Topical Review

The problems of treating adolescent asthma: what are the alternatives to inhaled therapy?

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The prevalence of asthma in children and adolescents continues to increase world-wide, with asthma remaining the most common chronic illness of childhood. Morbidity is high in the latter age group, indicating that many adolescents with asthma symptoms are not receiving appropriate treatment for their condition.

Inadequate symptomatic control should alert the physician to the possibility of non-compliance, which is not limited to those patients with a poor understanding of their condition. Psychosocial problems, such as isolation and low self-esteem, are inherent in adolescents with asthma due, in part, to the highly visible nature of symptoms and the method of delivery of current inhaled therapy. Compliance with therapy in adolescents in particularly low if the dosing regimen is more than twice daily, with poor inhaler technique contributing to ineffective control.

Failure to take asthma medication can result in asthma exacerbations and increased disease severity, with the resultant need for powerful medication and hospitalization (incurring substantial patient and healthcare costs). Although better management techniques, such as tailoring medication and individualizing treatment regimens may improve compliance in this group, there is an obvious need for alternative treatment options.

An effective and well tolerated oral tablet therapy, with a simple unobtrusive regimen, would provide a potential solution to the high level of non-compliance seen in this age group. The leukotriene receptor antagonists offer a practical alternative amongst existing oral therapies, and their efficacy and simple oral dosing regimen may prove valuable in increasing compliance in adolescents.

Introduction

The prevalence of asthma in children and adolescents continues to increase world-wide (1), with asthma remaining the most common chronic illness of childhood (2,3). In 1996, the world-wide prevalence of wheeze, a predominant symptom of asthma, was reported in approximately 14% of 13–14 year olds (4). In 1997, prevalence was reported to be higher, at 32%, in the U.K. with similar rates in the U.S. and New Zealand at 22% and 30%, respectively (2,5).

Asthma in adolescents (defined by the World Health Organization as spanning the ages of 10–19 years) (6) is associated with higher mortality rates when compared with rates in younger children with asthma. For example, between 1990 and 1992, the U.K. mortality rate due to asthma in 10–14 year olds was three times that of 5–9 year olds and the rate for 15–19 year olds was six times that of 5–9 year olds (7). Morbidity in this age group is also unacceptably high; almost all adolescents with asthma report that their symptoms interfere with daily activities such as lessons and physical activity (2). In the U.S. poor control of asthma results in over 10 million missed school days per year (8).

Whilst the prevalence of asthma in adolescents continues to rise, there are indications that many adolescents with asthma symptoms are not receiving treatment for their condition. In nearly 500 Danish adolescents aged 12–15 years, 25% were recorded as having asthma-like symptoms and only 70% of these had been diagnosed with asthma (9). This was despite the presence of symptoms of cough, wheezing, dyspnoea and at least one positive test result for asthma. Similarly, in a U.K. study of nearly 28,000 12–14 year olds, over 30% reported symptoms of wheeze, with only 50% having been diagnosed with asthma (9). This was despite the presence of symptoms of cough, wheezing, dyspnoea and at least one positive test result for asthma. Similarly, in a U.K. study of nearly 28,000 12–14 year olds, over 30% reported symptoms of wheeze, with only 50% having been diagnosed with asthma. Only 20% of the adolescents in this study had received drug treatment for wheezing and asthma in the past year (2).

The high morbidity and mortality rates in adolescents with asthma indicate that under-diagnosis and under-treatment of this condition is a major problem in this age group (2).

Psychosocial problems associated with adolescent asthma

The need for asthma therapy, particularly when administered in a visible manner, identifies the adolescent with their...
condition and can discriminate them from their peers. This can lead to isolation from peer interaction, sport and other activities. Adolescents are constantly striving to achieve independence from their parents, a process that is hampered by regular attendance at clinics, with the doctor discussing treatment with the parent and not the adolescent.

Adolescents have a great need to be accepted by their peers and are dependent on them for approval of their behaviour. A recent survey in the U.K. showed that 10% of adolescents worry about the effect of asthma on personal relationships, and one in five adolescents do not like taking their asthma medication in front of others (10). Increased knowledge of asthma among healthy adolescents is associated with a more positive attitude towards, and a greater acceptance of those with asthma (11).

Feelings of isolation amongst adolescents with asthma may be compounded by delays in the physiological changes that occur during adolescence; 45% of children with asthma experience delays in the onset of puberty and tend to be smaller and less sexually mature than their peers (12). As treatment with inhaled corticosteroids has been associated with growth suppression (13), this knowledge may create a barrier to achieving full compliance with this type of therapy.

Frequent absence from school and social activities may cause adolescents with asthma to suffer psychological disturbances of self-esteem and self-image. Moderate and severe persistent asthma appears to be associated with increased incidence of particular categories of psychiatric problems in children and adolescents, in particular internalized anxiety disorders with anxious/depressive symptoms (14). Feelings of helplessness, depression and hostility, seen particularly with severe asthma, may result in disregard for treatment (15). The risk of serious behavioural problems in adolescents with severe asthma is nearly three times that in young people who do not have asthma (16).

The desire of adolescents to be accepted by their peers may lead to risk-taking behaviour. Adolescents with a past history of asthma show a stronger intention to become smokers than non-asthmatics and identify closely with the image of smokers (17). One theory for this is that these adolescents are making a statement that they are not threatened by the stigma of their disease and that they can smoke because they have healthy lungs. It appears that self-image is more important than health status when understanding attitudes towards smoking.

The possibility of having an asthma attack during exercise results in many adolescents withdrawing from physical activity. Studies have shown that 30–40% of adolescents with asthma either have to stop in the middle or miss out on sports completely, with 77% of children with asthma aged 4–17 years having difficulty with certain sports (18,19). Missed sport, and days off school in general, cause added stress with more than one third of adolescents with asthma worrying that it will affect their future career options (10).

It is clear that asthma causes particular problems in the adolescent age group. Psychosocial factors, including depression and poor interpersonal skills, are inherent in adolescents with asthma and have been shown to have an adverse impact on compliance with asthma therapy (20). In addition, the highly visible nature of asthma, the symptoms and the use of inhaled therapy, isolates the adolescent from their peers. This, possibly combined with concerns about side effects with inhaled corticosteroids, may lead to poor compliance.

Non-compliance with inhaled asthma therapy

In mild, intermittent asthma, short-acting beta-agonists are traditionally used alone as first-line therapy, with inhaled corticosteroids being prescribed with increasing disease severity. Compliance with inhaled medication is generally poor during the long-term treatment of asthma and incorrect inhaler use is common (21). In adults with mild-to-moderate asthma, compliance has been reported to be as high as 73% with an inhaled asthma medication prescribed three times daily. However, actual compliance as measured by canister weight change was much lower, with only 15% of adults using their inhaler an average of 2.5 or more times per day (22). Similarly, another study in patients aged 18–70 requiring treatment with regular inhaled steroids and beta-agonists, showed that only 14% of patients took the prescribed twice-daily dose of inhaled asthma medication on more than 80% of days (23).

A medication required more than twice daily adds restraints to daily life, especially in adolescents, and may result in one or more missed doses (24). Incorrect dosing may lead to ineffective control of asthma symptoms, causing the adolescent to believe that treatment is not working and, therefore, not worth taking. In a study in children with asthma aged 8–12 years who required both inhaled corticosteroid and beta-agonist therapy, self-reported and electronically monitored compliance with inhaled corticosteroids were measured. More than 90% of children exaggerated their use of medication (25). The median reported use of inhaled corticosteroids was 95%, whereas the median actual use was 58%, demonstrating that actual compliance is much less than that reported by patients. The results also indicated a striking relationship between poor corticosteroid adherence and exacerbation of asthma (25). Evidently, asthma therapy needs to be consistent; however, the high level of non-compliance in this age group can lead to poor asthma control, a problem that needs to be addressed (25).

There are concerns regarding impaired growth and incorrect association with anabolic steroids (26,27). There is no conclusive evidence to demonstrate any long-term systemic side effects associated with the use of inhaled corticosteroids. However, the concern about possible side effects, whether justified or not, can lead to poor compliance. The risk–benefit ratio of corticosteroids in paediatric asthma is acceptable, although the possibility of premature osteoporosis in patients with perhaps 30–40
years' regular use cannot be excluded (28). In order to minimize the potential risk of high-dose corticosteroids, dosing should be kept at the minimum needed to achieve adequate asthma control. Non-corticosteroidal add-on therapy with a long-acting beta-agonist or a leukotriene receptor antagonist (LTRA) could be considered as an alternative to increasing the corticosteroid dose. A greater benefit from add-on therapy is normally seen compared with doubling the dose of inhaled corticosteroid (29-32).

Implications for increased morbidity and mortality associated with poor compliance with asthma therapy in this age group emphasize the importance of treating adolescents as a separate and special group with individual needs (6).

### Finding a solution to the problem of non-compliance

By tailoring medication to the adolescent, allowing them more control over their disease with a choice of alternative treatments, compliance in this group may be improved. A good approach is to build a partnership between doctor and adolescent, allowing discussion of management and treatment options (33). Educating parents to allow the adolescent control over decisions is essential, although the parent will have an important role in reinforcing the belief that treatment is safe and effective. The treatment guidelines available should be used flexibly and should be individualized to suit the lifestyle of the adolescent, not the parent (34). An approach involving discussing healthy lifestyle, rather than disease, may be important in adolescents not willing to accept that they have asthma (35).

Education alone, however, is not enough to ensure compliance. Although steroid phobia may be overcome by educating the adolescent and parent to dispel any speculative beliefs, adolescents often do not understand what they are told about asthma (10). In a study of children aged 8-12 years with asthma receiving inhaled corticosteroids and beta-agonists, both children and parents took part in an extensive asthma education programme and all demonstrated knowledge of the roles of beta-agonists and corticosteroids in their therapy (25). Subsequently, when self-reported compliance was compared with Chronolog-assessed compliance (an electronic device monitoring time and date of actuation), actual compliance was recorded as 58% compared with the patient-reported level of 93%. The number of doses taken at correct intervals was also low at approximately 30%. More importantly, the consistency of diary entries detailing the child's medication regimen reflected a clear understanding of the treatment schedule, although this did not correspond with actual use (25). Those children with severe asthma attacks that required additional treatment with oral corticosteroids were shown to be far less compliant than those who achieved adequate asthma control (median compliance of 14% and 68%, respectively) (25).

Since the dosing regimen of therapy can have a significant impact on patient compliance, especially if it affects the lifestyle of the average adolescent, efforts to simplify the regimen are beneficial. Compliance with a variety of dosing regimens was assessed in children aged 9-16 years with moderate-to-severe asthma, a factor likely to increase compliance. Small groups of children received inhaled corticosteroids at different prescribed dosing regimens. When inhaled medication was prescribed four times daily (n = 6), it was found to be taken as prescribed on 18% of days and, when administered three times daily (n = 3), on 34% of days. Furthermore, reducing the dosing frequency to a twice-daily regimen (n = 5) resulted in a major improvement in compliance with medication then being taken as prescribed on 71% of days (24).

Absolute percentage compliance values in this study need to be interpreted with caution, due to the small sample size and the relevance of these findings to patients who require regular therapy for mild-to-moderate rather than moderate-to-severe asthma. Nevertheless, it appears that reducing the dosing frequency of inhaled medication in adolescents with asthma is beneficial in terms of compliance. These findings are similar to those documented in a review of 26 compliance studies in a variety of chronic conditions in adults, indicating that improvements in compliance are seen when the dosing regimen is reduced from a thrice- to twice-daily regimen. In this review there appears to be little difference in compliance between thrice- and four-times daily or between once- and twice-daily regimens (36).

Many adolescents also have difficulties with the method of delivery of inhaled asthma therapy and, even in adolescents whose condition is stable on regular inhaled therapy, over 70% make one or more mistakes when using their metered dose inhaler. Furthermore, following intensive education, 14% of adolescents still fail to demonstrate an adequate inhaler technique (37). This suggests that for a small proportion of adolescents who do appear to comply well with their treatment, compliance may be unintentionally reduced by the complexity of using an inhaled therapy.

Although corticosteroids are the mainstay treatment in asthma, the introduction of new therapeutic options allows alternatives to be considered, which may help to improve compliance.

### Does oral therapy offer a useful alternative in treating adolescent asthma?

Oral therapy avoids the obvious problems associated with inhaler technique and, in addition, non-steroidal oral therapy may reduce 'steroid phobia' which may create a barrier to achieving good compliance. For the clinician, an ideal alternative oral therapy for use in this age group should also provide similar control over asthma symptoms and exacerbations to low-dose inhaled corticosteroids, the mainstay of current asthma treatment. Non-steroidal oral asthma treatment options offer a potential solution to
improve asthma control by improving compliance in this difficult-to-treat patient population.

Currently available oral anti-asthma treatments excluding oral corticosteroids include theophylline, ketotifen—an anti-histamine with anti-anaphylactic properties—and the leukotriene modifiers, zileuton, zafirlukast, montelukast and pranlukast.

THEOPHYLLINE

Theophylline, available as both short- and long-acting preparations, is an oral bronchodilator that may also have anti-inflammatory effects (38-41). Theophylline has been shown to improve compliance compared with inhaled therapy in adolescents and may therefore be of benefit in this respect. In a retrospective review of medical records and pharmacy claims data from 276 patients with asthma who had concurrent prescriptions for theophylline and anti-inflammatory agents, data from 119 medical records were considered suitable for calculation of compliance rates. In this group, both adults and adolescents (aged 18-65 years and 12-17 years, respectively) complied significantly better with theophylline (especially the adolescents) than with inhaled corticosteroids or inhaled cromolyn (Fig. 1) (42). This study is severely limited because by measuring compliance using retrospective pharmacy claims data, it is assumed that the prescriptions were actually taken as dispensed—with the potential for over-estimation. Clinical trials using more direct measures of compliance may show more accurate values. Nevertheless, the study does allow some comparison between compliance for oral and inhaled medication. Limited efficacy, frequent side effects including nausea and headaches, and concerns regarding theophylline toxicity at higher doses have, however, discouraged its use as an alternative to low-dose inhaled steroids (43).

KETOTIFEN

Ketotifen is an oral H1-antagonist with inhibitory effects on the histamine-mediated allergic response. Anti-inflammatory properties have also been documented, although the mechanism of action in inflammation has not been clearly established (1,40). However, the benefits of treatment with ketotifen appear to be limited. In a long-term trial in children aged 2-6 years of age with chronic asthma receiving ketotifen, analyses of frequency of acute exacerbations, symptoms, concomitant medication and parental and physician preference showed there were no significant differences between ketotifen and placebo groups (45).

LEUKOTRIENE MODIFIERS

Zileuton is a 5-lipoxygenase inhibitor that inhibits the synthesis of leukotrienes produced by the action of 5-lipoxygenase on arachidonic acid. These leukotrienes are produced from inflammatory cells such as mast cells, eosinophils and basophils, and are implicated in the pathogenesis of asthma, inducing smooth muscle
contraction, eosinophilic infiltration, vascular leakage and bronchoconstriction (46-48). Zileuton can inhibit inflammatory changes in the pathophysiology of asthma (49), and inhibits bronchospasm in patients with exercise-induced asthma (50). However, the need for a four-times daily dosing regimen, which is accompanied by elevated liver transaminase levels (51), is a major disadvantage of this drug, limiting its usefulness in adolescent asthma.

The leukotriene receptor antagonists (LTRAs), zafirlukast and montelukast block the effects of leukotrienes at their receptor. These agents appear to prevent inflammation by inhibiting the activity of leukotrienes in target organs such as the lung. Both drugs are generally well tolerated and require less frequent dosing than zileuton as they are once- or twice-daily medications. In mild asthma, zafirlukast blocks both early and late responses to allergen challenge and also attenuates the associated increase in non-specific airway hyperreactivity (52). In addition, the LTRAs have been shown to reduce cellular infiltration and activation of inflammatory cells (53-55).

The LTRAs are effective in reducing day- and night-time asthma symptoms, reducing rescue beta-agonist use and improving lung function in placebo-controlled trials (54-57). There is also evidence that treatment with LTRAs reduces the frequency of asthma exacerbations in adults with mild-to-moderate and severe asthma (54, 56-59). A recent meta-analysis of five 13-week trials with zafirlukast twice daily showed that the risk of requiring oral corticosteroids was reduced by approximately 50%, compared with placebo in patients with asthma receiving only beta-agonists as required (Fig. 2) (60). Montelukast has been shown to reduce the number of days with asthma attacks by 31% compared with placebo in adults with chronic stable asthma, although the number of overall attacks was not significantly reduced (54). However, in a highly selected adult asthma patient population, montelukast was shown to be less effective than inhaled beclomethasone dipropionate, although both treatments provided significant improvements over placebo (61). In patients who are likely to comply well with treatment, this study therefore supports the use of inhaled corticosteroids as the first-line treatment of choice in patients with mild persistent asthma. No double-blind efficacy comparisons have been performed with an LTRA versus a low-dose corticosteroid in symptomatic adolescent patients. However, a 4-week randomized cross-over study in adolescents with stable asthma, aged 12-17 years, showed that 70% of adolescents preferred therapy with zafirlukast compared with only 27% preferring an inhaled corticosteroid delivered by a metered dose inhaler (37). This preference for oral asthma therapy with zafirlukast compared with inhaled beclomethasone was seen to a greater degree in adolescent asthmatics than adults (62).

Twice-daily dosing of zafirlukast in adults has been shown to be associated with a high mean compliance rate of 80% (monitored by a computerized capped bottle). Mean adherence to this oral therapy (total days with two tablets taken at the correct interval/total days on treatment) was 64%, about twice the literature values for adherence with twice-daily inhaled asthma treatments, assessed using similar inhaler technology to the computerized capped bottle (23, 63). A factor possibly contributing to high compliance rates with the LTRAs may be that improvements are seen within days of starting treatment (54-57).

![Fig. 2. Incidence and risk of asthma exacerbations requiring oral corticosteroid rescue therapy in 1664 patients treated with zafirlukast or matching placebo. Data for the meta-analysis were obtained from five 13-week placebo controlled trials performed in steroid naïve patients (60). The risk of an asthma exacerbation requiring oral steroid treatment on zafirlukast 20 mg b.d. was significantly less than that on placebo (Odds ratio = 0.58; 95% Cl. 0.34-0.97) \( \cap \). placebo b.d.; \( \{ \), zafirlukast 20 mg b.d. \( P = 0.01 \).]
Non-compliance with inhaled corticosteroids in adolescents may in part result from no immediate positive effect on symptoms; compliance may therefore be poorer if patients perceive that therapy is having no immediate effect (43).

The ability to participate in school sports and social activities may help to alleviate feelings of isolation prevalent among adolescents with asthma, and LTRAs have been shown to reduce the number of days absent from school by over 50% (64). An additional property of the LTRAs important in this age group is that they provide prolonged protection against bronchoconstriction induced by triggers such as exercise and cold air (43), reducing the need for more frequent and obtrusive inhaled medication to control or prevent asthma symptoms. A study in children aged 6–14 years showed that zafirlukast, administered 4 h before exercise reduced exercise-induced bronchoconstriction by at least 50% compared with placebo (65). Montelukast also inhibits exercise-induced bronchoconstriction in children with asthma and there is no evidence of tachyphylaxis when given for up to 12 weeks (66).

LTRAs are an effective controller therapy in mild persistent asthma and may therefore provide a useful alternative controller treatment option in adolescents with mild persistent asthma unwilling or unable to take low-dose inhaled corticosteroids.

Conclusion

The transition from childhood into adulthood is a period of intense emotional and psychological change. For those with asthma, long-term treatment requirements pose an additional burden. In particular, the highly visible nature of both asthma symptoms and the use of inhaled therapy have been shown to have an adverse impact on compliance with asthma therapy. Non-compliance with asthma therapy is particularly high in the adolescent age group and has implications for continuing high levels of morbidity and mortality. Improved patient management and education may improve compliance, but there remains a need for alternative treatment options in some patients.

Oral therapy is simple to take and unobtrusive, factors which appear to result in increased preference for oral treatment in this age group. Whilst inhaled corticosteroids are likely to remain the first-line treatment of choice in adolescents with asthma, the benefits of oral agents support their use as alternative controller therapy. In particular, the increased compliance, rapid onset of action, good control over exacerbations and prolonged protection from exercise-induced asthma seen with the LTRAs make them a valuable alternative amongst currently available oral therapies.

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