DRUG TREATMENT IN BRONCHIAL ASTHMA

Pages with reference to book, From 25 To 29

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Bronchial Asthma, defined as reversible airflow obstruction which can resolve spontaneously or by therapy is a common problem in Pakistan.

Successful treatment of Asthma depends upon, scientific diagnosis and rational drug therapy according to the severity of the disease, monitored by airway function. Every patient of cough and wheeze is not necessarily suffering from Bronchial Asthma. To distinguish Asthma from other conditions a peak flow meter should be used, which is simple and can be used even by the patient himself.

An impressive range of drugs is available, but usually disease is poorly treated. For best results the treatment must be according to the pattern of the disease. Assessment, initial and during treatment must be monitored by ventilatory studies. Peak expiratory flow rate will, when serially done, distinguish between mild and infrequent, exercise induced, early morning attacks only, or severe and chronic types.

Most infections which precipitate an attack of asthma are viral in origin and the routine use of antibiotics is not required unless a super added bacterial infection is confirmed. Three types of Bronchodilators are available. $2 adrenorecepto r agonist, Methylxanthines and anticholinergics as shown in the table.

Table

DRUGS	DOSAGE			
	<3 yrs	3–6 yrs	7–15 yrs	Adults.
BRONCHODILATORS:				
A. β_2–adrenoreceptor agonists				
I. SALBUTAMOL (Ventolin, Broncholin).				
Aerosols. (100µg/puff)		100µg bd	100µg bd/tid	200µg tid/qid
Syrup (2 mg/5ml)	1mg bd	1mg tid	2mg tid	4mg tid/qid
Tablet (2 and 4mg)	–	–	2mg tid	2-4mg tid/qid
Injections(Reserved for acute attack only) intramuscular/subcutaneous (.5mg/ml)			500µg or 8µg/kg 4 hourly, if necessary	
Intravenous/infusion (5mg/5ml)			250µg or 4µg/kg, 4 hourly if necessary.	
II. TERBUTALINE (Bricanyl)				
Syrup (0.3mg/ml)	0.75mg tid	0.75–1.5mg tid	1.5–3mg tid	1.5–3mg tid
Tablets (2.5mg)	–	1.2mg bd	1.2–2.5mg bd	2.5–3mg bd
III. PROCATEROL (Meptin)				
Tablets (50 µg)	–	–	–	50µg Nocte/bd
B. Methylxanthines				
I. Theophylline sodium glyconate (Theophylline)				
Syrup (30mg/ml)	75mg bd	75mg tid	150–300 mg tid	300-600mg tid
Tablets (300mg)	–	–	150-300mg tid	300-600mg tid
II Theophylline Ethylene-diamine (Aminophylline)				
Tablets (100 – 250mg)	–	–	100-250mg tid	250-500 mg tid/qid
Injections (250mg/10ml) Intravenous/infusion			5mg/kg stat 0.3–0.5mg/kg	(250mg stat) maintenance
C. Anticholinergics				
Ipratropium Bromide nebuliser				0.5–1mg, nebulised
D. Corticosteroids				
Aerosol (Belcomethasone dipropionate) (50µg/puff)	–	50 µg bd	50–100µg bd/tid	100 µg qid
Tablet (Prednisolone) (1 and 5 mg)	–	–	–	20–60mg daily
Injections (hydro cortisone succinate) Intravenous/infusion			5mg/kg stat 3–4mg/kg/6 hourly	(250 mg) (100mg)
E. Sodium Cromoglycate (Intal)				
Capsules (20 mg)			20mg qid	20mg qid
F. Ketotifen (Zaditen)				
Syrup		½ tea spoon bd	1 tea spoon bd	1 tea spoon bd
Tablet (1 mg)			1 mg bd	1mg bd

A combination is usually used, as they have different modes of action on the bronchial smooth muscle. Ahlquist[1] in 1948 demonstrated that adrenergic drugs are mediated through at least two different receptor systems alpha (a) and Beta (B), stimulation of alpha receptor is associated with vasocon strict ion, increased uterine contraction and relaxation of intestinal smooth muscles, while stimulation of

Beta receptors was associated with inhibition of smooth muscle contraction in the respiratory tract, and myocardial stimulation. Lands[2] and colleagues demonstrated that Beta adrenergic effect could further be distinguished into (B, and B2. (B,causing myocardial stimulation and (B bronchodilation.
B agonists selectively stimulate $2 adrenergic receptors in the bronchial wall, and have very little effect on B receptors in the heart.
Salbutamol, Terbutaline and Fenoterol have a similar therapeutic effect, although some studies suggest Terbutaline and Fenoterol to have longer duration of action[3,4] $2 antagonists are the drugs of choice in asthma treatment. They are available in aerosols, as well as tablets and syrup. Aerosols are much more effective and failure of response is generally due to poor technique with the inhaler leading to inhaler abuse. The patients technique should be checked on each visit to the clinic. Inspite of this a fair number of patients find it difficult to synchronise the delivery of aerosol with deep inspiration. Nebulised delivery should be reserved for acute attacks, or for patients unable to master aerosols. Correct use for metered dose inhaler can produce the same degree of bronchodilation as a nebuliser if the dose difference is recognised.[5] Aerosol preparations are free of side effects, though occasional tremors (usually due to over dosage) and slight tachycardia may occur. No significant tolerance has been demonstrated on long term use.[6]
Oral preparations are less effective than aerosols, and the incidence of side effects is higher. Parentral .therapy of Salbutamol and Terbutaline is reserved for severe acute Asthma,[6]

METHYLXANTRINES

The mechanism of theophyllines action on bronchial smooth muscle relaxant remains elusive. There are different theories i.e. phosphodiesterase inhibition, [7] prostaglandin antagonist[8]effects on intracellular calcium[9] and increased binding of cyclic AMP to CAMP protein, [10] has been described (cAMP) cAMP-binding.
Theophylline like other methylxanthines i.e. caffeine, can produce cerebral vasoconstriction transient increase in plasma glucose and inhibit uterine contraction[11,16] serum concentration >10 pg/ml increase contractility and reduce experimentally induced fatigue of diaphragmatic muscle[12,13] decrease the work of breathing[14,7] and enhance mucocilliary clearance. [15]
Theophylline is well absorbed in the gastrointestinal tract, but the rate of elimination varies considerably. Cardiac failure, liver diseases, and some drugs like, Erythromycin, Cimetidine, Ailopurinol, and oral contraceptives are known to decrease the rate of elimination while it is increased in children, cigarette smokers, and with some drugs like carbamazepine, phenobarbitone, phenyton and rifampicin.[13,16] Plasma levels of 10-20 mg/mi produce optimal control with low incidence of side effects, which are anorexia, vomiting, convulsions, cardiac arrythmias and sudden death. Slow release preparations are most effective, they are often prescribed in combination with inhaled B agonist. Initial dose is between 250mg to 300mg, and if tolerated well, and symptoms are not controlled adequately the dose should be increased by 150-250mg per week.
Intravenous aminophylline remains the main treatment of acute Asthma attack. For patients not taking Theophylline the initial Loading dose is 5mg/kg by slow intravenous injection over 20 minutes. Plasma levels can be maintained by continuous intravenous infusion, dose varying from 0.2 mg/kg to 0.8 mg/kg/hr. (average 0.5 mg/kg/hour) depending upon the smoking habits and other associated conditions present.

ANTICHOLINERGICS

The parasympathetic nervous system via the vagus nerve, is responsible for a mild degree of bronchial smooth muscle tone. In Asthma, anticholinergics can produce bronchodilation by inhibiting the constriction produced by inhalation of allergens as irritant dust, histamine and methacholine.
Ipratropium bromide is an analogue of atropine, clinical experience does not show any advantage over 132 -agonist or Theophylline. Some reports suggest that it may enhance the effect of B2-agonist in

patients with severe Asthma and chronic bronchitis with partially reversable airflow obstruction.[15,16] Dose of nebulised Ipratropium bromide is 500ug or 1 mg which should be diluted in saline rather than water.

B2-agonist remain first line of treatment, nebulised ipratropium bromide should be added if the response to other bronchodilators is not adequate. Two drugs alternately can be used with the interval of 60-120 minutes.

CORTICOSTEROIDS

The exact mode of action is unknown. They appear to modify type III and type IV hypersensitive responses, and might have some action on B2 receptors increasing the response of smooth muscle to B2 stimulation.[3] Corticosteroids interfere with the generation of arachidonic acid from cell membrane, by inducing the synthesis of proteins macrocortin and lipomodium, thus reducing the production of inflamatory mediators which might have some effect on Asthma.[16] When symptoms of Asthma are not satisfactorily controlled by combination of Bronchodilators even with higher dosage, oral steroids should be added to the regimen, once they are controlled ,dose should be reduced gradually, and stopped if control is maintained by bronchodilators. However maintenance dose may be required which can be delivered by aerosol Beclomethasone dipropionate. A dose of 100ug (2 puffs) three times a day appears to be equivalent in effect to prednisolone 7.5mg per day orally[19] and results in lesser lowering of plasma cortisol, the only side effect being candidiasis.[20]

Corticosteroids are effective in preventing the development of severe asthma. When ever the controlled Asthma worsens inspite of Bronchodilators, oral prednisolone 20mg/day should be given as a single dose for 7-14 days, this will effectively prevent development of Acute Asthma. In case of acute severe Asthma intravenous hydrocortisone in doses of 5mg/kg should be given as loading doses followed by 3-4 mg/kg every 6 hours. Once improvement occurs oral prednisolone 40-60 mg should be started, intravenous hydrocortisone continued for 6-12 hours, simultaneously. Steroid response is delayed for 4-6 hours hence early use is advisable. [21] If intravenous route is used then the oral doses of 30 mg/days should be continued at least for 7 days. Long term use of inhaled corticosteroids amongst children with chronic asthma have no effect on growth, and most children can learn to use aerosols. [22]

SODIUM CROMOGLYCATE

It is a prophylactic drug, which has no effect on the acute attack. It acts primarily by stabilising the sensitised mast cell, preventing degranulation. It is more effective in children and in 'Extrinsic' Asthma in which a fair number will obtain some benefit. In poorly controlled asthma 6-8 weeks trial in the doses of 20mg qid should be given. Few cases of 'Intrinsic' asthma will also show some improvement. Sodium cromoglycateis free of any side effects, apart from some nonspecific irritation in few patients.

KETOTIFEN

An oral preparation for prophylaxis has also been used in both extrinsic and intrinsic asthma with good results.[23]

Isoprenaline, Ipradol (Hexoprenaline), Ephedrine and adrenaline are no more in use due to their side effects.

Sedatives in severe Asthma should be used with caution. Any depression of respiratory centre may be lethal. Morphine should never be given, even barbiturates are dangerous. Prome. thazine hydrochloride 20-50mg in adult, with its prolonged atropine like action and wild sedation, may be helpful in hocturnal asthma. Diazapam is also safe.

SODIUM BICARBONATE

Patients in status asthmaticus are acidotic with pH much below 7.25 thus soda-Bicarb should be given intravenously and the dose regulated by pH which should be maintained to about 7.3 (usual dose 1-2 meq/kg/6 hourly).

INTRAVENOUS FLUIDS

In status asthmaticus pushing oral fluids are not very helpful and dehydration should be corrected by intravenous 5% dextrose, saline (3 liters in 24 hours if none by mouth).

OXYGEN

Asthma is also associated with hypoxia although cyanosis, a grave sign develops late. Oxygen should be given (40-50%). Nebuliser should be driven by oxygen rather than compressed air when ever possible.

There is no room for Bronchoscopy in diagnosis or treatment of Bronchial Asthma. The response of the drugs can, and should be monitored by respiratory function tests using spirometersif available otherwise peak flow meter will suffice.

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