, Hospitak" jet-nebulizer flow 9  $\text{l}\cdot\text{min}^{-1}$ )

NaCl 1.5 ml + salbutamol 0.5 ml			
Time	Cup $\text{mmol}\cdot\text{kg}^{-1}$	Airstream $\text{mmol}\cdot\text{kg}^{-1}$	p
start	240±8	245±9	NS
5 min	254±4	268±1	NS
10 min	285±11	345±28	NS
15 min	366±40	-	-
NaCl 3.0 ml + salbutamol 1.0 ml			
Time	Cup $\text{mmol}\cdot\text{kg}^{-1}$	Airstream $\text{mmol}\cdot\text{kg}^{-1}$	p
start	230±1	235±1	NS
5 min	239±2	257±7	NS
10 min	251±2	267±9	NS
15 min	266±2	290±2	0.015

NS: nonsignificant.

#### Osmolality dependence of flow in drug carrier solution (NaCl); determinations in the cup and the airstream

No differences were observed when 3 ml of NaCl were nebulized with either the Novair or the Pari device during the first 10 min. At 15 min the values were significantly higher ( $p < 0.05$ ) for the device with lower flow (Novair); this was only seen in the set of experiments with osmolality determined in the cup but not in the airstream (table 2).

Table 2. – Comparison of the two jet-nebulizers with different flow when nebulizing 3 ml of NaCl; values in the cup and in the airstream are given

NaCl 3.0 ml in the cup			
Time	Novair $\text{mmol}\cdot\text{kg}^{-1}$	Pari $\text{mmol}\cdot\text{kg}^{-1}$	p
start	287±8	283±2	NS
5 min	296±11	290±2	NS
10 min	319±6	301±7	NS
15 min	399±14	322±10	0.040
NaCl 3.0 ml in the airstream			
Time	Novair $\text{mmol}\cdot\text{kg}^{-1}$	Pari $\text{mmol}\cdot\text{kg}^{-1}$	p
start	292±11	311±2	NS
5 min	323±1	350±29	NS
10 min	371±8	360±8	NS
15 min	503±40	391±18	NS

NS: nonsignificant.

#### Discussion

Baseline osmolality of the pure  $\beta_2$ -agonist solutions differed from brand to brand. Alterations in osmolality levels during nebulization could easily be followed in the filling cup and paralleled those in the airstream. Small volumes of sodium chloride became more hypertonic than larger volumes during nebulization, the commercially ready-to-use salbutamol and terbutaline were particularly hypertonic after nebulization in contrast to the simple

nebulizer solutions which were made to be diluted to 4 ml with saline. Osmolality of the beta<sub>2</sub>-agonist solutions did not increase so much on nebulization if the larger (3 ml) volume of saline was used to dilute it and finally the BDP, salbutamol and fenoterol solutions used undiluted remained very hypotonic.

From these data the question arises as to whether these changes in osmolality might affect the bronchial tone. Several drug solutions which we tested were initially hypo-osmolar, and this hardly altered during nebulization. The hypotonicity of DSCG, salbutamol (0.5% solution), fenoterol (0.5% solution) and BDP might, as far as bronchoconstriction could occur, be harmful and is probably as bad as the hypertonicity which results with mixtures of beta<sub>2</sub>-NaCl or with ready-to-use solutions.

Our findings confirm the data of O'CALLAGHAN *et al.* [2] who found changes in the osmolality during nebulization of a mixture of salbutamol and saline. Our results extend their findings on other beta<sub>2</sub>-agonists and show that similar changes are present not only in the filling cup but also in the airstream. Instability and inappropriate tonicity of solutions for inhalation as compared to physiological ionic composition of plasma, tissue and secretions, have been reported earlier with ultrasonic and jet type nebulizers [6, 7]. In the latter it has been shown that these nebulizers concentrate the salt in the liquid of the nebulizer during vapourization when unsaturated air is issued [7]. As a consequence, the ratio of salt and water in the aerosol became less than the same ratio in the liquid in the nebulizer which was, however, dependent upon the type of nebulizer used. Our results demonstrate that in the Hospitak nebulizer (which is marketed in the UK and other European countries under the name Kendall Upmist) changes in osmolality of the liquid in the nebulizer parallel those in the aerosol.

A putative harmful effect of the measured changes in tonicity of the solution upon airway function was not subject to investigation in this paper. It is well known, however, that adverse reactions to inhalation therapy may be caused by hypo- or hyper-osmolality, acidity, preservatives or bacterial contamination of drug solutions. Change in osmolality of the periciliary fluid is believed to be a stimulus for bronchoconstriction, and there seems to be a difference in the nature of the response to hypertonic or hypotonic solution [8]. In asthmatic adults a fall of the forced expiratory volume in one second (FEV<sub>1</sub>), representing bronchoconstriction, was not seen with hypo- or hyper-osmotic stimuli in the range of 150–549 mosmol [9]. However, these observations were made after inhalation of ultrasonically produced aerosols; others reported increased sensitivity for osmotic provocation when osmolality increased above a level of 320 mosmol·l<sup>-1</sup> [10].

The efficacy of inhalation treatment with mixtures of beta<sub>2</sub>-agonists and saline has been proven over decades by clinical experience. If paradoxical reactions occur, which is theoretically possible, it remains to be determined whether this is limited to babies or small infants. A recently published study showed that the potency of beta<sub>2</sub>-agonist was greater than the osmotic stimulus and, thus, concealed any potential bronchoconstriction [11].

These results are consistent with reports already published [12].

Bronchoconstriction was demonstrated for ipratropium bromide suggesting that the hypotonicity of this solution was responsible for the paradoxical reaction [13]. However, the commercially available ipratropium bromide exhibited an osmolality of 7.5 mmol·kg<sup>-1</sup>, a very low value which we did not observe in our tested solution. On the other hand, when ipratropium bromide was mixed with saline no detrimental effects were seen, even in babies [14]. These observations are consistent with ours, that pure solutions of commercially available beta<sub>2</sub>-agonists which are hypo-osmolar become iso-osmolar when mixed with saline (figs. 3 and 4 for baseline values).

The increase of osmolality during nebulization is not fully understood. Our results however support the hypothesis that the content of sodium chloride is of some importance. On the other hand, the major changes always occur to the end of a nebulization period, when the cup empties. There are several possible explanations of this effect. Firstly it might be that the solutions of beta<sub>2</sub>-agonists with saline are unstable and, therefore, change their hygroscopic character when exited by the air jet. Secondly it is known that up to fifty percent of a liquid nebulized by the Venturi effect of compressed gas becomes permanently entrapped upon the baffle, and the balance between aerolized and condensed liquid is a prerequisite for proper aerolization. If the total amount of liquid becomes too small, a certain amount of evaporation may occur. Thirdly, it is normal practice to drive air compressed nebulizers with dry air which enhances evaporation. Whether the same changes would occur if water saturated air is used is unclear. However, our results also revealed that air flow does not greatly influence the osmotic changes during nebulization despite the dependence of particle size from flow.

The present results demonstrate, as was anticipated by O'CALLAGHAN *et al.* [2], that osmotic changes occur during nebulization of commercially available nebulizer solutions. Whether these changes, however, are of importance for every asthmatic child remains to be determined. The recommendation to use higher starting volumes in the filling cup to compensate for hypertonicity is in our mind over-cautious [11]. Based on the results of studies on babies, which have been challenged on the basis of being unreproducible due to technical problems [12, 14, 15], generalized recommendations of increasing filling volume in the nebulizer cup, as given by O'CALLAGHAN [2], are not justified and need further confirmation with refined techniques.

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*Modifications d'osmolalité dans les solutions pour nébuliseur.* M.H. Schöni, R. Kraemer.

RÉSUMÉ: Des effets paradoxaux (bronchoconstriction au lieu de bronchodilatation) ont été observés après inhalation de beta<sub>2</sub>-mimétiques par des enfants asthmatiques; il fut supposé que cela pouvait être du à des changements d'osmolalité et de pH dans la solution pour aérosol. Nous avons étudié les modifications relatives à l'osmolalité dans des solutions pour aérosols disponibles dans le commerce au cours de 5, 10 et 15 minutes de vaporisation au moyen de deux nébuliseurs à compression commercialisés (flux de 9 l·min<sup>-1</sup> et de 12 l·min<sup>-1</sup>). L'osmolalité dans le récipient du nébuliseur et dans la vapeur émise fut déterminée par mesure de la microosmolalité. Dans une solution physiologique de chlorure de sodium vaporisée à partir de volumes initiaux de 1 ml, 2.5 ml, 3 ml et 5 ml, l'osmolalité (282±7 mmol·kg<sup>-1</sup> au départ) augmenta jusqu'à 432±18 mmol·kg<sup>-1</sup>, ceci en fonction du volume et du temps. Les solutions originales de salbutamol (solution prête à l'emploi) et de terbutaline (ampoules respules) étaient isotoniques, tandis que le fénotérol, le cromogylcate disodique (DSCG), le dipropionate de béclométhasone (BDP) et la solution de salbutamol à 0.5% (pour appareils aérosols) étaient hypo-osmotiques (60-100 mmol·kg<sup>-1</sup>). Lors de la vaporisation de 1.5 ml de soluté physiologique et de 0.5 ml de la solution active originale (salbutamol, terbutaline, fénotérol) durant 10-15 min, l'osmolalité des mélanges augmenta jusqu'à 420-500 mmol·kg<sup>-1</sup>. Par contre, les mélanges associant beta<sub>2</sub>-mimétiques et DSCG ou BDP demeurèrent hypo-osmolaires. Des changements d'osmolalité identiques à ceux observés dans la solution pour aérosol furent détectés dans la vapeur émise. Ce travail met en évidence les modifications osmotiques se produisant après 10-15 min de vaporisation; elles varient en fonction de la composition du mélange et de la quantité de solution dans le récipient du nébuliseur. Quand l'on observe des effets paradoxaux chez les patients soumis à un traitement par inhalation, il faut tenir compte de ces variations osmotiques.

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