

Review Article

A review of once-daily delivery of anti-asthmatic drugs in children

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Determining which drug is suitable for, and which patient can benefit from, a once-daily dose of prophylactic treatment is important for practitioners who want to improve therapeutic compliance in children with asthma. According to the literature, once-daily delivery of cromolyn sodium, nedocromil or beclomethasone dipropionate must be avoided. On the other hand, switching from a twice-daily to a once-daily regimen is efficient and safe only in children with well-controlled asthma using nebulized or dry-powder budesonide, dry-powder fluticasone propionate, flunisolide, or sustained-release theophylline. Such information is not available for long-acting β_2 -agonists, except for oral bambuterol. Initiating a once-daily treatment in previously untreated children can only be based on low doses of inhaled budesonide or on an oral drug, montelukast. Further studies in children with severe asthma or treated with metered-dose inhalers and spacer devices are required before recommending a once-daily drug delivery in such situations.

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Asthma is the most common disease that occurs in children, and nearly 20% of pediatric patients require daily prophylactic treatment because of persistent or severe asthma (1, 2). However, one major problem in asthmatic patients, and particularly in children, is compliance. In 8–12-year-old children, electronic monitoring over a 13-week period has demonstrated a 58.4% median use of inhaled corticosteroids and a strong relationship between the lowest rates of compliance and the risk of an exacerbation requiring oral steroids (3). Even with optimal patient follow-up in a clinical trial, adherence to prophylactic asthma treatment is only 77%, whereas estimated compliance (as judged by using daily diary cards) is 93% (4). Reasons for non-compliance to long-term medications are multiple, including poor understanding, fear of steroid side-effects, adolescence, and a wish to be just like everyone else. Solutions proposed for resolving non-compliance are equally numerous (5, 6). One of these propositions consists of simplifying the treatment program by reducing the frequency of drugs administration from twice daily, as usually recommended, to once daily (7).

To our knowledge, there is no clear evidence that once-daily scheduling results in better compliance or quality of life than if anti-asthmatic treatment is administered twice daily, but patient preferences favor the once-daily regimen over twice-daily administration (7). Such a change in treatment clearly raises questions about drug efficacy. Moreover, if efficacy is preserved, can prophylactic asthma treatment be prescribed once daily for each drug and for each child, whatever the age, the device and the asthma severity? The aim of this review is to guide clinicians in their decisions by presenting and discussing, drug-by-drug, the possibilities for once-daily administration in children with asthma.

Cromolyn sodium (sodium cromoglycate) and nedocromil

Both cromolyn sodium and nedocromil are considered to possess anti-inflammatory properties and have been recommended in the stepwise approach for managing asthma in children (2). Most of the early studies conducted

with cromolyn sodium in the late 1960s and 1970s adopted a four-times daily dosing schedule (8). The dosing interval was studied subsequently in a pediatric study conducted over 3 months, where patients took cromolyn sodium four times daily during the first month, three times daily during the second month and, when possible, twice daily during the third month (9). Most of the patients (77%) tolerated a twice-daily dosing schedule. However, despite pulmonary function tests being higher during the month when cromolyn sodium was taken twice daily than at baseline, a functional deterioration was observed between the months when cromolyn sodium was taken three times daily and twice daily. Consequently, cromolyn sodium is usually delivered three times daily, with a possible reduction to twice daily in only a few selected patients.

To our knowledge, only one pediatric study, published as an abstract, demonstrated that a twice-daily dosing regimen was as efficient as a four-times daily regimen with inhaled nedocromil (10). The same findings were observed in adults (11). No data currently support the once-daily delivery of nedocromil.

Inhaled corticosteroids

Clinical trials designed to determine whether a reduction in the dose frequency of inhaled corticosteroids to once daily is associated with similar efficacy to that with more frequent administration, have been conducted on only a few occasions in children. Moreover, not all of the available inhaled corticosteroids or devices used to deliver the drugs have been studied in children, including, in particular, pressurized metered dose inhalers used with spacer devices.

Budesonide

Budesonide has been studied in great detail, but pediatric trials have only investigated budesonide Turbuhaler or budesonide nebulized suspension. In a double-blind, randomized, parallel-group study, 163 children (7–16 years of age) with mild asthma that had not previously treated with anti-inflammatory drugs, received either 100 µg or 200 µg of budesonide Turbuhaler once daily in the morning, 200 µg twice daily, or placebo, for 12 weeks (12). All three treatment regimens provided protection against exercise-induced bronchoconstriction and were well tolerated. In another study of 340 treatment-naïve patients (12–70 years of age) with mild-to-moderate asthma, budesonide 400 µg Turbuhaler given once daily in the morning or evening was as

effective and tolerated as the same total dose given twice daily (13). Campbell et al. (14) observed a similar result in 167 children on 0–200 µg/day inhaled steroid with asthma symptoms and sub-optimal peak flow values who were randomly allocated budesonide Turbuhaler for 8 weeks, either 400 µg once daily (in the morning) or 200 µg twice daily. Moller et al. (15) studied the effect of switching from twice-daily to once-daily treatment in 206 asthmatic children 5–15 years of age, whose asthma was well controlled with 200–400 µg/day of budesonide Turbuhaler. He found that pulmonary function tests, symptom scores and bronchodilator use of children receiving once-daily treatment in the morning were not different from those of children receiving twice-daily treatment. However, it seems important to note that the children studied had no basal bronchial obstruction and that the duration of the study was only 12 weeks. Indeed, in adults with a mean predicted forced expiratory volume in one second (FEV_1) of 73.6%, twice-daily doses of 400 µg of inhaled budesonide were more effective than a single dose of the same total daily dose (800 µg) at bedtime in the long term (1 year) control of asthma (16). Another important finding concerns the effect on growth of the once-daily dosing of inhaled budesonide. A recent study conducted in 24 children, 5.6–12.5 years of age, showed that 800 µg of budesonide administered once daily in the morning had a sparing effect on short-term lower leg growth and collagen turnover as compared with 400 µg administered twice daily (17). The hypothesis that the effects on growth may be less pronounced during once-daily dosing than with twice-daily dosing could be applied to inhaled corticosteroids other than budesonide, including intranasal corticosteroids (18, 19).

Concerning budesonide nebulized suspension, this drug was compared in a dose of 0.25 mg once daily, 0.25 mg twice daily, 0.5 mg twice daily or 1.0 mg daily, for 12 weeks, in 480 children aged from 6 months to 8 years with moderate persistent asthma previously treated with inhaled steroids (31%), cromolyn sodium (72%) and/or theophylline (10%) (20, 21). The improvement conferred by once-daily nebulized doses of 1.0 mg budesonide in the morning has been found to be equivalent to that given with twice-daily doses, and was independent of the use of a mouthpiece or a facemask for inhaling the drug. In another study enrolling 359 infants and young children not adequately controlled with bronchodilators or non-corticosteroid anti-inflammatory treatments, all budesonide inhalation suspension doses (0.25 mg, 0.50 mg, or

1.0 mg), given once daily in the morning, produced significant improvements in symptoms and significant decreases in rescue medication use compared with placebo (22). However, significant improvements in FEV_1 were only obtained in the 0.5- and 1.0-mg groups.

In conclusion, once-daily administration of nebulized or dry-powder budesonide is as efficient and safe as a twice-daily administration of the same dosage, in both corticosteroid-naïve children with asthma and stable pediatric patients already receiving an inhaled corticosteroid. This may be explained by the release from airway cells of the reversibly esterified part of each dose of budesonide when, after an initial saturation of the glucocorticosteroid receptors, some unoccupied receptors reappear (23).

Fluticasone propionate

Once-daily delivery of fluticasone propionate has been mainly studied in cohorts of adult patients; only a few between 12 and 16 years of age were included. These studies revealed convincing data for using 200–500 µg of fluticasone propionate powder once a day in moderate asthma or 1 mg of fluticasone propionate delivered from a metered-dose inhaler once daily in severe asthma rather than the same total dose delivered twice daily (24–27). Only one study, published as an abstract, demonstrated, in 295 children with stable, mild-to-moderate asthma, the equivalence of fluticasone propionate 50 µg twice daily and 100 µg nocte, via the Accuhaler (28). To date, no study has investigated the combination of fluticasone and salmeterol dry powder in the same device as a once-daily schedule.

Beclomethasone dipropionate

We found no pediatric study that had investigated beclomethasone dipropionate, and only three such studies have been conducted in adults (29–31). Two studies showed a significant deterioration of asthma when switching patients from standard doses of beclomethasone dipropionate twice or three times a day to the same daily dose once a day (29, 30). On the other hand, the last study demonstrated, in moderate asthma controlled with a twice-daily dose of inhaled beclomethasone dipropionate, the equivalence of a single dose of 1,000 µg of beclomethasone dipropionate, delivered either in the late afternoon or at bedtime, and a twice daily dose of 500 µg of beclomethasone dipropionate (31). Particular attention should be given to the new hydrofluoroalkane-134a beclomethasone dipropionate delivered from

Autohaler breath-actuated device (QVAR), for which some clinical studies are starting to be published in children (32).

Flunisolide

For patients (306 adults and children) with asthma that was controlled with 500 µg of inhaled flunisolide twice a day, switching to 1,000 µg once a day (in either the morning or evening) was effective in maintaining control of asthma over a 12-week period (33). However, reducing in the same patients the dose to 500 µg once daily led to a deterioration in asthma control.

Mometasone furoate

Two recent studies compared, over a 12-week period, the efficacy and safety of once-daily delivery of mometasone furoate dry powder inhaler, 200 µg or 400 µg, with placebo in patients (age-range: 12–70 years) with asthma previously treated only with short-acting inhaled β_2 -agonists (34, 35). All active treatments improved asthma compared with placebo, but the higher dose of mometasone furoate induced additional improvement in morning expiratory flow rates compared with the lower dose.

Triamcinolone acetonide

A recent multi-national, randomized double-blind placebo-controlled study demonstrated the efficacy of 900 µg of triamcinolone acetonide hydrofluoroalkane-134a pressurized metered-dose inhaler given once daily in the evening to adult patients with mild-to-moderate persistent asthma compared with 450 µg twice daily for maintaining asthma control (36).

Anti-leukotriene drugs

At present, leukotriene receptor antagonists are only approved for use in pediatric patients with asthma in some countries with different lower age limits: 5–12 years for zafirlukast (Accolate) and 2–6 years for montelukast (Singulair) (37). From the pediatric point of view, montelukast is the most interesting of all the anti-leukotrienes because of its once-daily dosing requirement (a 5-mg chewable tablet in the evening for children 6–14 years of age and a 4-mg suspension for 2–6-year olds). Moreover, the data in asthmatic children younger than 6 years of age suggest its value in an age-group where only few efficacious treatments for asthma have been documented (38).

Long-acting β_2 -agonists

To our knowledge, no study has compared in children the once- or twice-daily delivery of inhaled salmeterol or formoterol. In adults, Faurschou et al. (39) studied salmeterol in two different doses (50 μg twice a day or 100 μg nightly) in the treatment of poorly controlled nocturnal asthma despite corticosteroids, oral long-acting bronchodilators, or both, and found that the two dose schedules were equally effective and significantly better than placebo. Formoterol, because it has a sustained effect on airway function [an improvement of 20–30 l/min in the peak expiratory flow (PEF) rate is seen 12 h after dosing], has been approved for use once or twice a day in European adults (40). However, in patients taking inhaled corticosteroids, formoterol 24 μg once daily induced a similar degree of sub-sensitivity to adenosine monophosphate bronchial challenge, as also observed to occur with formoterol 24 μg twice daily (41).

Once-daily oral bambuterol (20 mg in the evening) provided a highly effective, convenient, and less expensive alternative to twice-daily inhaled salmeterol (50 μg each dose) for relief of nocturnal symptoms in adult patients treated with inhaled and/or oral steroids for moderate-to-severe asthma (42, 43). Two recent studies have compared in children with asthma the safety of bambuterol (an oral solution in 2–5-year-old children, of 10 mg in the evening; or tablets in 6–12-year-old children, 10 or 20 mg in the evening) to that of terbutaline three times daily for 1 year (44, 45). The two drugs showed a comparable and favorable safety profile. Moreover, the efficacy variables (PEF or *FEV*, asthma symptoms, restlessness, other reported symptoms, use of inhaled β_2 -agonists, night-time awakenings) were similarly improved in both groups. Because of its 24-h duration of action and its mode of delivery, the authors concluded that oral bambuterol should be the preferred bronchodilator agent in children (44, 45).

Theophylline

Once-daily sustained-release theophylline in children with asthma has been studied on several occasions. However, data are difficult to compare because different sustained-release formulations were used in these studies. Moreover, all studies were conducted in children ≥ 7 years of age and therefore data cannot be extrapolated to younger children.

Treating asthmatic children with only a once-daily dose of sustained-release theophylline

before bed has been found to be clinically efficient, as demonstrated by improvement of symptomatology and pulmonary function tests (46–48). Plasma theophylline levels were usually found to be below the therapeutic range 24 h after once-daily dosing and/or were characterized by large variations (46, 49, 50). Evening dosing allowed a better effect on the airways than morning dosing, but induced a greater variability in theophylline levels (46, 50). When compared to twice-daily dosing, the once-daily dosing of theophylline induced a larger peak-to-trough fluctuation and a higher percentage of pediatric patients with sub-therapeutic theophylline levels in the second 12-h period in two studies of three (51–53). In a single-blind, randomized crossover trial comparing two sustained-release formulations of theophylline in 36 children, a single dose at bedtime was significantly associated with higher morning PEF rates and plasma theophylline levels at 11.00 h than two doses per day (54).

A decrease in the evening serum theophylline level was noted when children with nocturnal asthma that had previously been controlled with sustained-release theophylline twice daily, were treated with the same dose of theophylline once a day for 10 weeks (55). Their pulmonary function tests and symptoms remained unchanged. Adding sustained-release theophylline once daily, at 20.00 h, to the prophylactic treatment of children continuing to have troublesome nocturnal wheeze or cough induced clinical efficacy and satisfactory serum theophylline levels (48). Recently, once-daily theophylline was shown to reduce serum eosinophil cationic protein and eosinophil levels in induced sputum of adults with asthma (56). This indicates that there is an anti-inflammatory, as well as a bronchodilatory, effect.

Conclusion

A once-daily dose of prophylactic treatment is important to consider in children with asthma for improving acceptance of treatment. At present, only a few drugs have been studied in sufficient detail in children to recommend a once-daily delivery. However, from this review, we can offer some advice:

1. Some drugs cannot be prescribed once a day, particularly cromolyn sodium and nedocromil.
2. In children with well-controlled asthma (and only in this case) switching from twice-daily to once-daily treatment, with the same total amount of drug administered per 24 h, has proved efficient and safe when treatment

includes nebulized or dry-powder budesonide, dry-powder fluticasone propionate, flunisolide, or sustained-release theophylline. Such a switch should be avoided with beclomethasone dipropionate. Once-daily delivery of salmeterol and formoterol has not been studied in children, but oral bambuterol may represent an interesting alternative.

3. A once-daily treatment in children with hitherto-untreated asthma rests only between oral drug (montelukast) and low doses of inhaled budesonide (dry powder or nebulized suspension).
4. The optimum period of the day for administration of the drug has not been completely resolved as, in the different studies, treatments are delivered sometimes in the morning and sometimes in the evening. However, the usual practice recommends taking medication at bedtime, because families have usually more time in the evening than in the morning.
5. Other studies are needed, particularly in children with severe asthma and in children treated with metered-dose inhalers and spacer devices, to indicate when once-daily treatment is effective.

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