Clinical Efficacy of Nebulized Drugs

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ABSTRACT

There is a mandatory need for effortless drug administration to young children since the prevalence among them of recurrent wheezing is 15-20%. It is becoming increasingly evident that many of these children respond dramatically well to beta2-agonists and topical steroids; accordingly this sub-group of children should be treated as asthmatics. The dose of topical steroids is critical as opposed to that of beta2-agonists which are often administered in doses well above the minimal effective dose. Budesonide suspension has proven its efficacy in adults in a study of 21 patients with asthma treated with budesonide suspension delivered from a nebulizer activated during inspiration versus metered dose inhalation (MDI) via a large-volume spacer. Nebulized in this manner the suspension exhibited a dose-dependent effect, apparently equipotent to the MDI administration as evaluated from daily peak expiratory flow measurements and symptom scoring. Continuous nebulization of budesonide in 18 schoolchildren with bronchial asthma similarly showed a dose-dependent improvement of lung function and symptom score, though in a 1:2 potency ratio as compared to MDI administration, probably due to loss of nebulized aerosol during expiration. In a subsequent study of 23 young children unresponsive to beta2-agonist therapy, nebulized budesonide was without demonstrable effect. Recently, a study of 31 young children with steroid-dependent asthma demonstrated a significant improvement from continuous nebulization of budesonide 1mg twice daily. In conclusion, the efficacy of nebulized budesonide has been convincingly demonstrated in patients with reversible symptoms of asthma. However, we still need to define the minimal effective dose to be recommended in the treatment of young children.

INTRODUCTION

The clinical data on the effect of nebulized steroids are a poorly documented area. The question is not whether topical steroids are efficacious drugs, since they are well documented as being highly efficacious in adult patients, in schoolchildren, and even in young children and infants with asthma. But with nebulization we need to know whether the drug is delivered, and at what concentrations. As

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clinicians we need to be able to compare the doses given by nebulization with a known gold standard such as the metered dose inhaler (MDI). Only seven studies on these issues have been reported in the literature.

**STUDIES OF EFFICACY**

**Beclomethasone**

Three of the seven studies concerned beclomethasone dipropionate, the first of which was published seven years ago (Webb et al., 1986). Although 20 children were admitted, only 13 completed the trial and were included in the results. The study was of randomized, placebo-controlled crossover design with treatment periods of eight weeks. Beclomethasone dipropionate 150μg was administered an uncertain number of times during the day, nebulized from a Pari Inhalerboy. Active treatment was found to have no significant effect.

In a second, parallel, placebo-controlled study (Storr et al., 1986), 29 children with asthma were given beclomethasone, 100μg twice daily from an Acorn nebulizer, for a six-month treatment period. There was a significant improvement in the clinical scoring of wheezeinass, as well as in the number of times they had to take a beta2-agonist.

The third study was also of parallel, placebo-controlled design (Carlsen et al., 1988). Forty-four children were given beclomethasone, 100μg twice daily from a Pari nebulizer, for an eight-week treatment period. The criteria for inclusion in the trial were that they had been admitted to hospital with acute bronchiolitis and had subsequently suffered from recurrent wheezing - children whom we may consider as asthmatic patients. Treatment had a pronounced effect on symptom scores, the use of rescue medication, and the length of time until the first respiratory illness or the first episode of bronchial obstruction. The increase in time until the next episode of bronchopulmonary obstruction was highly significant (p=0.01). The time to maximal effect of inhaled steroids in these patients was 6-10 weeks which is quite long.

A fair conclusion from these three studies of beclomethasone would be that the nebulized drug may have a clinical effect in the concentrations used. However, we need to know how its efficacy and relative potency compared with the known data from MDIs, before we can recommend this formulation for clinical use.

**Budesonide**

Subsequent published studies have all employed budesonide in suspension. The first included 23 children with a mean age of 10 months (range, 3-17 months). They were 'infants considered to have severe asthma, because all suffered from recurrent coughing and wheezing unresponsive to nebulized beta-agonist' (Van Bever et al., 1990). The study was of crossover, placebo-controlled design with four-week treatment periods. Budesonide 500μg was given twice daily from an Econeb nebulizer. Active treatment had no significant clinical effect.

There are, however, several points to note about the study before drawing conclusions. The number of patients was small, increasing the risk of a type II error; the treatment period was short for establishing maximal effect; the nebulizer output was unknown; and, finally, since children who are unresponsive to a beta2-agonist would not normally be termed asthmatic, an alternative diagnosis should probably be considered for some of the children included in the study.

The second budesonide study included 31 children with a mean age of 27 months (range 10-60 months) who had severe asthma and had been prednisone-dependent (a minimum of 0.75mg/kg on alternate days) for the previous two months (Ilangovan et al., 1993). They were treated twice daily with budesonide 1000μg nebulized from a Hudson nebulizer. The study was of parallel, placebo-controlled design with an eight-week treatment period and an eight-week open follow-up treatment period. The children showed significant improvement in clinical scoring as well as in the requirement of oral...
prednisolone. In the run-in period the children were given health scores which improved significantly during the period of active treatment, whether this preceded or followed the placebo period. This study seemed to attest to the efficacy of the drug.

STUDIES OF RELATIVE POTENCY

The question of relative potency has been addressed in two further studies reported to the meeting of the European Respiratory Society in Freiburg in 1989. One was of randomized, crossover, placebo-controlled design and included 18 children, aged 6-15 years, with asthma. Treatment was with either 500μg, 1.0mg or 2.0mg budesonide twice daily delivered by continuous nebulization to dryness from a Pari nebulizer. At the end of the study the children were treated with budesonide 200μg twice daily from an MDI via a spacer. The outcome showed that nebulizer treatment had a dose-dependent effect on symptom scoring, lung function, and the use of rescue medication, as well as producing a dose-dependent decrease in urinary cortisol, thus confirming the delivery of the drug to the child. The relative potency ratio between nebulized suspension and MDI was 1:2 (Pedersen, 1989).

The second of these studies was another randomized, crossover, placebo-controlled trial in 21 adult asthmatic patients, who were treated with budesonide suspension 1mg or 2mg twice daily, delivered by intermittent nebulization to dryness by a Wright nebulizer, or with budesonide 0.8mg twice daily from an MDI via a spacer. The results showed dose-dependent effects on symptom scoring, peak flow and use of rescue medication, as well as on plasma budesonide levels. The potency between nebulizer and MDI was 1:1 (Bisgaard, 1989).

CONCLUSION

Nebulized budesonide suspension has a beneficial dose-dependent effect in bronchial asthma which is apparently equipotent with that of budesonide delivered by metered dose inhalation. This conclusion is based on data from studies employing daily symptom scoring, peak expiratory flow measurements and efficient breath-activated nebulization.

REFERENCES


QUESTIONS

SMALDONE: Why do you think the study of Van Bever et al. failed to show a significant effect of active treatment? Did the infants get the drug?

BISGAARD: There are several points to note about the study; the number of patients was small, increasing the risk of a type II error; the period of treatment was short for establishing a maximal effect; the output of the nebulizer was not known; and, lastly, since children unresponsive to a beta2-agonist would not normally be regarded asthmatic, an alternative diagnosis should probably be considered for some of those children who were included in the study.

SMALDONE: The urine was analysed for cortisol in subsequent studies but not in that study?

BISGAARD: Not in that study, no.

SMALDONE: That is important. It could be that for some reason the drug was ineffective in that population, but it also could be that it did not reach the children.

BISGAARD: Most probably.

MICHAEL NEWHOUSE (Ontario, Canada): The last study showed that budesonide was equipotent whether delivered by MDI or nebulizer. This must be the only study I have ever seen in which an MDI with holding chamber was similar in its efficiency to a nebulizer. I would be very interested in knowing the efficiency of the particular nebulizer used.

Secondly, relatively large amounts of drug were used in both systems. But the amount that we would expect to reach the lower respiratory tract with a nebulizer is much less than we would expect with an MDI. Could it be that there is a plateau to the response curve with both systems and that, in fact, they are not equipotent at all, but that if large enough doses are chosen, the responses will be much the same?

BISGAARD: Are we on the plateau part of the dose-response curve? No, we are not since we continue to see the dose-related increases in peak flow, in symptom score and so forth.

Regarding the nebulizer we used. It was a Wright nebulizer driven by a CR60 compressor giving a flow rate of 8L/min, which is very efficient. We used face-masks, but note that nebulization was intermittent. It was finger triggered. The patients did not have the same loss of aerosol during expiration that we would normally see during continuous nebulization. They inhaled and activated the nebulizer and that may explain the documented equipotency.

NEWHOUSE: It may be useful to be able to use nebulizers as an alternative to MDIs and a holding chamber, or a holding chamber with mask. But nebulizers are extremely expensive and cumbersome, the parents have to fiddle with drug solutions, the children have to keep them on for 10 minutes, and so on. There are many disadvantages to nebulizers. It seems to me that this is a backward step. We are much better off if we can use a pressurized canister system and a holding chamber with a mask and low resistance; put it on the child's face, and 5 seconds later the dose of medication has been delivered. It is important to discuss practicality and cost benefit.

BISGAARD: I could not agree more. But the mainstay of treatment in young children and infants is the jet nebulizer, at least in Europe; therefore steroid treatment has to be available for these devices. But for the future I fully agree that we should develop better delivery systems.

QUESTION: At least one of the studies had a rather short treatment period of four weeks. Is there a period effect? And, if so, how would it influence the results?

BISGAARD: There is certainly a risk of a period effect. It would influence the results by tending to increase the risk of a type II error. But as we saw an effect, I do not think we have that problem. If we had not seen an effect I would have been very worried. The Van Bever study had a similar crossover design and a four-week treatment period; the lack of effect of active drug could be ascribed to carry over.

QUESTION: In order to quantify the dose, various volume fills were used, in some 2ml, in others 4ml; some nebulizing machines ran for 5 minutes and some ran to dryness. We are trying to equate one form of medication, the MDI, for which we know precisely to the milligram what is delivered to the patient, with another, the nebulizer, for which the dose in the respirable fraction is an unknown quantity. Many nebulizing machines leave more than half the 2ml fill unused. The patient may not inhale the amount of drug that is actually available. Would you clarify the situation?
BISGAARD: The study documenting equipotency between nebulized suspension and MDI was the one in which the Hudson nebulizer with breath-activated nebulization was used. This is a very efficaceous nebulization. Certainly, a considerable dose of steroid is retained in the nebulizer, but equally certain is that a plastic spacer retains a considerable fraction of the steroid aerosol. Previous studies comparing the dose-delivery from nebulizers and MDI has not to my knowledge used breath-activated nebulizer systems, which may explain the relatively poor performance of the nebulizers.

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