How much nebulised budesonide reaches infants and toddlers?

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Abstract

The amount of budesonide suspension actually delivered to six subjects (aged 4-30 months) by a jet nebuliser and spacer system (System 22) was determined. Two nebulisations were performed in each subject using a filter at the exhalation outlet of the inhalation chamber. An inhalation filter was additionally attached between the facemask and the spacer in the first test. The drug was inhaled during the second test. The nebuliser equipment was washed with ethanol and the amount of drug deposited was determined.

The amount of budesonide deposited in the exhalation filter increased when the inhalation filter was omitted. Only 14% of the nominal dose (500 µg) of budesonide was found in the inhalation filter, increasing from nine to 19% with increasing age. Approximately 75% of the nominal dose was found in the nebuliser equipment.

These findings must be considered when deciding the nominal dose of budesonide suspension to be given to infants and toddlers.

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Delivery of inhaled drugs to infants and toddlers presents problems as they cannot cooperate sufficiently to use available drug inhalers. Pressurised metered dose inhalers connected to spacers with valve mechanisms and facemasks are prescribed for drug delivery to many infants. This technique, however, is not ideal as the existing valves used in the spacers function poorly at low inspiratory flows. There is also growing concern about the propellants used in the metered dose inhalers. Consequently nebulisers are often used for drug delivery by the inhaled route to infants and toddlers.

Budesonide, an inhaled corticosteroid, is available as a suspension for nebulisation. The dose recommendations are (as for all inhaled corticosteroids) based on information from clinical studies in adults and children in whom lung function can readily be measured. This information is then extrapolated to form guidelines for dose recommendations of the inhaled drug when treating infants and toddlers. Little information is available about doses of inhaled corticosteroids required to treat asthma in early childhood.

As part of a clinical trial we wanted to determine the amount of drug actually reaching the patients when using a nebuliser for drug delivery and following the accepted guidelines for drug dosage.

Subjects and methods

Six male infants and toddlers with a mean age of 15.7 months (range 4-30 months), all with bronchial asthma, were included in the study after informed consent from their mothers. The patients participated in a clinical trial approved by the regional ethics committee in which they received regular treatment with budesonide suspension for nebulisation delivered by the same nebuliser equipment as used in this study.

Jet nebulisation was performed by System 22 (figs 1 and 2); an Acorn nebuliser (Medic-Aid) connected to a Mizer inhalation chamber (Medic-Aid) driven by a CR60 compressor (Medic Aid) at 8 l/min. A facemask (Vital Signs Inc) closely fitted by an air inflatable cuff was connected to the Mizer's drug outlet and held firmly onto the face of the subject.

Two nebulisations were performed on the same day for each patient during an outpatient visit. In the first nebulisation (test 1) two Respirgard-II MQ-303 filters (Marquest Medical Products) were used, one between the facemask and the Mizer's drug outlet (inhalation filter) and the other at the opposite end of the T tube (exhalation filter) (fig 1). In the second nebuli-

Figure 1 Outline of the inhalation equipment used in test 1. F=facemask, I=inhalation filter, E=exhalation filter, M=Mizer, A=Acorn nebuliser.

sation (test 2) only the exhalation filter was used, thus the patients inhaled the drug (fig 2). The decrease in pressure over the Respigard-II filter at a flow of 60 l/min is equivalent to approximately 6 mm H₂O. By sucking 25 doses of budesonide (each 0.4 mg) from a Turbuhaler (Astra) through the filter it was found that as little as 0.21% of the total dose passed through the filter (unpublished data). One commercially available respule of 500 µg budesonide suspension (250 µg/ml) was used for each test. The nebulisation time was five minutes for one patient and seven minutes for the other patients.

Each part of the nebulisation equipment was thoroughly washed with spectrometrically pure ethanol and the residual amount of budesonide was determined by reversed phase high performance liquid chromatography at Astra Draco.

Statistical analysis was performed with a

personal computer Number Cruncher Statistical System package, and the values are given as means with 95% confidence intervals (CI) in parentheses unless stated otherwise. Correlation analysis was performed by the Spearman rank correlation test. Differences were considered significant under the 5% level.

Results

The table gives the various amounts of budesonide suspension found in the filters and in the washings of the nebuliser parts. Of the total amount of 500 µg budesonide used in each of the 12 tests a mean of 301 µg (280–321 µg) was deposited in the nebulisers, a mean of 45 µg (32–58 µg) in the Mizers, and a mean of 26 µg (13–38 µg) on the exhalation filters. This gives a total mean of 378 µg which is about 76% of the nominal dose.

A mean of 70 µg (46–95 µg) budesonide was deposited on the inhalation filter (test 1), which is 14% of the nominal dose. No budesonide was found in the facemasks in test 1, but in test 2 a mean of 6 µg (0–15 µg) was found.

The deposition of budesonide on the exhalation filter in test 2 (mean 38 µg; 20 to 56 µg 95% CI) was significantly higher ($p<0.03$) than in test 1 with the inhalation filter present (14 µg, 0 to 28.6 µg 95% CI). Six respules were analysed and had a remaining mean amount of 43 µg (17 to 69 µg) budesonide.

There was no statistically significant difference between the amount of budesonide deposited in the nebuliser equipment in test 1 compared with test 2.

The amount of budesonide deposited on the inhalation filters increased with increasing age (table) from 9% of the nominal dose in the four month old infant to 19% in the 30 month old toddler. The Spearman correlation factor was 0.71, but this was not statistically significant due to the low number of patients.

A mean amount of 32 µg budesonide was not accounted for in test 1.

Discussion

To determine a therapeutic dose of an inhaled corticosteroid for any patient it is essential to know the dose delivered to the patient and the size of the drug droplets. Newman *et al*¹ found that median mass diameter of a budesonide suspension delivered by an Acorn nebuliser and

Figure 2 Outline of the inhalation equipment used in test 2. F=facemask, E=exhalation filter, M=Mizer, A=Acorn nebuliser.

Amount of budesonide found in various parts of the nebulising equipment for each subject for test 1 (with filter at inhalation) and test 2

Subject No	Age (months)	Test	Budesonide found (µg)					
			Nebuliser	Mizer	Inhalation filter	Exhalation filter	Facemask	Respule
1	4	1	317	44	49	33	—	—
		2	321	41	—	49	0	—
2	13	1	342	26	48	4	—	27
		2	241	18	—	9	2	25
3	4	1	308	41	77	2	—	34
		2	318	31	—	39	1	21
4	15	1	291	30	56	6	—	73
		2	249	51	—	45	5	76
5	30	1	283	60	107	31	—	—
		2	308	99	—	57	18	—
6	28	1	341	43	85	7	—	—
		2	287	55	—	30	8	—

CR60 compressor was 5.2 µm. The droplet size of the nebulised suspension is therefore within the optimum respirable range. In a second study Newman *et al*² showed that the output of budesonide suspension with the Acorn nebuliser and the CR60 compressor was 35% of the nominal dose when using a volume fill of 2 ml. Clinically, however, information about the amount of drug actively inhaled is equally important as the detailed knowledge of output by a nebuliser system. Our results show that less than 20% of the nominal dose reached the patient.

The reason for this discrepancy is difficult to explain. We chose a nebuliser equipped with a spacer to avoid spilling of the drug into the environment by a continuously working nebuliser. This would otherwise have occurred as the minute volume of infants and toddlers is smaller than the aerosol output by the nebuliser and compressor system at 8 l/min. Even the nebuliser and spacer system seems to be of limited benefit in terms of drug delivery to the patient, however, as local deposition in the spacer occurs when the nebuliser's output exceeds that of the minute volume of the patient. The deposition in the Mizer was, however, small compared with the almost 75% of the nominal dose found in the nebuliser, the latter finding agreeing with previously reported results.²

As steroids are soluble in lipids (in contrast to the commonly used β₂-agonists and sodium cromoglycate), any water based drug delivery must be in the form of a suspension. This increases the viscosity of the suspension, slowing down the nebulisation time even though the aqueous part of the suspension is readily nebulised. The nebulising time did not influence our results, however, which may be explained by the findings of Newman *et al* that the optimum nebulisation time for a budesonide suspension is five to six minutes.² Other studies with water soluble substances have shown similar results, such as that of O'Callaghan *et al* who suggested that the optimum nebulisation time for sodium cromoglycate was five minutes, by which time 80% of the total drug output was nebulised.³

The amount of drug not accounted for in test 1 (mean 32 µg) may have escaped through the air entrainment hole on top of the spacer or remained in the respule.

The exact amount of drug deposited and its distribution within the lungs in our patients is not known. Silverman has argued that drug delivery by jet nebulisers to a freely breathing young infant is negligible.⁴ Watterberg *et al*, however, stressed that giving drugs by this route, albeit with a small yield, was not futile.⁵

The variation (approximately 10%) of dosage deposited in the nebuliser equipment was not greater than would be expected from commercially available systems. The finding that as little as 15–20% of the nominal dose was available under optimum conditions for inhalation by these patients is worrying, however.

Unfortunately there are limited ways of delivering inhalation steroids to toddlers and infants, though various spacer devices attached

to metered dose inhalers do exist. As there is increasing concern about the propellant gases in the metered dose inhalers, nebuliser solutions or suspensions of drugs are becoming more important as a means of drug administration. Furthermore, Zainudin *et al*, measuring the deposition of bronchodilators in the lungs of adults, found a significantly higher peripheral deposition of drugs using a nebulised solution rather than dry powder or metered dose inhaler.⁶ They also showed that gastrointestinal deposition was significantly lower with the nebulised solution compared with the metered dose inhalers, though the total amount of drug delivered by these two systems did not differ significantly. These results obtained in adults may not be directly transferable to children. It may be assumed, however, that the amount of respirable particles reaching the lungs rather than the gastrointestinal tract in infants is higher with nebulised rather than pressurised aerosol drug delivery.

An unexpected finding in our study was the discrepancy of drug deposition on the exhalation filters with an inhalation filter present or absent. This phenomenon was seen in all our subjects and a rationale for this is lacking. As the resistance in this hydrophobic filter is low it is unlikely that this influenced the results. It may be speculated that some of the drug 'stuck' to the inhalation filter which, when this was omitted, would be exhaled and deposited on the exhalation filter. This raises the question that our estimates of available drug to the subjects might even be too optimistic!

When treating infants with inhaled corticosteroids it is imperative to keep the potential systemic side effects to a minimum. Thus even if the amount of drug delivered to the infant is similar using a metered dose inhaler with a spacer attached or a nebuliser, it seems advantageous to use a nebuliser for this type of drug. However, with as much as 80% loss of active drug with the current nebuliser systems, the costs of treatment could potentially be greatly reduced if more efficient delivery systems were available. The important conclusion to draw is that the huge loss of active drug to the delivery system must be considered when treatment dosage is determined for the individual patient. Furthermore it is important to establish which factors determine the drug delivery for inhalation with respect to the age and tidal volume of the patient.

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