Asthma in childhood: drug therapy

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Conflict of interest

Sarinho E received fees for giving lectures and for participating in clinical researches sponsored by Merck Sharp and Dohme, GlaxoSmithKline, Astra Zeneca and Novartis.

Description of the evidence collection method

A critical analysis of articles from the MEDLINE database was carried out using the following keywords (MeSH terms): asthma, asthma/epidemiology, asthma/therapy, oxygen therapy, prednisone, prednisolone, dexamethasone, mineralocorticoids, glucocorticoids, adrenal cortex hormones, bronchodilators, albuterol, terbutaline, fenoterol, salmeterol, formoterol, budesonide, fluticasone, bambuterol, leukotriene receptor antagonists, montelukast, omalizumab, aminophylline, administration and dosage, administration, oral, administration, inhalation, inhalation devices, intramuscular injection, intravenous injection, subcutaneous injection, treatment outcome, side effects, risk factors, mortality, hospitalization.

Degree of recommendation and strength of evidence

A: Experimental or observational studies of higher consistency.

B: Experimental or observational studies of lower consistency.

C: Case Reports (non-controlled studies).

D: Opinion without critical evaluation, based on consensuses, physiological studies or animal models.

Objectives

To make practical recommendations for the treatment of asthma in childhood, based on a critical analysis of evidence published in the medical and scientific literature.

Introduction

Asthma is the most prevalent chronic disease in childhood. In Brazil, the prevalence of active asthma in schoolchildren and adolescents is estimated at 19% and 24%, respectively, with regional variations (**B**)[1].

The use of more specific medications with fewer side effects has made the treatment for asthma safer and more effective. The approach of the asthma attack must be started by evaluating how severe the crisis is, which determines the treatment to be immediately instituted. The prophylactic treatment allows the disease control by decreasing the frequency and severity of the attacks and improves the child's quality of life (**A**)[2,3].

Drug treatment of the asthma attack

1. Can the evaluation of asthma attack severity be made based on clinical parameters?

The use of clinical scores, associated with oximetry measurements and peak expiratory flow contributes to assess the severity of the attack. Measurements, carried out after the initial use of inhaled β-adrenergic agents, are better predictors of asthma attack severity than the same measurements pre-treatment. Pre-treatment oximetry (≤ 93%) is a parameter with high specificity; however it has low sensitivity for attack severity (respectively, 92% and 35%). When determining the attack severity, the main clinical parameters is the assessment of the mental state, dyspnea, capacity to complete sentences, use of accessory musculature, presence of wheezing, respiratory and heart rates. The clinical score that is usually employed is the modified Wood-Downes score (**A**)[3-5]. The peak flow (PF) measurements can be obtained in children as early as from kindergarten and show a direct association with the forced expiratory volume in one second, or FEV_1. In patients older than 12, the PF, at the emergency service, constitutes a good tool to evaluate the severity and evolution of the asthma attack.

Moreover, in young children (> 6 years) comparing PF and FEV_1 shows good association – positive and significant Pearson's coefficient ($r = 0.23$, $p = 0.0008$).

PF values equal to or above 40% after 15 minutes of treatment suggest a favorable outcome with a sensitivity of 74%, specificity of 100% and positive predictive value of 100%. Values < 30% are predictive of an adverse outcome with a sensitivity of 54%, specificity of 93% and positive predictive value of 87% (**A**)[6,7].

Recommendation

Clinical evaluation (clinical scores) is recommended, associated with oximetry measurements and peak expiratory flow to determine the severity of the attack (**A**)[3-7].

2. Must the treatment of severe attack always be carried out at the hospital?

The patient with a severe attack should be hospitalized. Although rare, mortality from asthma is a possibility that should be considered in severe patients (**A**)[8,9]. Early oxygen administration can prevent severe hypoxia that is associated with mortality. Oxygen therapy is indicated for signs of respiratory failure and when the oximetry is below 93% (**A**)[4].

Recommendation

Considering the efficacy of hospital therapy and the possibility of a fatal outcome, it is recommended that the patient with a severe asthma attack always be hospitalized (**A**)[4,8,9].

3. Is the inhaled route more effective than the oral one for bronchodilator (BDL) use during the attack?

The preferred route for bronchodilator use is the inhaled one. Comparison with the oral administration showed that the action of inhaled BDL is faster and has fewer side effects (**A**)[10].

In the treatment of moderate to severe attacks in emergency services, high and repeated doses of β_2-agonists are the initial therapy of choice. The β_2-agonist can be administered at intervals of 10 to 30 minutes or up to four inhalations at a time. BDL therapy under continuous nebulization is also effective for the treatment of acute asthma attack; however, there is little evidence in the pediatric age group. In adults, hospitalization rates were reduced in patients treated with continuous nebulization in relation to intermittent inhalation (RR: 0.68, 95% CI: 0.5 to 0.9) with the best responses being observed in patients with severe lower airway obstruction (RR: 0.64, 95% CI: 0.5 to 0.9). There were no significant differences regarding side effects between the two forms of bronchodilator administration when the mean differences were evaluated with respect to the basal heart rate (-2.87, 95% CI: -6.0 to 0.3) and blood pressure parameters (-1.75, 95% CI: -5.6 to 2.1) (**A**)[11].

Recommendation

The inhaled route is preferred for β_2-agonist use during the asthma attack (**A**)[10,11].

4. In children, is the use of bronchodilators through dose-metered inhaler as effective as the jet nebulizer? Even in severe attacks?

In children with mild to moderate asthma, the use of a dose-metered inhaler to administer bronchodilators results in similar effects to that of using a jet nebulizer (**B**)[1] (**A**)[2,3]. The dose-metered inhaler requires less time for using it and the side effects are also less frequent (with aerosol use). A systematic review of studies that compared the use of bronchodilators with spacers or nebulizers in children showed that the relative risk for hospitalization in children using spacers, compared with those who used nebulizers was 0.72 (95% CI: 0.47 to 1.09). The emergency service stay duration was shorter with the spray attached to spacers, with a difference of less 0.53 hours (95% CI: -0.62 to -0.44 hours). The mean heart rate was lower with the use of spacers, with a difference of less 6.27% of the basal frequency (95% CI: -8.29 to -4.25% basal) (**A**)[12].

In children younger than five years, the use of dose-metered inhalers shows better results than the use of β_2-adrenergic agent in the jet nebulizer. The use of dose-metered inhalers decreased the rate of hospitalization (OR: 0.42, 95% CI: 0.24 to 0.72, p = 0.002), and this decrease was more significant among children with moderate to severe attacks (OR, 0.27, 95% CI, 0.13 to 0.54, p = 0.0003). The clinical evaluation was also greater with the use of dose-metered inhalers, assessed by the clinical score improvement (mean difference of 0.44, 95% CI: 0.68 to 0.20, p = 0.0003). However, it is important to consider that for some children, especially those younger than three years, anxious or in overall poor health, there is a difficulty in the effective administration of the medication. Lack of coordination between inspiration and device use is one of the reasons for the use of spacers with mouthpieces or face masks (**A**)[12,13].

Recommendations

Administration of bronchodilators to treat asthma attacks in children can be accomplished by means of dose-metered inhalers or jet nebulizer. The metered-dose inhaler spacers should be coupled with a face mask or mouthpiece. In severe asthma attacks, when the child shows decreased cooperation or capacity to use the medication, jet nebulizer is recommended (**A**)[12,13].

5. Is the efficacy and safety of short-acting bronchodilators (salbutamol x fenoterol x terbutaline) similar among them?

Salbutamol, fenoterol and terbutaline are short-acting bronchodilators commonly used in asthma attacks. Comparison of efficacy in the treatment of asthma shows similar bronchodilator effect, with an action onset in about 5 minutes and similar intensity and duration for the three drugs (**B**)[14]. There is evidence of greater toxicity of fenoterol, which can be attributed to the higher doses sold in the formulas or the higher affinity with β_1 and α receptors. Comparison of side effects showed that the mean increase in heart rate was 29 bpm, 8 bpm and 8 bpm, respectively for fenoterol, salbutamol and terbutaline. Similarly, decrease in serum potassium was 0.76 mmol/L, 0.46 mmol/L and 0.52 mmol/L (**A**)[15].

Recommendation

The three bronchodilators have similar clinical efficacy. There is evidence suggesting higher toxicity with the use of fenoterol (**A**)[15].

6. In a severe attack, is the efficacy of the subcutaneous and intravenous routes higher than that of the inhaled one for β_2-adrenergic agent administration?

Inhaled route is preferred for the administration of β-adrenergic agents. Use of epinephrine and terbutaline subcutaneously is also effective, with the action onset in about 5 minutes and lasting for about 4 hours. Some clinical trials in children showed similar efficacy between the two routes, but the subcutaneous route may have more side effects. It may be an option in patients unable to use the inhaled route in emergency services (**B**)[16,17].

Few clinical trials have evaluated the use of intravenous β-adrenergic agents for the treatment of severe asthma. In adults, the comparison of intravenous and inhaled salbutamol shows greater efficacy and fewer side effects with the inhaled route (**B**)[18].

Recommendation

Inhaled route is preferably recommended for the use of β-adrenergic agents in asthma attacks. Subcutaneous and intravenous routes are associated with a greater incidence of side effects (**B**)[16-18].

7. Is the use of inhaled ipratropium bromide (IB), associated with β_2-agonist, more effective than β_2-agonist alone in the treatment of acute asthma attack in children?

Several studies have evaluated the use of IB associated with β_2-agonists in non-hospitalized patients in an attempt to reduce the duration of emergency service stay and prevent hospitalizations. In children treated in emergency services and who received inhaled albuterol and systemic corticosteroids, the addition of ipratropium to three inhalations of β_2-agonist carried out for 1 hour was not associated with a significant reduction in hospitalization rates (18% vs. 22% in the control group) (**A**)[3,19].

However, in children and adolescents treated in emergency services with severe attacks, IB can show some benefit. In these patients, adding IB repeated doses (2 doses of 500 μg at 20-minute intervals for a period of one hour) decreased the rate of hospitalization by 15.1%, in relation to the control group treated with β_2-agonist and corticosteroids. It is estimated that it would be necessary to treat 6.6 patients to prevent one hospitalization. Hospitalization rates did not differ between the two groups for patients with moderate attacks (**A**)[4,20].

In association with β_2-agonists, the use of high and repeated doses of IB (250 to 500 μg/dose at 20-to-40-minute intervals for an hour) was more effective than the use of a single IB dose in improving lung function. Adding a single IB dose to β_2-agonist did not reduce hospitalization rates, either (**B**)[1] (**A**)[2,21,22].

The use of this drug combination (repeated nebulized IB doses added to treatment with systemic corticosteroids and frequent administration of β_2-agonists) in hospitalized patients did not show any benefit with regard to time of hospitalization, clinical evolution or need for additional treatment (**A**)[6,23].

The association of IB to inhaled β_2-adrenergic agents in childhood has shown to be safe. Adding IB to β_2-agonists at high and repeated IB doses (250 or 500 μg per dose, every 20 minutes, two or three times), does not increase side effect symptoms, such as tremors, nausea and vomiting (**B**)[1] (**A**)[22].

Recommendations

In patients with mild to moderate asthma attacks, there are no benefits in the association of IB to β_2-agonist. Thus, this association is not routinely recommended for children and adolescents with asthma attacks (**A**)[3,4,19,20].

The early addition of multiple IB doses can be beneficial in reducing hospitalization rates of children with severe asthma attacks (**A**)[20].

8. Are inhaled corticosteroids effective for the asthma attack treatment?

Inhaled corticosteroids are not recommended for rescue treatment in asthma. There are few studies assessing the effect of rescue inhaled corticosteroids. According to the comparison of continuous beclomethasone or during crises (for two weeks), the continuous use was associated with fewer exacerbations (mean 0.97) than the intermittent use (mean 1.69) (**A**)[24]. A study in hospitalized adult patients showed similar efficacy between the use of inhaled corticosteroids at high doses or systemic use, but all patients initially received intravenous corticosteroids for 48 hours, in addition to inhaled β-adrenergic agent (**A**)[25].

Recommendation

Use of inhaled corticosteroids is not recommended for asthma rescue treatment in children (**A**)[24].

9. Is the oral route as effective as the intravenous one for corticosteroid use during the asthma attack? What about the intramuscular route?

The use of oral corticosteroids is as effective as the intravenous or intramuscular routes in acute asthma. Parenteral route is indicated only in severe cases where the drug oral administration is contraindicated. Comparison of two groups of children treated at the emergency room for moderate to severe asthma attacks and randomized to receive methylprednisolone (2 mg/kg) by oral or intravenous route, showed that after 4 hours of treatment, there was no difference in clinical and functional evolution (respiratory rate, pulse oximetry, clinical score and FEV_1). Forty-eight percent and 50% of the patients required hos-

pitalization, respectively, in oral and intravenous groups (non-significant risk increase = 2%, 95% CI = 21% -25%, p = 0.08) (**A**)[26].

Use of intramuscular corticosteroids (0.6 mg/kg in a single dose of dexamethasone) in children treated with acute asthma was also as effective as the use of oral corticosteroid (2 mg/kg/day of prednisone for five days). The clinical score variation after four days of treatment was similar in both groups (difference 0.2, 95% CI 0.4 to 0.7). The proportion of patients discharged and that required readmission in a follow-up period of two weeks was also similar in both groups (absolute risk increase of 1.8%, 95% CI: -5.4 to 9%) (**A**)[27].

Recommendation

During an acute asthma attack, the use of oral corticosteroids is as effective as the intravenous or intramuscular routes of administration (**A**)[26,27].

10. Does the recurrent use of oral corticosteroids for short periods bring side effects?

Use of oral corticosteroids for a short period of time, intermittently, over several years can result in a reduction in bone mass gain, and cause an increased risk of osteopenia in children with asthma (**B**)[28]. There are also changes in bone metabolism in adults who use this therapy (**B**)[29].

Although the side effects caused by the use of systemic corticosteroids are dose-dependent according to the evidence, they are also dose-cumulative (**B**)[28]. Thus, evidence shows that the administration of higher doses of oral corticosteroids for a short period of time should be recommended, instead of continuous use, in order to reduce the risk of adverse systemic effects (**B**)[30].

Recommendation

Use of oral corticosteroids for short periods of time is recommended to minimize side effects, which are dose-dependent and dose-cumulative (**B**)[28,30].

11. Is aminophylline effective in the treatment of severe asthma attacks? As initial drug treatment? As adjunct treatment? Is it safe?

The use of aminophylline became unnecessary in routine treatment of acute asthma, compared to the efficacy and safety of short-acting β_2-adrenergic aerosol, supplemented with oral steroids. Aminophylline confers no additional clinical benefits and may cause side effects by the small margin of therapeutic safety. A systematic literature review selected seven clinical trials and included 380 children with acute severe asthma requiring hospital admission. Six of these studies evaluated patients who failed to respond to the therapeutic use of β_2-adrenergic agents and corticosteroids. Addition of intravenous aminophylline to this treatment improved lung function in 6 hours, but there was no significant clinical improvement. There was no reduction in the duration of hospitalization and the need for inhaled medication. There is no conclusive evidence on the impact of aminophylline use on intensive care admission rates, the need for mechanical ventilation and oxygen therapy. There was a higher incidence of vomiting in the groups receiving aminophylline (**A**)[31].

A recent clinical trial showed a reduction in the duration of hospitalization in children who received aminophylline as compared to intravenous salbutamol in severe asthma attacks. Two groups of children aged 1 to 16 years with asthma attacks, receiving inhaled β-adrenergic agent and systemic corticosteroids were compared. Although there were no differences in the clinical score after 2 hours of treatment (mean score 6 and 6.5 for salbutamol and aminophylline groups, respectively, p = 0.93), there was a tendency toward a longer use of oxygen in the salbutamol group [(17.8 hours (95% CI 8.5 to 37.5) x 7.0 hours (95% CI 3.4 to 14.2)]. We also observed a significantly greater increase (p = 0.02) in the time of hospitalization of the salbutamol group [(85.4 (95% CI 66.1 to 110.2) hours x 57.3 hours (95% CI 45.6 - 72.0)] (**A**)[32].

Aminophylline has a narrow therapeutic safety margin and can have toxic and side effects. In comparison with the placebo group, in 31 children aged 5 to 18 years treated with inhaled β_2-adrenergic and systemic corticosteroids, the group receiving aminophylline had a higher incidence of nausea, vomiting, headache, abdominal pain and palpitations (absolute risk reduction of 37 % – $p < 0.05$) (**A**)[33].

Recommendation

Aminophylline is not recommended for the initial treatment of acute asthma. It can be used in severe cases with poor response to β_2-adrenergic agents and steroids (**A**)[31,32].

12. Is intravenous magnesium sulphate effective in the treatment of severe asthma attack? Is it safe?

The routine intravenous administration of high doses of magnesium sulfate in the beginning of the treatment of moderate to severe asthma episodes was not more effective than the β_2-agonists and corticosteroids alone (**A**)[34].

However, in patients older than six years of age, with moderate to severe asthma attack that did not respond to conventional treatment, there was lung function improvement and reduced hospitalization rates in the group treated with intravenous magnesium sulfate (**A**)[35].

It was also observed improvement in clinical scores and oxygen saturation, reducing the hospitalization time in the group treated with intravenous magnesium sulfate (**A**)[36].

At the doses used (25 to 75 mg/kg, single dose, infused slowly from 20 to 30 minutes), addition of magnesium sulfate to conventional treatment of acute asthma attack showed no increase in side effects, being safe (**A**)[36,37].

Recommendation

Routine addition of intravenous magnesium sulfate at the beginning of the treatment of acute asthma attack is ineffective (**A**)[34].

Addition of intravenous magnesium sulfate to the conventional treatment of children and adolescents with an asthma attack that did not respond to conventional treatment (inhaled β_2-agonists and systemic corticosteroids) is recommended as it improves lung function, oxygenation and clinical score and reduces the hospitalization rate (**A**)[35-37].

Further research involving all degrees of severity of asthma attacks and in younger children is necessary.

13. Can antileukotrienes be used in the treatment of asthma attacks?

There is no evidence to justify the use of antileukotrienes as a treatment for asthma attacks. The role of antileukotrienes is well-known as prophylactic therapy (**A**)[38]. There have been few studies that evaluated the efficacy of montelukast in home treatment of asthma attacks in children with intermittent asthma. Compared to placebo, the use of montelukast for seven days after an acute episode showed a modest effect in the prophylaxis of asthma. There was no difference regarding the use of health services for asthma (OR = 0.65, 95% CI: 0.47 to 0.89), as well as no decrease in the need for hospitalization and duration of subsequent episodes or use of β_2-agonists and corticosteroids. There was some symptom and nocturnal awakening reduction (14% and ARR was 8.6%, $p = 0.043$, respectively), as well as significant reduction in school and parental work absenteeism (37% and 33%, $p < 0.0001$ for both) (**A**)[39].

Recommendation

Antileukotrienes can be used in the treatment of persistent asthma, but there is no evidence to justify its use as treatment during an asthma attack (**A**)[38,39].

Maintenance drug treatment

14. Are inhaled corticosteroids effective and safe to prevent asthma attacks in childhood?

Inhaled corticosteroids are the first choice for the prevention and control treatment of persistent asthma in childhood. In mild persistent asthma, treatment with low doses of inhaled corticosteroids (budesonide – 200 mg/d) decreased by 14% the need for additional treatment for asthma in the first year of treatment compared to placebo. Use of budesonide was also associated with a higher increase in FEV_1 before and after bronchodilator use, when compared with placebo (2.24% and 1.48% of the baseline parameters in each group, respectively – $p < 0.001$) (**A**)[40].

Continuous treatment with corticosteroids is associated with decreased rates of hospitalization. In a historical cohort study, including 30,569 patients with asthma, the regular use of corticosteroids was associated with a 31% reduction in the rate of hospitalization for asthma (95% CI: 17-43) and 39% in readmissions (95% CI: 25-50). Regular use of corticosteroids may prevent approximately five admissions and 27 readmissions due to asthma in 1,000 patients per year (**A**)[41].

Prophylactic treatment with inhaled corticosteroids is beneficial also in exercise-induced asthma (**A**)[40].

The continuous use of inhaled corticosteroids may cause a small reduction in growth rate, especially in the first year of use. Compared with placebo, budesonide was associated with a reduction of 0.43 cm/year ($p = 0.001$). Inhaled fluticasone was associated with a slight difference in height percentile, compared to placebo after two years (fluticasone: 51.5% vs. 56.4% placebo, $p = 0.001$). At the end of the treatment period, children who used inhaled corticosteroids or placebo had similar growth rates (**A**)[42].

Recommendation

Use of inhaled corticosteroids is recommended as first maintenance therapy choice for children with persistent asthma (**A**)[40,41]. This therapy may be associated with small delay in the growth rate during treatment, but growth velocity is normalized after the end of the treatment (**A**)[42].

15. Are long-acting β-agonists (LABA) safe for children?

LABA can be beneficial as adjuvant in the treatment of moderate to severe persistent asthma or not responsive to corticosteroids, as they may effectively promote asthma control with a satisfactory safety level (**A**)[40,43].

In older children and adolescents, these drugs should not be used as a single drug, as some studies have raised the possibility that they may be associated with serious events and asthma-related death. A recent systematic review of the literature emphasizes that the use of LABA as monotherapy reduces exacerbations requiring treatment with corticosteroids, but with significant increase in mortality associated with asthma (RR: 3.84, 95% CI: 1.21 to 12.14). The subgroup analysis suggests that in children, the use of salmeterol and duration of treatment for more than 12 months are associated with increased risk of serious adverse effects. The combination of LABA and IC reduces the risk of asthma exacerbations (RR ¼ 0.73, 95% CI, 0.67 to 0.79) and hospitalizations (RR ¼ 0.58, 95% CI, 0.45 - 0.74); children and the use of salmeterol are also associated with increased severe events compared to adults and the use of formoterol.

Recommendation

LABA can be beneficial as adjuvant in the treatment of moderate persistent asthma or not responsive to corti-

costeroids. If used, they should be associated with inhaled corticosteroids for the shortest time possible, because the risk of serious adverse events is associated with monotherapy, pediatric patients and time of use longer than 12 months (**A**)[40,43].

16. Are antileukotrienes superior to inhaled corticosteroids in asthma prophylaxis?

No. Many studies have shown the effectiveness of antileukotrienes in the treatment of persistent asthma, in addition to their beneficial effect in decreasing bronchial hyperreactivity in asthmatic children (**A**)[38,44,45]. However, inhaled corticosteroids are more effective in the prophylactic treatment of asthma. In adolescents aged > 15 years, treatment with antileukotrienes had lower efficacy when compared to inhaled corticosteroids (beclomethasone 200 mg – 2x/day). The combination of two drugs in adolescents with asthma not controlled with IC was beneficial and improved the clinical picture and pulmonary function (FEV_1). Also in adults with mild to moderate asthma, treatment with IC (beclomethasone – 200 mg – 2x/day) has superior efficacy to treatment with leukotriene. Further studies are necessary with children (**A**)[46,47].

Recommendation

Antileukotrienes are effective in controlling persistent asthma, but are less effective than inhaled corticosteroids, which are the drug of choice in this clinical situation (**A**)[47].

17. Is the specific recombinant humanized monoclonal antibody (anti-IgE omalizumabe) effective in preventing all types of asthma in childhood? Can it be used at any age range?

Omalizumab is recommended for patients with severe asthma not controlled by currently available medications and mediated by IgE. These patients can be characterized by presenting high IgE levels (around 30 mg/dL) and positive skin and/or specific IgE response to a common aeroallergen. In a systematic review, the use of omalizumab in adults and children with severe atopic asthma (IgE between 30 and 700 mg/dL) allowed the decrease or complete withdrawal of treatment with inhaled corticosteroids. The number of patients that decreased by up to 50% the use of IC was higher in the group receiving omalizumab than in the placebo group (OR = 2.50 95% CI 2.02 to 3.10) as well as the number of patients that completely stopped the use of IC (OR = 2.50, 95% CI 2.00 to 3.13) (**A**)[48].

To date, omalizumab has not been approved for patients younger than 12 years of age. Further studies are needed to evaluate the efficacy and safety in younger children. There are some promising trials in this age group. A randomized clinical trial included 334 children aged 6 to 12 years with moderate to severe atopic asthma who required inhaled corticosteroids. The proportion of children that were able to withdraw the steroid treatment was higher in the omalizumab than in the control group (55% x 39% - p = 0.004).

The proportion of children who received omalizumab and could reduce the dose of corticosteroids was also higher (p = 0.002) and this reduction was greater in the treated group (**A**)[49].

Recommendation

Omalizumab is recommended for patients with severe asthma non-controlled by currently available medications and mediated by IgE. It can be administered to children older than 12 years (**A**)[48].

18. Is bambuterol effective and safe for the treatment of all types of asthma in childhood?

Bambuterol is a β-adrenergic long-acting bronchodilator, a prodrug that is slowly metabolized into terbutaline. It is available in liquid form for oral use, as a single dose, once daily.

There is no evidence in the literature to support the use of bambuterol as the drug of choice in the treatment of asthma in childhood, as the route of choice for bronchodilators is the inhaled one and there are no comparative studies in children. A clinical trial in children aged 2 to 12 years compared bambuterol with daily use of oral terbutaline and showed that both showed to be equivalent and safe; however, the preferred route for administration of β-adrenergic agents (terbutaline) is the inhaled route (**B**)[50].

Recommendation

Bambuterol, a liquid bronchodilator used by oral route, is not recommended as the drug of choice in the treatment of asthma (**B**)[50].

19. Are chromones as effective as corticosteroids in the maintenance treatment of asthma in childhood?

No. Comparative studies have shown that inhaled corticosteroids are more effective in controlling persistent asthma. In pre-school children, the mean rate of exacerbations per year was 27% higher in children treated with cromolyn sodium than in those treated with budesonide (p < 0.001) (**A**)[51]. In schoolchildren, the use of cromolyn was not associated with improvement in FEV_1 after four months of treatment, whereas in the group receiving budesonide and fluticasone, the increase in FEV_1 compared to baseline values was 8.2% and 5.4%, respectively (p = 0.01 for both) (**B**)[52]. Moreover, younger children aged less than 36 months, treated with budesonide had lower exacerbation rates when compared with those treated with cromolyn (5.4% vs. 31.7%, p = 0.003), higher proportion of days without coughing (80% x 65 %, p = 0.014) and nights without coughing (89% vs. 78%, p = 0.016) during the treatment (**A**)[53].

Recommendation

Inhaled corticosteroids are more effective than chromones for the control of persistent asthma (**A**)[51,53] (**B**)[52].

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