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Pharmacological Aspects Regarding the Drugs used in Asthma for Pediatrics

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ABSTRACT

Asthma attack is a common allergic attack which more frequently occurs in children. It can increase the risk and enhance the morbidity. It is a severe life threatening condition that can lead to death. Children with chronic asthma are at risk of increased medication induced side effects, medication error causing worsening condition, and affect adverse outcome. The poor medication adherence, lack of knowledge regarding the disease and wrong usage of inhalers can lead to impaired quality of life and it is difficult to treat the severe condition. The common reason is uncontrolled exacerbation and persisting symptoms. Children with severe condition should be referred to a pulmonologist and educated about the correct usage of inhaler technique.

Key words: asthma, allergic attack, morbidity, inhaler

INTRODUCTION

Asthma is a condition of inflammatory disorder in the lower respiratory pathways. This can affect people of all ages and is characterized by episodic and symptomatic wheezing, chest tightness, shortness of breath, and coughing. Exposure to dust, dander from dogs or cats, pollen and other environment allergens can trigger the severe asthma attack. The aim of the medications used in asthma is to reduce the inflammation and severity of the disease. Children with severe and chronic asthma will show psychotic symptoms like anxiety and difficult to adapt their disease this can lead to poor medication adherence and management of asthma. Asthma attack can be life threatening and particularly recurrent so it is difficult to treat. According to CDC 2016 (Centre for disease control and prevention) prevalence of asthma in children aged 5-11 years were 9.6% and 12-17 years were 10.5% respectively [1].

Etiology of asthma includes genetics, environmental factors, triggers, various infections. The various environmental factors and lifestyle will depend up on the characteristic of asthma. Exposure to indoor allergens like food allergen, cockroach, mold, pets and outdoor includes pets and pollen. Some studies reported that the certain infection viruses protect against asthma, and some will initiate the asthma. The most common viruses for the exacerbation of the asthma are human rhinoviruses. In addition, the other triggers include the tobacco smoke, irritants, pollutants, exercise, weather, stress and drugs.

According to severe asthma research program (SARP), compared to adults, children have significantly higher number of eosinophils, IgE and allergen sensitization. Severe asthma can directly reduce the health related quality of life (HRQOL), lead to life threatening exacerbation and medication related side effects. So simple and validated HRQOL questionnaires are designed for asthmatic children to evaluate HRQOL in school aged children

For the treatment, diagnosis is very important to categorize the level of the asthma. The asthma can be more focused on

cell type (mast cell, eosinophil etc.), timing of symptoms (morning and night), trigger (allergens, viral, exercise and food) and reversibility (often). This can be done by the detailed analysis of the history of patient, physical examination of upper respiratory tract (chest and skin) and the outcome of spirometry. The diagnosis of asthma is based on the episodic symptoms and the allergic triggers[2, 3].

PATHOPHYSIOLOGY

Asthma can produce airway limitations, hyper responsiveness and chest tightness. These occur because of the mast cell release mediators (prostaglandins, histamines, leukotriene and thromboxane) which will lead to inflammatory response, this can lead to the bronchoconstriction, inflammation in the lining, edema and mucus plug formation.. Leukotriene have potent role in asthma, which will show more inflammation responses and their effect can also enhance inflammation response on the eosinophil, neutrophils and lymphocytes[4]. This inflammation causes smooth muscle contraction, increased collagen deposition and chest tightness. This can also lead to damage on the airway epithelial cell. Thus the anti-inflammatory drugs have fundamental role in the bronchial asthma[5].

CLINICAL MANIFESTATION

Asthma is an allergic disorder characterized by the symptoms like cough, wheeze, sneeze, breathlessness and chest tightness. The severity of disease is depending up on the symptoms of disease. This can occur at any ages, more common in men compare to women. The asthma attack is more predominant on early morning and night for most cases. The most symptom of the asthma is breathlessness due to the chest tightness. Usually the cough is dry but sometimes it is wet. Wet cough of different sputum color, the color can be white or green. Green color is due to the release of peroxidase from the eosinophil and neutrophils.

Allergens triggers will show hyper responsiveness, it can be allergic rhinitis, eczema, and conjunctivitis and skin irritation. Intrinsic (non allergic) and extrinsic(allergic) are the sub types of asthma with diff rent triggers.

Table 1: extrinsic vs Intrinsic

Allergic trigger factors	Non allergic trigger factors
House dust mite	Exercise
Pollen	Food and drinks
Fungal spores	Drugs and disease
Pet	Air pollution, smoking and climate change

To assess the accurate severity, clinical assessment is very important in the treatment .The clinical sigs including

- Respiratory rate
- Pulse rate
- Amount of wheezing
- Degree of breathlessness
- Degree of consciousness

The common presentation of asthma for pediatrics include

- Transient wheezing

The child may wheeze occasionally, but there may be no family history. This will be up to the 3 years and later disappear.

- Non atopic wheezing

This is another type, were the wheezing is continued after 3 years to the child. This may be occurring due to the family history. These children will respond to leukotriene antagonist.

- Late onset childhood asthma

In some cases the bronchial hyper responsiveness can be seen in puberty age. This is more affect to girls compare to boys. This is called late onset childhood asthma

DIAGNOSIS AND INVESTIGATION

The early diagnosis of asthma is based on the medical history and physical examination. Pulmonary function test are done to analyze the severity magnitude of disease.

- Spirometry

This is the most common lung function test to check the restrictive and obstructive airway disease, using forced vital capacity

(FVC) and forced expiratory volume (FEV) in 1 sec.. Spirometer is the device name.
FEV1/FEVC ratio:
<0.7 = obstructive lung disease
>0.7 = restrictive lung disease
In severe asthma condition the forced exhalation rate is very low, because the obstruction of airflow.

- Peak flow meter

Like spirometer, this will measure the peak expiratory flow rate, after a full inspiration. The advantage is it is simple and inexpensive. This has ability to detect airflow obstruction.

- Exhaled nitric oxide test

This test is used to measure the inflammation. The level of nitric oxide is more in the severe asthma patient. This occurs due to elevated of nitrous oxide synthase in respiratory mucosa. The eosinophilic inflammation can cause elevation of nitric oxide synthase.

- Eosinophilic count

The elevation of eosinophil count (>15%) can be seen in the severe asthmatic condition. The normal level of eosinophil is 1-6%. The level of eosinophil can be also increased in allergic bronchopulmonary aspergillosis and tropical eosinophilia.

- Total IgE

The level of total IgE is elevated in allergic asthma (>1000 ABPA). Anti IgE can be given to this patient.

- Sputum test

It is to analyze the amount eosinophil in sputum. This can check the differential cell count. Higher number of eosinophil count indicates the severe inflammation of airways.

- Pulse oximetry

The measurement of oxygen saturation is very important in asthma patients and this can be reduced in case of chronic wheezing.

- Blood gases

If the condition is very poor the measurement of blood gases can be done. The enhances of pco2 can be seen in worsen condition of asthma.

- Chest x-ray

This can be done only in case of persisting unilateral severe emphysema.

How to detect allergic trigger?

Allergic triggers can be detect by using allergic test, it is based on the principle of occurrence allergen specific IgE in tissues and can be implemented by estimating of IgE in blood. Enzyme linked immune sorbent assay (ELISA) also carried to detect the specific allergen by using IgE. [6-8]

Categories of asthma medications

The pharmacological controlling of asthma includes the use of bronchodilators, reliever medications, controller medication and medication for the reduction of risk. The agents which are used in bronchial asthma include beta 2 adrenergic blockers, corticosteroids, leukotriene modifier, like montelukast.

The asthma can be affected at any age so treating with the proper medication is very important. The high effective therapeutic drugs and appropriate drugs can reduce the severity and complications of asthma. The step wise allergic management (table 2) in children has been proposed. Treatment starts from step 1 at a low dose. And stepping up the medication for the control the disease. Step 5 is most worsen condition.[9]

Table 2: Stepwise pharmacotherapy management in asthmatic children

Step 1	Step 2	Step 3	Step 4	Step 5
RELIEVER THERAPY	As needed SABA	As needed SABA	or low dose	ICS/LABA
CONTROLLER THERAPY	low dose ICS	Low/medium ICS/LABA	Medium ICS/LABA	Add on treatment
OTHER COMMON CONTROLLER	Low dose ICS LTRA	Medium/high dose ICS+LTRA	high dose ICS+LTRA	Low dose OCS option

SABA, short acting beta agonist :ICS,inhaled corticosteroids :LABA,long acting beta agonist : LTRA,leukotriene receptor antagonist: OCS,oral corticosteroids.

MEDICATIONS USED

Short Acting Beta 2 Agonist

Short acting beta 2 agonists are agents used for acute asthma attack. They include salbutamol, levalbuterol, terbutaline, pirbuterol. The main drugs of choice of SABA which are inhaled salbutamol. But the other terbutaline which is not indicated for the younger patients. They are usually giving as the drug is needed, the more require indicate to increase the anti inflammatory action. This drug can provide more bronchodilator action. Compare to other drugs SABA have faster and more rapid action. Oral SABA are generally discouraged. The other second line agents are anticholinergics which include Ipratropium bromide. The combination of both SABA and the anti-cholinergic agents can result synergism effect. The combination can reduce the severe effect of asthma and hospitalization.

The dose include 6 puff MDI via spacer = 2.5 mg salbutamol (younger than 6 years) and given every 20 min in one hour, that is three doses. The mechanism of action includes beta agonist causes bronchodilation by inducing airways smooth muscle relaxation, reducing the inflammation and edema, improve broncho clearance. This drug has with less tachycardia and tremor. In adults, salbutamol or short acting theophylline can be prescribed. Oral short acting theophyllines are alternative to SABA, have slower action and higher risk of adverse effects than SABA. So they are not recommended in children[9-11].

Long Acting Beta 2 Agonist

Long acting beta 2 agonist (salmeterol, formetrol) are usually used with the combination of ICS (inhaled corticosteroids) like fluticasone or budesonide. Long acting beta 2 agonists should not be used as monotherapy the addition of ICS in a fixed dose is showing good outcome and not leading to any serious asthma related side effects than using ICS alone[9]. Salmetrol is available in both aerosol and an inhaled dry powder. Both forms are more effective than short acting beta 2 agonist in treating with moderate asthma and broncodilation action last for 12 hours[12].

The agonist binds on G protein and activating the adenytyl cyclase, which in turn activate protein kinase A, which trigger uncoupling of myosin and actin. This leads to smooth muscle relaxation and bronchodilation. The formoterol shows more action and efficacy than salmeterol. The formoterol is completely agonist were the salmeterol is partial.

The suggested dose of salmeterol for more than 4 years is 50 mcg two times a day and formoterol is 12 mcg at least 15 min[13]. The combination of LABA and ICS will show synergism effect compare to monotherapy. LABA were better than the SABA for different of lung function and there monitoring[14].

ORAL CORTICOSTEROIDS

This can be used only if the asthma is persisting for a longer period. The systemic corticosteroids are also available in management of severe exacerbation of asthma. Inhalation corticosteroid (ICS) is better compare to systemic CS in children.

The mechanism of corticosteroids is targeting the reduction of inflammatory mediators including eosinophil, mast cell, lymphocytes and proinflammatory proteins which causing the inflammation in the airways. This can also reduce the hyper responsiveness and bronchoconstriction in airways.

The ICS dose ranges in various ages [15](tab.3)

The other drugs are oral corticosteroids, they are very rare usage. The dose of these drugs should be reduced during asthma which is under control. Frequent use of corticosteroids can increase the adverse effects including hypertension, osteoporosis, and obesity. There is no guideline protocol for this in therapy for children[1]. But this can be added during severe asthma (stage 6) condition. Prednisolone (1-2mg/kg/day) is given early in treatment. Betamethasone (0.1-0.2

mg/kg/dose) in 2 to 3 times of administration. The other steroid includes Inj hydrocortisone (5-10 mg/kg 6-8). Steroid treatment should not exceed more than 14 days. Prednisolone is short acting and dexamethasone is long acting. Most of the oral and intravenous agents have the same efficacy[7]. Intravenous injections are shown (table 4)[5].

Table 3: Inhaled corticosteroids

Drug	Daily dose ug (age ≤ 5 years)	Daily dose ug (age 6–11 year)			Daily dose ug (age ≥ 12 years)		
	Low[a]	Low	Medium	High	Low	Medium	High
Betamethasone Dipropionate (CFC)	-	100–200	>200–400	>400	200–500	>500–1000	>1000
Betamethasone Dipropionate (HFA)	100	50–100	>100–200	>200	100–200	>200–400	>400
Budesonide (pMDI + spacer)	200	-	-	-	-	-	-
Budesonide (DPI)	-	100–200	>200–400	>400	200–400	>400–800	>800
Ciclesonide	160	80	>80–160	>160	80–160	>160–320	>320
Fluticasone propionate (DPI)	-	100–200	>200–400	>400	100–250	>250–500	>500
Fluticasone propionate (HFA)	100	100–200	>200–500	>500	100–250	>250–500	>500
Mometasone furoate	Not studied below 4 years	110	220–<440	≥440	110–220	>220–440	>400
Triamcinolone acetonide	Not studied	400–800	>800–1200	>1200	400–1000	>1000–2000	>2000

Table 4: Intravenous corticosteroids

Intravenous injection				
	Initial dose,		Maintenance dose	
	2-15yrs,	<2yrs ,	2-15yrs ,	<2 yrs
Hydrocortisone	5-7mg/kg	5mg/kg	5-7mg/kg every 6hrs	5mg/kg every 6-8hrs
Prednisolone	1-1.5 mg/kg	0.5-1.0 mg/kg	0.5mg/kg every 6hrs	0.1-1mg/kg every 6-12 hrs
Methylprednisolone	1-1.5 mg/kg	0.5-1.0 mg/kg	1-1.5 mg/kg every 6hrs	0.5-1 mg/kg every 6-12 hrs

LEUKOTRIENE RECPTOR ANTAGONIST

These agents are montelukast, pranlukast, zafirlukast and zileuton. This can reduce the exacerbation and bronchospasm of lungs. The agents will block the activation cysteinyl leukotrienes. Leukotriens have the key role in the asthma. Cysteinylleukotriens be able to cause bronchocontriction, mucusesecreation, plug formation etc. Studies report that these agents have lower effect than ICS and LABA. The most common drugs in this category are montelukast and zafirlukast. Studies also report that montelukast are effective in exercise induced asthma. The montelukast (4mg) chewable tablet is given in the bed time for the 2-5 year old child[16]. Montelukast has less adverse effect than zafirlukast, but hepatic dysfunction should be monitored[10]. It can be used first line agent in the mild to moderate asthma if ICS is not possible because many reports concluded that these agents are safe, convenient, non-steroidal, less side effect and oral administered agents[17].

METHYLXANTHINE

These include caffeine, theophylline and theobromine. The MOA of theophylline are they inhibits cyclic nucleotide phosphosditerase, thereby preventing convert of cAMP and cGMP to 5' AMP and 5'GMP, Inhibitions of PDEs will led to an accumulation of inter cellular cAMP and cGMP. Bronchodilation can occur when the rise of cAMP in cells. Also theophylline is a competitive antagonist on adenosine receptors, adenosine can cause contraction in airways by inhibition of adenosine can lead to bronchodilation. Theophylline also inhibits the release of mast cell and other inflammatory mediators[18]. This is usually administered in combination with LABA. These drugs have narrow therapeutic index and have high adverse effects. Chronic usage can lead to nausea, vomiting, hyperglycemia, and seizures[2]. The targeted dose range is 10 mg/kg/day. Maximum of

300/day. Many study results concluded that aminophylline allows accumulation of cAMP, which enhance the lung fuction[19]. The dose is 5 mg/kg given over 20 min with the ECG monitoring. The target therapeutic range for aminophylline is 10-20 mg/l and in this range it can help to improve the condition and achieve meaningful outcomes in severe exacerbation of asthma[8] .

MAGNESIUM SULPHATE

Magnesium sulphate is a bronchodilator. It will help relax the bronchial muscles and thus it is mainly used in case of severe asthma. This is commonly given as intravenous solution and occasionally as inhalers. The main mechanism of action is blocking the calcium channel, thus cause relaxes in the smooth muscle which can lead to bronchodilation. This also inhibits the histamine release from the mast cell. The IV mgso4 have rapid action and rapid renal clearance [20]. In 2014 large British trial set out to establish the effectiveness of magnesium sulphate. Intravenous magnesium sulphate is used in children to reduce any allergic attack and if the FEV is below 60%. The safe dose is a bolus of magnesium sulphate (50-75 mg/kg) and the prolong infusion of this (40 mg/kg/h) for 4 hours. It is very safe and adverse event have not been reported consistently with this agent[8].

OMALIZUMAB

It helps to improve lung function by reducing the exacerbation to a lesser extent and this is indicated in children only for severe allergic asthma which is poorly controlled by other drugs. It is recent added drug and it is very expensive. It is a monoclonal antibody and that binds to the fceRI portion of IgE and reduce their number. Thus this can reduce the severity and symptoms of asthma. And it has been licenced from 2003 by food and drug administration (FDA). The most common side effect is local reaction like pain at the site of administration. Many studies reported that the omalizumab have clinically high efficacy and safety in pediatrics. Omalizumab can be also used in various types of disease were IgE plays very important role like allergic rhinitis, food and drug allergy, urticaria, atopic dermatitis, mastocytosis, otitis media, contact dermatitis and nasal polyposis[21,22].

CHROMONES

Cromolyn sodium and nedocromil are anti inflammatory agents. In vitro studies reported that they will control the mast cell releasing mediators like histamine, leukotriens and others, those who have key role in asthma. Some studies report states that these can reduce the eosinophil count. So this can reduce the bronchoconstriction and able to dilate the airways. Both drugs are approved by food and drug administration (FDA). Many studies reported that cromolyn shows effectives in children more than 2 years and nedocromil shows more than 12 years. This can be used children of different age groups.

Table 5: Common asthma medication

Drug class	Generic name
Short acting beta agonist (SABAs)	Albuterol
	Metaproterenol sulfate
	Levaalbuterol tartrate
	Pirbuterol acetate
	Terbutaline sulphate
Long acting beta agonist(LABAs)	Salmetrolxinafoate
	Formoterol fumarate
	Alfomoterol tartrate
Inhaled corticosteroids(ICSs)	Budesonide
	Ciclesonide
	Flunisolide
	Beclomethasone dipropionate
	Fluticasone propionate
	Mometasonefuroate
LABA/ICS combination drugs	Formoterol /budesonide
	Formoterol/momentasone
	Salmetrol/fluticasone
Leukotriene receptor antagonist	Montelukast sodium
	Zafirlukast
Other anti asthma medication	Cromolyn sodium
	Methylprednisolone
	Omalizumab
	Prednisolone sodium phosphate
	Prednisolone

The dose cromolyn is, patient should start with 20 mg (nebulized) inhaled 4 times per day, children with less than 6 years the dose should be reduced. Nedocromil is an aerosol

dosage form, which supply 1.75 mg per actuation the recommended dose is 2 inhalation 4 times daily[23]. Cromolyn sodium is a important drug which can show prophylactic action in asthma and it is considering first line agent in united states. Most guidelines reported that, cromolyn sodium can be used for mild asthma condition and suppression of exercise induced asthma approximately 70% of patients [24]. Various class of drugs are used in bronchial asthma of having different mechanism of action (table 5)[25].

VITAMIN D DEFICIENCY

Some studies reported that deficiency of vitamin D also plays a role in the asthma. Vitamin D deficiency patient shows increased asthma severity and associated exacerbation. And the sufficiency of vitamin D in children is treated with inhaled corticosteroid and show better lung function and therapeutic outcome. So vitamin D level should be monitored in pediatrics with severe asthma condition[26].

PREVENTION

The goal of the treatment is to prevent the allergic condition. Moreover, it is very difficult to diagnose and treat the asthma in pediatrics. The outcome of medication is to reduce the symptoms and complications. Although the controller medication can reduce the morbidities and severity of disease. Lack of knowledge regarding the disease and drugs can lead to worsening condition. Proper medication adherence should be there for better treatment outcome. Pediatric patient should be known the proper usage of inhalers and medication. He should be avoid of standing from allergens and various allergens causing exposures[8,24].

CONCLUSION

Most of the guidelines show that the use of salbutamol is the most among all of the beta 2 agonists. This can treat acute asthma though addition of ipratropium bromide will enhance the effect. The combination of SABA or LABA with a corticosteroid shows a synergistic effect. Epinephrine should not be used in children. Oral corticosteroids are used only in moderate to severe asthma and high dose of inhaled steroids should not be replaced with the systemic steroids. The use of Mgso4 in severe asthma will show effect only in cases where the other initial treatment is unresponsive.

Since the asthma in children is common and life threatening, the appropriate dose and right drug should be preferred for the treatment. Alternative treatment should be followed only if the initial treatment is unresponsive. However implementation of standard asthma guidelines will prevent the co morbidities and complications. And more research need to be done regarding the disease and drugs[8,27].

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