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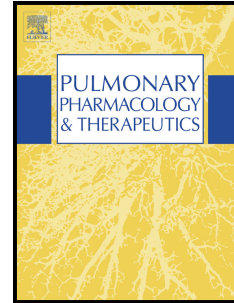
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Inhaled Corticosteroid Therapy with Nebulized Beclometasone Dipropionate

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Abstract

Inhaled corticosteroids (ICS) are the most effective anti-inflammatory agents for the management of chronic persistent asthma, and are therefore recommended as first-line antiasthmatic therapy in children and adults. In various settings, the administration of ICS via nebulizer rather than hand-held inhaler (HHI) may have certain advantages, as many patients with HHI fail to use these devices properly or efficiently. In particular, young children, the elderly, the acutely ill, and those with restricted dexterity may be unable to coordinate inhalation with actuation of the device or to generate sufficient inspiratory flow to operate breath-actuated devices effectively. Compliance with nebulized therapy may also be better than that with a pressurized metered-dose inhaler (pMDI) plus spacer.

Systematic reviews conclude that there is no significant difference in clinical effects between nebulizers and HHI. Performance and clinical effect of nebulization are influenced by several technical aspects such as the nebulizer-drug combination, nebulizer type, output and lung deposition. Among the currently available ICS, nebulized beclometasone dipropionate (BDP) has been in clinical use for more than 35 years, and has demonstrated marked clinical efficacy and a favorable tolerability profile in children and adults with chronic persistent asthma. The clinical efficacy of nebulized beclometasone is discussed in the present review using data from 13 published studies, which included a total of 1250 patients. Three multicenter, randomized, double-blind studies showed that nebulized BDP is as effective as BDP via pMDI plus spacer in a 2:1 dose ratio. Controlled trials involving 497 adults and children demonstrated similar clinical efficacy between nebulized BDP and either nebulized fluticasone propionate or nebulized budesonide. In all these trials, treatment-related adverse effects were generally uncommon, most were mild to moderate in severity, and most were associated with the respiratory system. Meta-analyses show that BDP, like other inhaled corticosteroids, has no major influence on patient height, urinary cortisol concentration, or bone metabolism, thus suggesting the absence of growth retardation or any marked effect on adrenal function or the hypothalamic-pituitary-adrenal axis when used in the approved dose range.

Overall, nebulized BDP appears to have a particularly important place in asthma therapy: as a general alternative to HHIs (e.g. in patients with poor HHI compliance); when patients such as children or the elderly are unable to operate HHIs because of poor hand–lung coordination, lack of cooperation, or low inspiratory flow rate; and when high dosages of ICS are required, such as in adults with severe, corticosteroid-dependent asthma.

Key Words: beclometasone dipropionate; chronic persistent asthma; hand-held inhalers; inhaled corticosteroids; jet nebulizers; nebulization; nebulizer therapy; ultrasonic nebulizers

1. Introduction

Inhalation therapy for asthma is an ancient treatment; indeed, the first use of such therapy can be tracked to India almost 40 centuries ago [1]. However, the predecessors of modern-day nebulization were probably the compressed-air nebulizers first used at health spas more than 150 years ago [2]. Subsequently, the pressurized metered-dose inhaler (pMDI) and breath-actuated dry-powder inhaler (DPI) were introduced in the 1950s and 1960s, respectively [1].

Among the first antiasthmatic drugs administered via nebulizers and pMDIs were the inhaled, nonselective β -agonists adrenaline and isoprenaline [1, 2]. However, these drugs were superseded by the selective, short-acting β -agonist salbutamol, and inhaled corticosteroids (ICS) such as beclometasone dipropionate (BDP), in the late 1960s and early 1970s [1]. Subsequently, BDP and ICS dramatically transformed the management of chronic asthma [3], and indeed, it is now widely recognized that regular long-term use of low-dose ICS is associated with effective symptom control, reduced disease severity, prevention of exacerbations, enhanced pulmonary function, and decreased mortality in patients with chronic asthma [4, 5].

Traditionally, nebulization involved application of an external force to convert a drug solution or suspension into an aerosol. Interestingly, the main predecessor to the modern-day, hand-held pneumatic nebulizer was the Wright nebulizer introduced in the late 1950s [2, 6]. This device, made of perspex, was based on gas flow, precise venturis, and baffles to provide aerosolized particles in the range 1–5 μm [6]. Major advances were then made in device, propellant, and formulation technology via theoretical modeling studies, particle-sizing techniques, *in vitro* studies of particle deposition, and pharmacokinetic and pharmacodynamic analyses [7]. Facilitating these advances were developments made in γ -scintigraphic, SPECT, and PET studies of pulmonary deposition and regional distribution after nebulized, radiolabeled drug administration to asthmatic patients [8].

This review details the current role of nebulized ICS therapy and that of nebulized BDP, particularly in children and adults with chronic asthma. Separate PubMed searches were performed using the search terms ‘inhaled corticosteroids’ AND ‘nebulizer’ AND ‘chronic asthma’; ‘beclometasone’ AND ‘nebulizer’ AND ‘chronic asthma’; and ‘inhaled corticosteroids’

AND 'nebulizer' AND 'drug deposition'. Based on their relevance to the current topic, specific citations were selected from the search results and then included in the review.

2. Treatment of the upper and lower airways

Inhaled drugs are used in various respiratory diseases and other conditions; such drugs have proved an effective means of delivering appropriate doses to affected areas of the airways in both the upper and lower respiratory tract. Important advantages of inhaled drugs over their systemically administered counterparts include the following [6, 9]:

- To achieve the same pharmacologic effect, inhaled administration allows the use of lower doses (μg vs mg levels with inhaled vs oral administration) that reach high local concentrations in the affected areas.
- The percentage amount of drug reaching the systemic circulation is lower as compared the oral route.
- Consequently, the systemic availability and associated systemic adverse events are lower with inhaled administration of drugs (e.g. with ICS, less suppression of the hypothalamic-pituitary-adrenal [HPA] axis).
- Faster onset of effect (e.g. the onset of action for inhaled salbutamol is within few minutes, compared with a value of about half an hour for oral salbutamol).

These advantages suggest that nebulization therapy can be used to effectively treat several diseases of the upper and lower airways, including allergic rhinitis, sinusitis, croup, cystic fibrosis, bronchiolitis, bronchopulmonary dysplasia, chronic bronchitis, chronic obstructive pulmonary disease (COPD) and asthma. Depending on the specific condition, nebulized drugs may include antibiotics, mucolytics, anticholinergic and adrenergic bronchodilators, corticosteroids or combinations of these.

There is relatively little evidence for nebulized drugs with regards to the treatment of inflammatory diseases of the upper airways. However, the pharmacologic rationale of targeting the mucosa, where allergic or inflammatory processes take place, is clear and has been confirmed by the widespread use of nebulization in clinical practice. Allergic rhinitis treatment guidelines suggest that intranasal corticosteroids are the most effective drugs for this indication, although

the majority of studies to date have involved specific nasal sprays rather than nebulizers [10]. Nevertheless, guidelines for the management of sinusitis in children consider inhaled corticosteroids as an adjuvant therapy used to supplement the effect of antimicrobials [11]. Indeed, low-dose BDP has been shown to significantly increase the activity of antibiotics against *Chlamydomypha pneumoniae* [12].

This review will focus on the use of nebulization therapy with corticosteroids, in particular BDP, for the treatment of asthma.

3. Nebulization in asthma

The first documented use of drug nebulization for asthma was in 1912, when Ephraïm used adrenaline to treat acute asthma [13]. ICS were first used in the 1940s when Tiffeneau used nebulized hydrocortisone, which provided slight improvements due to the systemic absorption of this formulation [14]. The subsequent introduction of ICSs such as BDP, which act directly on the lungs with minimal systemic effects, led to substantial improvements in asthma treatment [2].

3.1 Treatment guidelines

Detailed guidelines exist regarding the use of nebulizers and nebulized drug therapy in asthma: these include 1997 British Thoracic Society (BTS) guidelines [15], 2001 European Respiratory Society guidelines [16], and 2008 updated recommendations from the Global Initiative for Asthma (GINA) [17]. Importantly, ICS are the most effective anti-inflammatory agents for the management of persistent asthma, and are therefore recommended as first-line antiasthmatic therapies in children of all ages, adolescents, and adults [17]. Various studies have documented the antiasthmatic efficacy of ICS in the following respects: reduction of symptoms, airways' inflammation and hyper-responsiveness; reduction of the frequency and severity of exacerbations, and mortality; and improvement of pulmonary function, and quality of life [17]. Most notably, 93% of prescribed canisters contained low-dose BDP in the only available study to demonstrate a reduction in asthma mortality with ICS therapy [4]. Regarding specific recommendations for the use of nebulized ICS therapy, however, the abovementioned guidelines provide rather limited and sometimes discrepant viewpoints (Table 1) [15-17].

Such minimal and occasionally divergent information may result, to some extent, from the tremendous variability that exists between European countries in the proportions of physicians who prescribe nebulized ICS [18].

While guidelines recommend the use of a compressor-driven nebulizer with a face mask as a second choice to pressurized metered-dose inhalers in conjunction with a dedicated spacer with face mask for preschool children [17], nebulizers are still frequently used in clinical practice to overcome problems with inhalers' technique [16, 19], and nebulized corticosteroids have been shown to be effective [20]. Indeed, infants and many other subjects such as the elderly often lack the coordination and understanding necessary to use pMDIs [21]. Additionally, neuromuscular disorders, arthritis, or other diseases may restrict the ability of patients to use hand-held devices. Moreover, a recent survey of a population of children aged 1–5 years showed that nebulizers are the most frequently used devices in USA (81%) and Southern Europe (67%) whereas pMDIs plus spacer were most frequently used in Northern Europe [22]. In a randomized study, 60 hospitalized children with asthma aged 1–5 years were treated with salbutamol plus ipratropium bromide via an MDI plus spacer or nebulizer. A clinical score was measured at baseline and every 12 hours, showing no differences between groups in the score over time, or secondary outcome measures. Interestingly, nurses rated the nebulizer easier to administer ($p<0.01$) and better tolerated by patients ($p<0.01$) [23].

Although nebulizers have been widely used in asthma management for many years, it has been suggested that patients, nurses, and doctors may have a rather poor understanding of nebulizer use [24]. Moreover, present guidelines for asthma management are complex and do not provide sufficient, specific guidance on the selection of device and therapy from among the numerous device-therapy combinations currently available [25, 26]. Current guidelines also often fail to consider recent advances in nebulizer technology.

Large-scale, systematic reviews conclude that no significant differences in clinical efficacy exist between various inhalation devices (i.e. pMDI with or without spacer; DPI; or nebulizer) when these devices are used correctly [25, 27]. However, guidelines about device selection from the American College of Chest Physicians/American College of Asthma, Allergy, and Immunology suggest that major factors to consider in asthmatic patients comprise the following: device and

drug availability; patient age, and ability to use the device appropriately; can the device be used with several medications?; cost and reimbursement issues; medication delivery time; ease of use; and patient and physician preference [25].

3.2 Nebulization versus hand-held inhalers (HHIs)

Despite the lack of evidence-based differences in efficacy between inhalation devices, most physicians and asthmatic patients consider that the inhalation device chosen for treatment has a major influence on clinical outcome (i.e. when the same drug can be administered via different devices) [28]. For example, the ability of a patient to use the device appropriately and the resulting compliance may have an impact on clinical outcome. Moreover, differences in efficacy may be seen between real life clinical practice and randomized controlled trials, where non-compliant patients are often excluded from the analysis. Poor compliance with inhalation therapy is a major problem in all age groups, and indeed, it has been reported that fewer than 15% of asthmatic children use all of the preventive therapy they are prescribed [29]. A postal questionnaire survey, in which information was collated for 117 patients receiving home nebulized therapy, revealed poor compliance with nebulizer servicing and maintenance schedules (e.g. cleaning of filters, tubing, and chambers), and with the actual nebulized medication regimen; this highlights a clear need for greater patient education regarding nebulizer maintenance and nebulized medication use [30]. Nonetheless, compliance with nebulized therapy may be better than that with a regimen comprising of several actuations from a pMDI plus spacer [29]. A recent large observational study found that nebulized ICS reduced the risk of recurrent hospitalization by 53% as compared to non-nebulized ICS in children aged ≤ 8 years; this risk reduction was attributed to an improvement in compliance [31].

Traditionally, with pMDIs, as much as 80–90% of a nominal dose was delivered to the oropharynx, with substantial quantities subsequently ending up in the stomach and being absorbed from the gut [3]. It has also been widely documented that most patients with pMDIs fail to use these devices properly or efficiently [32, 33]. Despite such poor targeting of drugs to the airways, the inhaled route of administration was generally considered preferable to the alternative of administering the higher dosages required for efficacy via systemic routes. Drug delivery to the airways could be improved by using a spacer with a pMDI, although

oropharyngeal deposition and subsequent drug absorption from the gut remained considerable [3]. Breath-actuated pMDIs and, more recently, newly developed CFC-free pMDI extrafine solution formulations, have shown improved drug delivery to the lungs. Although DPIs were introduced to improve pulmonary drug delivery, these devices require stronger, faster inhalation by the patient [34, 35], and some patients, especially young children, the elderly [36, 37], and the acutely ill, may be unable to generate sufficient inspiratory flow to operate these devices effectively.

Nebulizers permit the convenient and effective administration of ICS, even at high doses. Thus, nebulized therapy with ICS may be particularly appropriate in adults with severe, steroid-dependent asthma, perhaps in part because ‘wet’ nebulization, rather than use of a pMDI, permits better mucosal coverage in the airways [29]. Such enhanced coverage, or greater ‘spreadability’ of nebulized droplets, may result from surface tension differences between the droplets and epithelial surfactant in the alveoli and airways [29].

Nebulized ICS therapy may also be a better therapeutic option than a pMDI plus spacer in uncooperative young children with asthma [29]. Indeed, nebulized therapy is easy to administer, and some data suggest that it can be administered when children are asleep, and unlike pMDI therapy, is not associated with the taste of a propellant. The contribution made to the efficacy of nebulized therapy by the simple, reassuring presence of the nebulizer device, may instill important patient and parent confidence in treatment, and may further enhance compliance. In several cases, parents may prefer nebulized to pMDI-plus-spacer therapy for an asthmatic child [29].

From a pharmacokinetic point of view, it is important to select an appropriate drug dose for nebulization that is always greater than the same drug administered with pMDI. This is because currently available nebulizers deliver a lower fraction of the prescribed dose than the pMDI plus spacer (approximately 10% versus 20–30%) and therefore larger doses need to be prescribed to compensate [27]. As regards short acting bronchodilators, the studies included in a Cochrane review comparing pMDI plus spacer with nebulizers used dosage ratios varying from 1:1 to 1:13 (higher dose for the nebulizer). However, only one of the included studies plotted a log dose-response curve, suggesting an equivalent dose ratio of 1:6 with the lower dose for the spacer [38].

In the BTS guidelines for asthma management, a nebulized dose of 2.5–5 mg of salbutamol is considered to be alternative to 4–10 puffs (100 µg per puff) via pMDI for acute asthma in children [39].

3.3 Technical Aspects of Nebulization

The effectiveness of nebulization therapy is determined by the drug-nebulizer combination. While the key aim of nebulized therapy is to deliver a therapeutic drug dose to the airways as respirable particles (1–5 µm) in a short time frame (in the order of 5 minutes) [15], between-device differences in nebulizer performance (i.e. final drug dose delivered to the airways) can be relevant [16]. This is often underestimated in clinical practice, where the drug is prescribed by the physician and the nebulizer equipment is selected by the patient, which can lead to differences in nebulizer systems administering the same antiasthmatic drug, thus resulting in variability in clinical efficacy [40, 41]. The principal factors influencing nebulizer performance are initial fill volume, the efficiency of aerosol production, and residual volume [16]. A fill volume of 2.0–2.5 ml is generally appropriate when the residual volume is < 1.0 ml, whereas a fill volume of about 3.0–4.0 ml is usually needed if the residual volume exceeds 1.0 ml [15].

The output and the mass median aerodynamic diameter (MMAD) of aerosol droplets differ markedly between various nebulizer types, with smaller particle size generally being associated with greater airway penetration. However, while particles of < 5 µm are mainly deposited in the central airways and can be indicated for the treatment of lower airways diseases such as asthma and COPD, particles of < 2 µm are needed to reach peripheral regions of the lungs, while particles of <10 µm are useful for treating upper airways disease such as sinusitis. Furthermore, a recently published in vitro study showed that there are significant differences in the particle size distribution of particles below 10, 5, and 2 µm produced by commercially available nebulizers, together with variations in performance depending on the drug and solution/suspension studied [43]. When the output was compared using four drugs for nebulization available on the market in Italy, beclomethasone and budesonide were efficiently nebulized, in terms of particles <5 µm >90% of all particles, by all the tested nebulizers, whereas higher variability was observed for flunisolide and fluticasone.

Together with the MMAD generated, another important factor affecting the efficacy of nebulized therapy is the means of nebulization employed: i.e. jet (pneumatic) or ultrasonic. Indeed, the type of nebulizer selected can influence the proportion of liquid nebulized, the amount of aerosol generated over time, and aerodynamic features of the aerosol produced. For example, a study involving preterm infants demonstrated that the pulmonary deposition of sodium cromoglycate was approximately 1.5–2-fold greater after administration via an LC[®] Star jet nebulizer (Pari, Starnberg, Germany), compared with an LS 290 (System, Villeneuve sur Lot, France) or Projet ultrasonic nebulizer (Artsana, Como, Italy) [44].

Basically, jet nebulizers comprise a nebulizing chamber, where aerosol is produced by gas flow through a solution or suspension; the gas is either compressed (air or oxygen) or generated by an electrical compressor, and most of these devices are designed to operate at a flow rate of 6–10 L min⁻¹ [15]. In a hospital setting, the hospital oxygen supply is sometimes used by clinicians as an alternative source of driving gas instead of compressor-driven nebulization. This practice is common in an intensive care setting, where patients on long-term oxygen therapy require nebulized drugs. However, attention should be paid to the flow rates of hospital oxygen sources as this can affect the efficiency of nebulization of the drug.

Ultrasonic nebulizers are standalone electrical devices, in which aerosol is produced by the vibration of fluid inside them. These nebulizers produce greater aerosol volumes and are quieter than their pneumatic counterparts [15]. However, heat generated by frictional forces induced in the ultrasonic wave generation may potentially inactivate thermolabile drugs, although the significance of this in practical terms is unclear. Furthermore, pneumatic nebulizers can be more efficient than ultrasonic nebulizers when an inhaled corticosteroid has to be used, as long as the latter is not recommended for suspensions or viscous solutions. In a pilot study, BDP 800 µg twice daily was administered for 9 weeks, via either of two jet nebulizers or an ultrasonic nebulizer, to 27 asthmatic outpatients [41]. The MMAD of aerosolized particles was smaller for the jet nebulizers (2.9–3.7 vs 5.8 µm), whereas the proportions of particles < 5 µm (84.2–93.7% vs 34.9%) or < 2 µm in diameter (7.6–9.5% vs 0.4%) were considerably greater for the jet nebulizers as compared to the ultrasonic nebulizer. At the end of the study, self-monitoring PEF significantly increased, and dyspnea, cough and salbutamol consumption significantly decreased (p<0.0005) in all groups with no differences between groups. The provocative dose of

metacholine causing a 20% fall in forced expiratory volume in 1 s (FEV_1) increased significantly in the three groups ($p < 0.05$) during the study with no difference between groups. As regards spirometric parameters recorded at visits, PEF was not different between groups at the end of study, whereas FEV_1 and FEF_{25} were significantly higher with the jet nebulizers than the ultrasonic nebulizer ($p < 0.05$). The results of this pilot study suggest that jet nebulizers can be more efficient in nebulizing corticosteroid suspensions, and spirometric parameters are more sensitive in detecting potential differences in efficacy between devices [41]. Indeed, certain ultrasonic devices are unable to efficiently nebulize corticosteroid suspensions and solutions. This was seen in an *in vitro* study, which showed that an ultrasonic nebulizer (Project 1000, Artsana) was unable to nebulize two different flunisolide solution formulations [45]. A summary of the advantages and disadvantages of jet and ultrasonic nebulizers is given in Table 2.

Co-administration of drugs in the nebulizer is a widespread practice and is considered one of the advantages of nebulizers versus HHIs. However, *in vitro* studies demonstrate that co-administration of nebulized drug formulations can markedly affect output and aerosol characteristics [46, 47]. Although increasing the dose of corticosteroids if nebulized together with salbutamol may overcome the reduction in corticosteroid output, there seems to be no rule on the output of different drugs when co-administered, as the output is dependent on the specific formulation of the drugs. It can be recommended to administer admixtures of drugs only if specific data are available on output characteristics of the resulting mixture.

Constant-output nebulizers have a traditional T-piece and produce aerosol continuously during inhalation, exhalation, and breath-holding [6, 40]. However, these devices are often considered inefficient and unreliable. Conversely, the most widely used of the nebulizer types, the breath-enhanced ('open-vent') nebulizer, introduced in the late 1980s, permits greater pulmonary aerosol release during inhalation. This design allows ambient air to be drawn through a 1-way valve during inspiration, followed by exhalation through a 1-way expiratory valve in the mouthpiece, and aerosol containment in the nebulizer chamber. During exhalation, exhaled gas passes out of the device via an expiratory valve in the mouthpiece, when aerosol is present in the device chamber. A subsequent development was introduction of the dosimetric ('breath-actuated') nebulizers that produce aerosol during inhalation only. These nebulizers demonstrated greater pulmonary drug deposition than the other two nebulizer types (~35% vs ~15% of a

nominal dose), with reduced loss to the apparatus and ambient air; theoretically, these are the most efficient nebulizers, but they are more expensive and bulky [6, 40]. An extension of the dosimetric principle was the development of an adaptive aerosol delivery device, which evaluates a patient's breathing over several seconds and then gives out drug 'pulses' during pre-specified periods of the inspiratory phase. Various other nebulizer categories have now also been introduced, such as the modified piezoelectric nebulizer, high-pressure microspray nebulizer, and electrohydrodynamic device [6]. The latter three types of device are portable, and represent a convergence of pMDI and nebulizer characteristics; the devices have been termed metered-dose liquid inhalers [6].

4. Nebulization in young children: special considerations

Nebulization is the only alternative to pMDIs plus spacer in children younger than 5 years of age, as long as DPIs are not indicated in this age group due to the inability of these breath-actuated devices to produce sufficient inspiratory flows. There are also various anatomical, physiological and emotional factors peculiar to young children that give rise to significant difficulties and challenges for aerosol delivery [48].

The differences in upper airway anatomy between infants and adults partially explain the preferential nose breathing and the difficulty observed when attempting to target aerosols to their lower respiratory tract [49]. Nasal breathing has been shown to be much less effective in delivering aerosol to the lungs than mouth breathing due to high resistance, relatively high flow velocity and turbulence [50]. As a result, the lung targetable fraction of an aerosol for young children is lower compared with older children, adolescents and adults; therefore, the prescribed dose may be similar, due to the fact that young children often require a range of ex-aerosol generator doses similar to adults [51].

In children below the age of 3-4 years, a well-fitted facemask is a potential option for efficient treatment because inhalation therapy through a mouthpiece is often ineffective in this age group [52]. The use of a facemask requires a tight seal between the face and the mask to reduce drug waste, avoid deposition in the eyes, and to ensure delivery of an appropriate dose to the airways [53]. Another common issue in aerosol delivery is crying, which occurs in 38% of children,

particularly when inhaled therapy is administered while children are awake [54]. This complication can have a detrimental effect on airway deposition as a consequence of an insufficient seal between the mask and the child's face. Due to the difficulty in designing randomized controlled trials to investigate the effect of children's behavior on drug deposition in the respiratory tract, there have been different opinions on the clinical consequences of crying during nebulization. For example, improved drug deposition as a result of deep inspiratory breaths during crying has been suggested in the past. Nevertheless, some studies show that the reduction in lung deposition can be up to four-fold greater, and may be accompanied by an increase in gastrointestinal absorption because crying or screaming children adopt abnormal breathing patterns, which is characterized by prolonged expiration followed by short gasps (i.e. a high inspiratory flow velocity) leading to greater aerosol impaction in the throat and frequent swallowing [48].

To overcome the problems associated with aerosol use while children are awake, administration during sleep can be a valuable option, as sleep is associated with more regular breathing, lower breathing rate and lower inspiratory flows (i.e. factors that improve aerosol delivery to the lower airways) [55]. However, it should be noted that this technique will only work if the sleep is not compromised. Indeed, *in vitro* studies with a breathing simulator showed the potential for improved drug delivery to the lungs during sleep, but *in vivo* studies reported a high percentage of children waking up, which resulted in a half the drug deposition as compared to administration during an awake state [56]. To address this issue, administration during sleep can be made with a hood, thus avoiding contact with the child's face. Administration with a nebulizer hood has been shown to be as effective as a facemask and preferred by both children and parents [57], although the consequences of drug deposition on the face and skin are still not fully known.

5. Nebulized BDP

To date, BDP is the only inhaled corticosteroid included in the World Health Organization list of essential drugs [58]. The drug was first introduced in 1979 for use in nebulizers (as a suspension), but was previously available in CFC-propelled pMDIs. It is now also available as a solution for use in CFC-free, HFA inhalers, both extrafine and non-extrafine formulations [59]. Importantly, the original BDP product for nebulization was formulated in a multi-dose bottle; subsequently,

however, to provide safer dosage and better hygiene, this product was replaced in Italy by BDP in unit-dose vials in 1993. Sterile, preservative-free, unit-dose vials of BDP were then introduced in 2003 to comply with a new production standards guideline released from the FDA (21 CFR Part 200 [Docket No. 96N-0048] RIN 0910-AA88 Sterility Requirement for Aqueous-Based Drug Products for Oral Inhalation). This formulation of BDP suspension for nebulization can provide 20% respirable fraction when nebulized with Pari Boy compressor and an LC plus nebulizer (Pari Turbo Boy, Pari, Germany) with an MMAD of 3.3 microns [60].

5.1 Pharmacologic profile

Pharmacodynamic characteristics (glucocorticoid receptor binding) and lung delivery determine the relative clinical efficacy and pharmacokinetic properties (oral bioavailability, lung retention, and systemic clearance) and contribute to the comparative therapeutic index of ICS. Secondary pharmacokinetic differences (intracellular fatty acid esterification, high serum protein binding) that have been suggested to improve duration of action and/or therapeutic index are unproven, and current comparative clinical trials do not support the hypotheses that they provide an advantage. All of the inhaled corticosteroids demonstrate efficacy with once-daily dosing, and all are more effective when dosed twice daily. Current evidence suggests that all of the inhaled corticosteroids have sufficient therapeutic indexes to provide similar efficacy and safety in low to medium doses. Whether or not some of the newer inhaled corticosteroids offer any advantages at higher doses has yet to be determined [61].

The 'ideal' pharmacokinetic (PK)/pharmacodynamic (PD) profile for an ICS in terms of optimal benefit-to-risk ratio comprises the following features: high pulmonary deposition; high receptor binding; prolonged pulmonary retention; marked lipid conjugation; minimal oral bioavailability; small particle size ($< 5 \mu\text{m}$); low pharyngeal deposition; high plasma protein binding; rapid metabolism and clearance from the plasma; and, therefore, low systemic concentration [62-64].

BDP possesses several of these important PK/PD characteristics. BDP is a prodrug specifically targeted to the lungs, with relative receptor affinity (expressed with reference to a receptor affinity of dexamethasone of 100) as low as 53. Indeed, most (95%) of an inhaled BDP dose is hydrolyzed by esterase enzymes in the lungs to the active metabolite 17-beclometasone

monopropionate (17-BMP) [65], which has a relative receptor affinity of 1345 [62, 64]. Furthermore, the esterases that activate BDP are present in the lungs to a greater extent than the oropharynx, thus improving oropharyngeal safety [66].

Furthermore, BDP is highly bound to plasma proteins (87%), has a rapid plasma elimination half-life (0.1–0.5 h), and has a high value for total clearance (150–230 l h⁻¹) [62, 65], thus suggesting a relatively limited potential for systemic adverse effects. Aerosols of BDP generated by jet nebulizers are known to produce small particles (MMAD 2.9–3.7 µm; see section 3.3)[40], thus facilitating pulmonary deposition, and modern-day nebulizers have low rates of oropharyngeal aerosol deposition [6].

The pharmacokinetic profile of nebulized BDP was evaluated in a study involving 12 healthy males treated with either 1600 µg of BDP via pMDI or 1600 µg and 3200 µg given via Pari Boy compressor and an LC plus nebulizer (Pari Turbo Boy, Pari, Germany).[67] The results of this study suggest that a dose of 3200 µg of nebulized BDP is equivalent to 1600 µg of BDP via pMDI in terms of systemic exposure to the active metabolite 17-BMP and systemic effects on the HPA axis evaluated as serum and urinary cortisol levels. Therefore a double dose of BDP suspension for nebulization administered by nebulizer compared with BPD via pMDI poses no risks with regard to safety [67].

5.2 Clinical efficacy

The clinical efficacy of nebulized beclometasone is discussed in the present review using data from 13 published studies, which included a total of 1250 patients, of which 394 were adults and 856 were infants and children aged 2 months and above. Four clinical trials showed that nebulized BDP 300–800 µg/day maintained pulmonary function and markedly improved symptoms, with a generally favorable tolerability profile, in 156 asthmatic infants and children [68-71]. In one of these trials [68], a multicenter, randomized, double-blind study, 65 asthmatic children received nebulized BDP 800 µg once daily (n=32) or 400 µg twice daily (n=33) for 12 weeks, after a 2-week run-in period with the twice-daily schedule. Pulmonary function improved in both groups during the run-in period, with the improvement maintained throughout the trial. Further, both once and twice daily nebulized BDP significantly increased mean morning peak

expiratory flow rate (PEFR, $+54.32 \text{ l min}^{-1}$; $p=0.002$ and $+20.83 \pm 8.41 \text{ l min}^{-1}$; $p=0.02$, respectively). At the final study visit, 80–92% of children in the once-daily group had symptom-free days and nights, 95% had good overall asthma control, and about two-thirds reported no use of rescue medication [68]. A small-scale study also revealed that nebulized BDP 400 μg three times daily for 5 days significantly ($p<0.05$) reduced symptom scores and the number of acute attacks in infants with recurrent wheezing during upper respiratory tract infection [72]. In a randomized double-blind trial, 44 children aged 6–24 months with recurrent obstructive episodes after acute bronchiolitis in infancy were treated either with nebulized BDP or placebo for 8 weeks. Children were evaluated monthly for a year afterwards and also if they had acute respiratory illnesses with or without bronchopulmonary obstruction. Children on placebo had significantly higher obstructive scores during the study period, and they were treated with inhaled beta 2 agonists and theophylline for longer periods of time during the follow-up period. In contrast, the beclometasone treated group had significantly fewer symptomatic respiratory illnesses and fewer episodes of bronchopulmonary obstruction during the follow-up period [71].

Regular treatment with nebulized BDP has also been shown to be more effective than as-required (prn) treatment with salbutamol in preschool children with frequent wheezing in a 3-month, double-blind, randomized trial enrolling 276 children aged 1–4 years. Twice-daily nebulization of BDP 400 μg (plus prn salbutamol) was associated with a significant increase in the percentage of symptom-free days compared with nebulized prn salbutamol alone (Fig. 1, Fig. 2). Moreover, this trial investigated for the first time treatment with a prn BDP/salbutamol combination; this combination was not superior to salbutamol alone for the primary outcome and also did not differ from regular beclometasone for the primary and several important secondary outcomes [73].

5.2.1 Nebulized BDP is as effective as BDP via pMDI plus spacer

Randomized, double-blind studies have shown that nebulized BDP is equally as effective as BDP administered via a pMDI plus spacer in children and adults with asthma [74-76]. In a multicenter trial, for instance, 151 children aged 6–16 years, and with moderate-to-severe asthma exacerbations (as defined by the National Heart, Lung, and Blood Institute [NHLBI]), were randomized to receive 4 weeks' treatment with nebulized BDP 800 μg twice daily ($n=75$), or

BDP 400 μg twice daily administered via a pMDI plus spacer ($n=76$) [74]. Over the course of the trial, respective increases in the primary study endpoint, morning PEFr, were +38.1% and +41.3%, with no significant difference between the two treatment regimens. In addition, statistically significant improvements, of similar magnitude in both groups, were noted in mean values for the following parameters: evening PEFr (+36.9% vs +36.2%); FEV_1 (+42.9% vs +40.0%); forced vital capacity (FVC; +27.8% vs +33.3%); symptom scores (morning scores were reduced from 1.8 to 0.4 in both groups); and the use of rescue medication (reduced from 0.8–0.9 to 0.2–0.3 puffs per day in both groups). Overall, approximately 90–100% of investigators and patients rated the study treatments as ‘good’ or ‘excellent’, with no significant differences between the treatments [74].

A similarly designed, multicenter trial was conducted in 124 adults (aged 18–70 years) with NHLBI moderate-to-severe asthma, and who were randomized to 12 weeks’ treatment with nebulized BDP 1500–2000 μg twice daily ($n=63$), or BDP 750–1000 μg twice daily administered via a pMDI plus spacer ($n=61$) [75]. Mean morning PEFr increased significantly in both groups: from 308.7 to 319.2 l min^{-1} in the nebulization group; and from 301.5 to 309.3 l min^{-1} in the pMDI group. There was no significant difference between the two groups. Further, statistically significant improvements, and of a similar magnitude in both groups, were evident in evening PEFr, FEV_1 , FVC, and symptom scores [75]. In a smaller study testing airways’ hyper-responsiveness with methacholine in adults with mild asthma, similar improvements in PC_{20} (the provocation concentration of methacholine required to reduce FEV_1 by 20%) were noted in patients treated with nebulized BDP 1600–3200 $\mu\text{g d}^{-1}$ or BDP 800 $\mu\text{g d}^{-1}$ administered via a pMDI plus spacer [76].

5.2.2 Nebulized BDP is as effective as nebulized fluticasone propionate (FP)

A large, multicenter, active-control study demonstrated similar clinical efficacy between nebulized BDP 2400 $\mu\text{g d}^{-1}$ ($n=103$) and nebulized FP 2000 $\mu\text{g d}^{-1}$ ($n=102$) in a total of 205 randomized adults (aged 18–65 years) with moderate persistent asthma (NHLBI/WHO criteria) [77]. Both treatments were administered via jet nebulizer over a 12-week period, and the primary efficacy endpoint was investigator-assessed change in PEFr from baseline to week 12. The primary endpoint significantly increased ($p=0.0002$) in both groups, as did mean PEFr values

expressed as percent of predicted: i.e. from 71.0% to 77.1% (BDP, $p=0.0001$); or from 70.1% to 76.9% (FP, $p=0.0002$). Differences between the two groups in these parameters were not statistically significant. The same was true for the proportion of patients with asthma exacerbations (2% with BDP vs 5.1% with FP), and for the significant improvements from baseline showed in the following parameters: FEV₁, FVC, mean morning and evening PEFs, asthma symptom scores, and the number of patients free of daytime symptoms (table 3). One or more adverse events were reported in 22.5% of BDP and 32.0% of FP recipients; however, these events were generally mild, and the incidence was not significantly different between the two groups [77].

5.2.3 Nebulized BDP is as effective as nebulized budesonide (BUD)

A detailed, recent review of the comparative efficacy of various ICS documented that most studies, reviews and meta-analyses of BDP vs BUD had reported similar efficacy for the two ICS in terms of improved asthma symptoms and airways' function [59]. The papers cited compared BDP administered via a nebulizer or HFA-containing pMDI with BUD administered via a nebulizer or DPI [59]. In two of the constituent studies, nebulized BDP 800 $\mu\text{g d}^{-1}$ demonstrated efficacy similar to that of nebulized BUD 750–1000 $\mu\text{g d}^{-1}$ in infants and young children with severe persistent asthma [78], and in children with mild-to-moderate persistent asthma [79]; both treatment regimens, administered via jet nebulizers, had generally favorable safety and tolerability profiles [78, 79]. Thus, in a multicenter study, 120 infants and young children aged 6 months to 6 years were randomly treated with BDP ($n=58$) or BUD ($n=62$) for 12 weeks [78]. The primary endpoint, the proportion of patients without a major exacerbation, revealed values of 40.4% for BDP versus 51.7% for BUD (not significant between groups); further, no significant differences were noted between the two groups regarding reduction in the mean number of minor plus major exacerbations (-37.5% vs -23.3%), and the mean time to first major exacerbation (46.3 vs 46.1 days). Statistically significant reductions from baseline ($p\leq 0.007$), with no significant differences between the two groups, were also noted in the following parameters: the mean number of days of oral corticosteroid therapy (-66.7% vs -58.3%); the mean number of rescue medication doses (-61.8% vs -57.8%); the mean number of days with

wheezing (−53.1% vs −64.3% in the BDP and BUD groups, respectively); and the mean number of days and nights with cough (Fig. 3) [78].

In a multicenter study, 127 children aged 6–14 years with mild-to-moderate persistent asthma (NHLBI criteria) were randomized to BDP (n=66) or BUD (n=61) for 4 weeks [79]. The primary endpoint, change in mean PEF_R from baseline to the final study visit, revealed increases from 177.5 to 246.6 l min^{−1} in the BDP group, and from 180.4 to 260.9 l min^{−1} in the BUD group (no significant difference between treatments). In addition, no significant differences were noted between the two groups in terms of increases in FEV₁ (+14.9 vs +21.8 % predicted) and FVC (+10.5 vs +14.9 % predicted) [p<0.001 vs baseline]. Statistically significant changes from baseline (p<0.001), with no significant differences between the two groups, were also evident in the following parameters: rescue salbutamol use (−0.32 vs −0.36 puffs per day); asthma symptom scores (−0.44 vs −0.36; Fig. 4); nocturnal awakenings because of asthma (−0.22 vs −0.28 in the BDP and BUD groups, respectively); and episodes of diurnal dyspnea and asthma exacerbations. Only 6 patients experienced adverse events, which were mild to moderate and did not require treatment withdrawal [79].

5.3 Safety of nebulized BDP

As with all nebulized ICS, BDP will be absorbed from the lungs, thus giving rise to some, albeit relatively limited, systemic bioavailability (see section 3.3) and the potential for systemic adverse effects. Such effects that have manifested during long-term treatment with high-dosages of ICS include adrenal suppression, easy bruising, growth retardation, and reduced bone mineral density [17]. Some cross-sectional studies have also linked ICS with cataracts and glaucoma. In addition, a recent study with fluticasone propionate has linked use of this ICS (either alone or in combination with a long-acting β_2 -agonist, salmeterol) with an increased risk of pneumonia in patients with COPD, particularly those aged >65 years, with a forced expiratory volume in 1 second <30% of predicted, and a body mass index <25 kg m^{−1} [80-83]. The mechanisms and significance of these findings are still being investigated.

Marked differences exist in the safety profiles of various ICS, and indeed, the risk of systemic adverse effects is dependent on: ICS dosage and potency; the inhalation device employed;

systemic bioavailability; first-pass hepatic metabolism; and plasma half-life of the ICS fraction systemically absorbed from the lungs and gut [17]. Importantly, inhaled BDP has been in clinical use for more than 35 years [59], and has been generally well tolerated. Traditionally, with a CFC-containing pMDI, the most common adverse effects were oropharyngeal candidiasis, which only rarely required treatment withdrawal, hoarseness, and/or sore throat [83]. Despite some concerns about the potential for growth retardation with high-dose ICS, a small-scale study in preschool asthmatic children revealed that nebulized BDP 300 $\mu\text{g d}^{-1}$ for 6 months had no significant effect on height [70], and a meta-analysis of 21 studies involving 810 asthmatic patients found no statistical suggestion that BDP was associated with growth impairment at high dosages, long treatment durations, or in patients with the most severe asthma [84].

Interestingly, one small-scale study reported that long-term treatment with aerosolized BDP had no effect on adrenal function in asthmatic children aged 12–26 months [85], and another trial in 15 asthmatic patients found that neither high-dose BDP nor BUD, each administered via pMDI plus spacer, had a significant effect on plasma or urinary cortisol levels, thus suggesting a lack of effect on adrenal function and the HPA axis [86]. A larger study also documented significantly greater ($p < 0.05$) suppression of plasma and urinary cortisol after inhaled FP compared with BDP in adult healthy volunteers [87]. However, a recent Cochrane Collaboration systematic review comparing FP with BDP or BUD for chronic asthma in adults and children was unable to calculate an overall pooled treatment effect for the effects of FP and BDP/BUD in suppressing plasma or urinary cortisol levels because of limitations in data reported from randomized controlled trials, although there was some indication that FP is more potent in suppressing 24-hour urinary cortisol levels than BDP/BUD [88].

Regarding nebulized BDP, clinical trials reveal that this ICS formulation is generally well tolerated [68, 74–80]. A postal questionnaire completed by 117 patients using nebulized therapy for asthma, bronchiectasis, or chronic obstructive pulmonary disease identified that chest tightness, dry eyes, dry mouth, headache, tachycardia, and tremor were frequent adverse effects [30]. However, in the aforementioned trials, treatment-related adverse effects induced by nebulized BDP were generally uncommon [68, 74–79]. Most such effects were mild or moderate in severity [68, 74, 75, 77, 79], and were usually associated with the respiratory system [75, 79].

In most cases, no or only a few patients discontinued treatment because of adverse effects [68, 75-77, 79]; BDP had no major influence on the time course of patient height, on urinary cortisol concentration [70, 78], or bone metabolism [78]; and investigators' opinions of BDP tolerability were 'good' or 'excellent' for 97–100% of patients [74, 75].

Importantly, in comparative clinical trials, nebulized BDP demonstrated a tolerability profile similar to that of BDP administered via a pMDI plus spacer [74-76] (one trial [76] listed no significant difference in the proportions of patients with treatment-related adverse events: 9.5% vs 8.2%); similar to that of nebulized BUD [78, 79]; but slightly better than that of nebulized FP (22.5% vs 32.0% of patients experienced adverse events; difference not statistically significant) [77].

6. Conclusions

As outlined in several major, definitive guidelines, ICS remain the mainstay of treatment for chronic persistent asthma. Recent, 'across-the-board' advances in inhalation-device technology (i.e. for both HHIs and nebulizers) mean that if these devices are used correctly, they produce similar clinical efficacy. Regarding nebulizers, some of the latest devices have enhanced rates of pulmonary drug delivery, and are quieter and more portable than their predecessors, such that nebulized ICS have retained a key role in asthma management.

Nonetheless, in some regions, improved asthma management strategies may be needed to ensure greater awareness and understanding of issues pertaining to nebulizer use among patients and healthcare professionals. For example, patients may benefit from improved instruction about the correct use and maintenance of nebulizers, and from enhanced encouragement and support in terms of adhering to prescribed antiasthmatic schedules. For healthcare professionals, additional research into the comparative efficacy and tolerability of specific nebulizer/ICS combinations versus HHIs would be useful. Incorporation into definitive asthma management guidelines of specific recommendations about appropriate nebulizer/ICS selection, from the multitude of currently available device-drug combinations, would also be helpful.

Importantly, nebulization is a convenient means of administering ICS, and patients may often comply better with nebulized than pMDI-plus-spacer therapy. Nebulization also provides an effective alternative in difficult-to-treat patients such as young children (e.g. use of a facemask while awake or a nebulizer hood during sleep). Furthermore, patients and parents may prefer a nebulizer to an HHI because of the reassuring feeling of security that the presence of a nebulizer provides. Thus, among currently available ICS, nebulized BDP has demonstrated efficacy and tolerability profiles at least similar to those of BDP via a pMDI plus spacer, nebulized FP, and nebulized BUD in children and adults with chronic persistent asthma. Overall, nebulized BDP appears to have an important place in asthma therapy: as a general alternative to HHIs (e.g. in patients with poor HHI compliance); when patients such as children, the elderly, and those with restricted hand dexterity because of comorbid conditions are unable to operate HHIs because of poor hand–lung coordination, lack of cooperation, or low inspiratory flow rate; and when high dosages of ICS are required, such as in adults with severe, steroid-dependent asthma.

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Table 1 Key, sometimes contradictory, comments from recent guidelines regarding the role of nebulized ICS therapy in asthma management [15-17]

BTS guidelines [15]	ERS guidelines [16]	GINA guidelines [17]
<ul style="list-style-type: none"> Nebulizers have a role when large doses of inhaled agents are required, and when pts cannot use HHIs because of advanced age, severity of illness, or other reasons. Many elderly pts (aged ≥ 65 y) are unable to use pMDIs appropriately because of finger weakness, poor coordination, cognitive impairment and/or amnesia; nebulized therapy may be a suitable alternative in such pts. Nebulizers are most widely used in the emergency treatment of asthma, but are also used to provide drug prophylaxis, and in pts with chronic severe asthma. Currently, no RCTs of nebulized ICS therapy have been conducted in adults with asthma. However, such therapy may permit reduction of maintenance oral steroid therapy in children and adults with asthma (grade B evidence) [15,16]. Direct, comparative RCTs of ICS administered via a nebulizer vs HHI are now required. Using a mouthpiece with a nebulizer improves pulmonary drug deposition, and reduces the amount of drug landing on the face. If a face mask is used with a nebulized ICS, eye and face washing is required after each nebulization, and all pts should be given a postdose drink. 	<ul style="list-style-type: none"> Nebulized ICS therapy has been used to replace oral steroid therapy in children and adults with moderate exacerbations of asthma. However, there are no clinical data indicating superior efficacy for ICS administered via nebulizer vs HHI plus spacer in pts with acute or chronic asthma. Intrinsic differences among nebulizers available in Europe may lead to ≥ 10-fold differences in pulmonary drug delivery. Such delivery is markedly increased when breath-actuated vs other nebulizers are used. The former devices have shown pulmonary drug deposition similar to that from correctly used HHIs plus spacers. A nebulizer system with good CEN performance, in terms of output and droplet size, should be the one selected for clinical use. This may lead to lower drug doses, or reduced treatment times, improved patient convenience, and reduced treatment costs. Nebulized ICS therapy has an oral steroid-sparing effect (grade A evidence), as does ICS therapy administered via HHI. Face masks should generally be avoided with nebulized ICS therapy; i.e. to prevent steroid administration to the face and eyes. 	<ul style="list-style-type: none"> “Nebulized aerosols are rarely indicated for the treatment of chronic asthma in adults.” “Nebulizers have rather imprecise dosing, are time consuming to use and care for, and require regular maintenance. They are mainly reserved for patients who cannot use other inhaler devices.”
<p>BTS = British Thoracic Society; CEN = Comité European de Normalisation; ERS = European Respiratory Society; GINA = Global Initiative for Asthma; HHI = hand-held inhaler; ICS = inhaled corticosteroid; pMDI = pressurized metered dose inhaler; pts = patients; RCT = randomized controlled trial; y = years.</p>		

Table 2 Advantages and disadvantages of jet and ultrasonic nebulizers [15, 40, 86]

Jet (pneumatic) nebulizers (JNs)	Ultrasonic nebulizers (UNs)
ADVANTAGES	
<ul style="list-style-type: none"> • Easy to use — only require simple, tidal breathing, with no breath-holding • Dosage modification and compounding are possible • Effective in pts with low inspiratory flow or volume • High doses can be administered • Both solution and suspension formulations can be delivered efficiently 	<ul style="list-style-type: none"> • Easy to use — only require simple, tidal breathing, with no breath-holding • Dosage modification and compounding are possible • Higher output rate and volume than JNs • High doses can be administered • Quieter than JNs • More portable than JNs • Small residual volume
DISADVANTAGES	
<ul style="list-style-type: none"> • Longer duration of treatment than UNs • JNs reduce reservoir solution temperature, which may reduce nebulizer output • Unlike UNs, JNs increase drug concentrations in the reservoir • Often larger equipment size than UNs • Between-device variability in performance • Require an external power source • Potential for contamination because of poor cleaning • The wet, cold spray may be unpleasant if a face mask is used • The wet, cold spray may be unpleasant if a face mask is used 	<ul style="list-style-type: none"> • Greater MMAD than JNs • UNs can markedly increase reservoir solution temperature, which may lead to drug degradation • More expensive and fragile than JNs • Unlike JNs, UNs may not be suitable for nebulization of suspensions or viscous solutions • Increased viscosity and surface tension reduce the capacity for nebulization • Heat generated due to frictional forces may inactivate thermolabile drugs • Require an external power source • Potential for contamination because of poor cleaning • Possible airways' irritation with bland solutions • Potential for electrolyte imbalance in infants with

continuous inhalation

MMAD = mass median aerodynamic diameter; **pts** = patients.

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Table 3: Symptoms and exacerbations in a trial comparing nebulized BDP and fluticasone [74]

	Beclometasone (n=103)		Fluticasone (n=102)	
	Baseline	After 8 weeks	Baseline	After 8 weeks
Symptom score [#]	4.7	6.3*	4.6	6.3*
Patients reporting “excellent” symptom score (%)	15.7	52.9	12.0	46.0
Daytime symptom-free patients	13	43	10	35
Night-time symptom-free patients	22	51	21	48
Use of rescue medication (puffs/day)	2.8	2.0	2.6	2.1

[#] eight-point scale (1-8) ranging from “poor” to “excellent”; *p<0.001 vs baseline; no significant difference between treatments in any comparison

Figure Captions

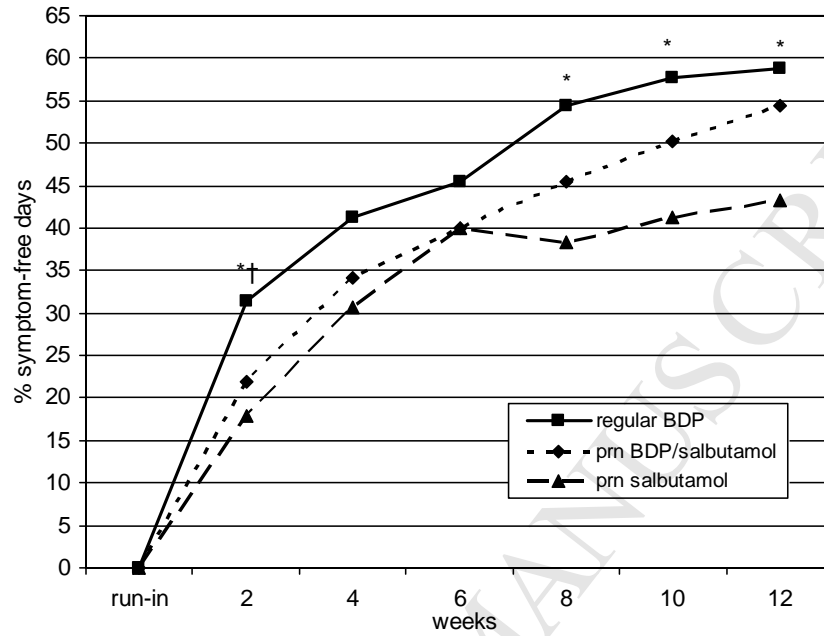
Fig. 1. Mean increase in percentage of symptom-free days compared with baseline during therapy with regular nebulized BDP, prn BDP + salbutamol or prn salbutamol [73].

Fig. 2. Percentage of symptom-free days is greater with regular nebulized BDP therapy in children with preschool wheeze [73].

Fig. 3 Nebulized BDP and nebulized budesonide (BUD) are equally effective in reducing cough in infants and young children [78].

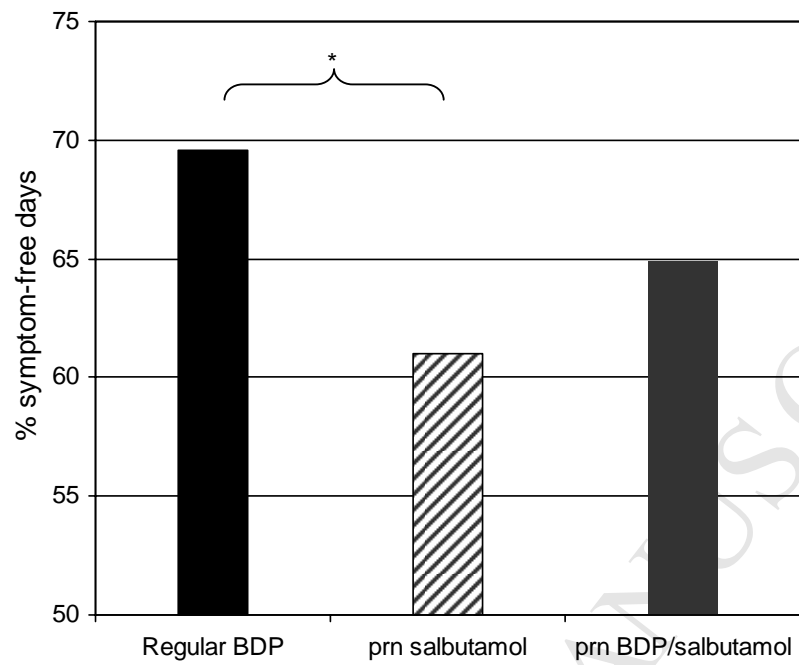
Fig. 4 Nebulized BDP and nebulized budesonide (BUD) are equally effective in reducing symptoms in children (aged 6–14 years) [79].

<<Fig. 1>>



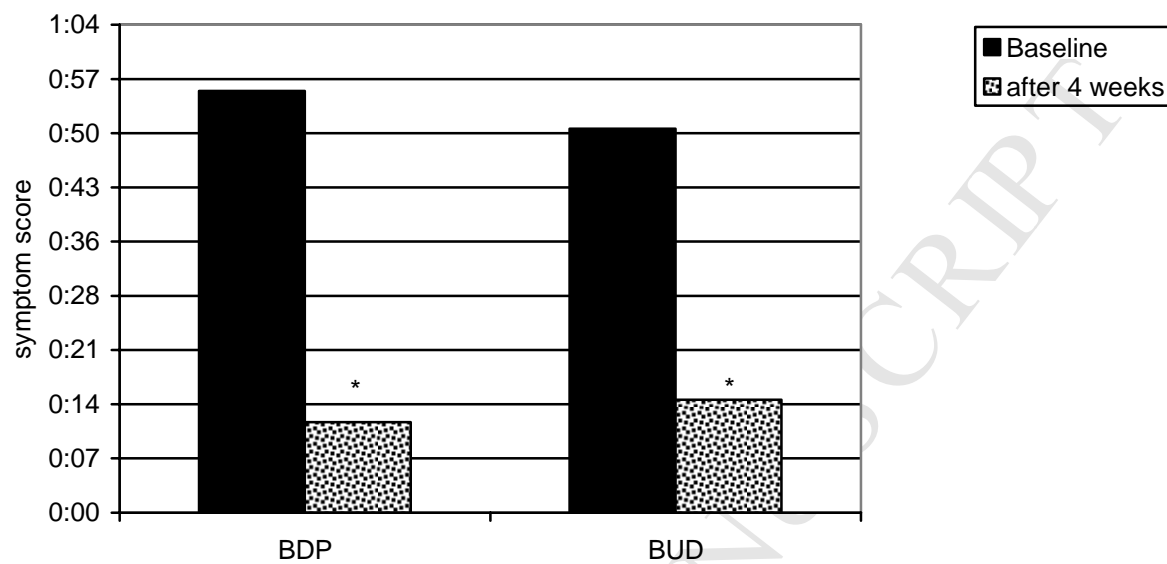
† p<0.05 vs prn BDP/salbutamol; * p<0.05 vs prn salbutamol; BDP= beclometasone dipropionate

<<Fig. 2>>



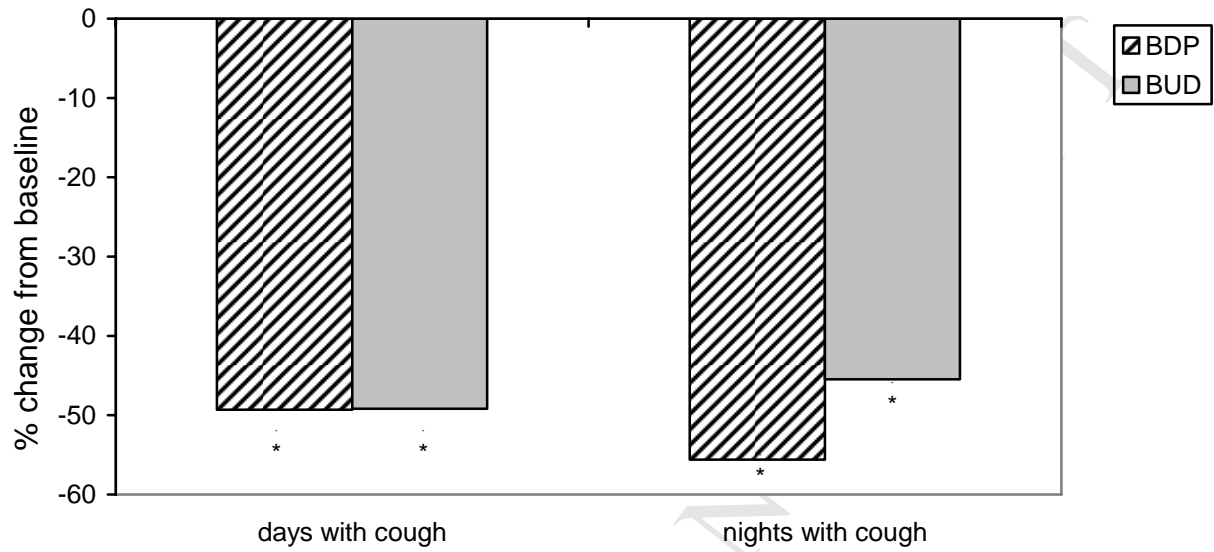
* $p < 0.05$ vs prn salbutamol; BDP= beclometasone dipropionate

<<Fig. 4>>



Scale ranging from 0 (no symptoms) to 4 (severe symptoms); * $p < 0.001$ vs baseline; No significant difference between treatments; BDP= beclometasone dipropionate; BUD=budesonide

<<Fig. 3>>



*p<0.05 vs baseline for all changes; No significant differences between groups; BDP=beclometasone dipropionate; BUD=budesonide