

The Pharmacological Basis of Drug Treatment in Bronchial Asthma

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Several drugs are now available for the treatment of bronchial asthma and the choice between them is based on considerations which involve an understanding of the basic pharmacological mechanisms.

The reversible airway obstruction in asthma is caused by bronchospasm, oedema of the mucous membrane and hypersecretion by mucous glands. Different drugs act selectively on these factors and it is therefore important for an effective treatment to ascertain the dominating factor. Thus, the severity of asthma is generally determined more by the inflammatory component than by the bronchial muscle constriction, and bronchospasm is usually reversible by bronchodilators, whereas airway obstruction due to bronchial inflammation is largely refractory to the bronchodilators and can only be reversed by steroids.

The pathophysiology of asthma appears from Fig. 1. The bronchial smooth muscle tone is influenced by multifactorial events, which include the release of allergic-inflammatory mediators, the influence of drugs, irritation, emotion, and regulation of the autonomic nervous system (9). Parasympathetic activity increases the tone, whereas sympathetic via norepinephrine and adrenaline has a relaxing effect, which is due to stimulation of β_2 -receptors. Norepinephrine and adrenaline have a contractive α -stimulating effect as well, but under non-infectious conditions this seems to be of no importance, since the bronchi only contain a few α -receptors. Many of the allergic-inflammatory mediators, which

are released by immunological and non-immunological events, cause bronchoconstriction, inflammation of the mucous membrane and mucous hypersecretion. The mediators appear from Fig. 1. They include mast cell-derived histamine and SRS-A (slow-reacting substance of anaphylaxis), bradykinin, which is released from plasma, and the cell-derived prostaglandins (9, 10). The bronchoconstrictory effect of these mediators is complex, since it often involves both a direct contraction of the smooth muscle (local effect) and a vagally mediated reflex bronchoconstriction (5, 25). The vagal reflex is triggered by stimulation of the sensory nerve endings ("irritant receptors") in the epithelium of the airways (Fig. 1) not only by the mediators, but also by inhalation of widely different "irritants", both allergens and non-allergens such as dust, cigarette smoke, sulphurdioxide, ammonia, cold air, and also emotional factors. The effect of the non-specific irritants may explain asthma attacks induced by industrial pollution and by smoking. Similarly, plugging of the airways with mucus is possibly also due to a combination of a local effect and a vagal reflex caused by allergic-inflammatory mediators and irritants (13, 25).

Sympathomimetics

Sympathomimetics are our most important drugs in the management of asthma. In most cases a rapid and effective reduction of the airway obstruction is achieved by these drugs

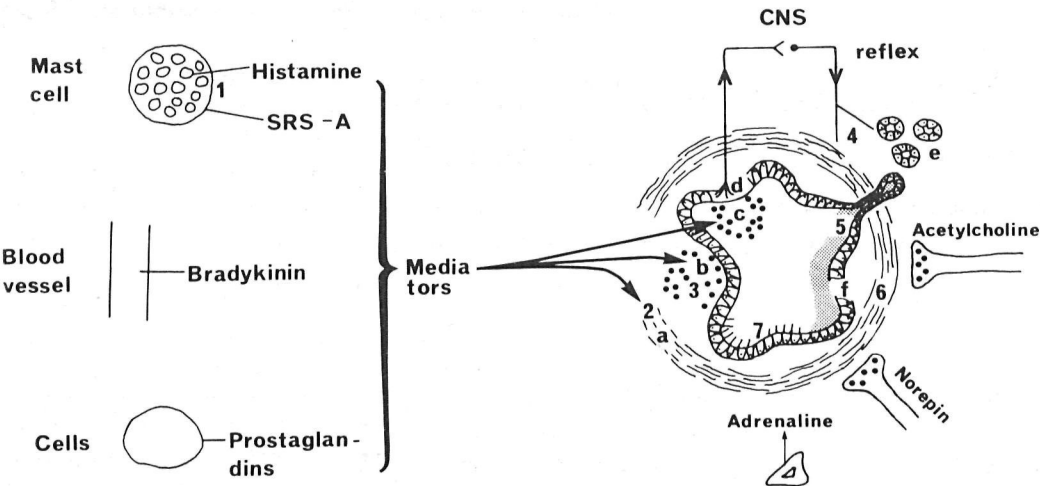


Fig. 1: Pathophysiology and pharmacology in bronchial asthma.

- a: smooth muscle; b: oedema; c: mediators and irritants; d: irritant receptors; e: mucous cells; f: epithelium.
- 1) Sodium cromoglycate and sympathomimetics counteract the release of histamine and SRS-A.
 - 2) Antihistamines counteract the direct bronchoconstrictory (local) effect of histamine.
 - 3) Glucocorticoids counteract the inflammation.
 - 4) Anticholinergics counteract reflex-mediated bronchoconstriction.
 - 5) Glucocorticoids may reduce the high viscosity of mucus.
 - 6) Sympathomimetics and theophylline have a general bronchorelaxing effect.
 - 7) Sympathomimetics increase the mucociliary transport.

in the course of a few minutes (Table 1). The improvement depends primarily on a general bronchorelaxing effect due to a β_2 -receptor stimulation (Table 2), which counteracts all the various bronchoconstrictory stimuli induced by allergic-inflammatory mediators, drugs, irritants, etc. Therefore, these drugs are our most effective remedy for the acute asthma

Table 1
Representative sympathomimetics

	Mode of administration	Broncho-relaxation duration (hours)	Side effects	
			Heart stimulation	Pressor effect
Adrenaline	inj., inhal.	0.5-1 ¹	+	+
Ephedrine	peroral	4-8	+	+
Isoproterenol	inhal.	0.5-2 ¹	+	0
Orciprenaline (Alupent)	inhal. peroral	3-5 ²	+	0
Rimiterol (Pulmadil)	inhal.	1-3 ¹	(0)	0
Salbutamol (Ventoline)	inhal. peroral	4-6 ²	(0)	0
Isoetharine (Numotac)	peroral	4-6 ²	(0)	0
Terbutaline (Bricanyl)	inhal. peroral	4-7 ²	(0)	0
Fenoterol (Berotec)	inhal.	4-8 ²	(0)	0

¹ Bronchodilatory effect is obtained within 1 min and maximal effect in the course of a few minutes.
² Inhalation: The effect is obtained after a few minutes and can be maximal after 5 min. Peroral administration: The effect is obtained after 15-30 min and is maximal after approx. 2 h.

attack. The important effect is a result of intracellular regulation of the smooth muscle tone. Beta₂-receptor stimulation leads to activation of the adenylate cyclase enzyme located in the cell membrane of the bronchial smooth muscle, which in turn stimulates the synthesis of cyclic AMP. An increase in the cyclic AMP level facilitates the sequestering and transport of calcium out of the cell, and the fall in calcium would relax the contractile proteins (9).

Another effect which may contribute to the prevention of the airway obstruction is an inhibitory effect on the liberation of mast cell-derived mediators, which depend on beta₂-receptor stimulation. This entirely preventive action of sympathomimetic drugs is shared with sodium cromoglycate. Furthermore, beta₂-stimulation may also facilitate the transport of viscous mucus in asthma by increasing the impaired mucociliary clearance (7, 8, 14). A more speculative action of beta₂-stimulation is an inhibition of the vascular permeability by a direct effect on the venular endothelial cells (12).

The representative sympathomimetic drugs, their effects and side effects appear from Tables 1 and 2. The classical drugs, adrenaline and ephedrine, stimulate both alpha-, beta₁- and beta₂-receptors. The alpha- and beta₁-

stimulation are usually responsible for the untoward effects. The vasoconstrictory effect of these drugs, which might increase the blood pressure, is due to stimulation of alpha-receptors located in the smooth muscle of the vessels, and stimulation of beta₁-receptors in the heart is responsible for the risk of cardiac toxicity including arrhythmias and ventricular fibrillation as a result of an increase in the heart rate, conduction velocity, and automaticity. In most cases it is therefore recommended to abandon these drugs in favour of the new selective beta₂-stimulating drugs (see below) and hereby avoid these side effects. In paediatrics adrenaline and ephedrine will, however, still be applicable, since the alpha-stimulating effect of these drugs counteracts oedema of the mucous membrane in the lower airways, which in children plays a relatively big role in airway obstruction.

Isoproterenol and orciprenaline represent a therapeutic progress, these drugs being without pressor effect. However, they still imply the risk of cardiac toxicity. Presumably, this explains some of the sudden deaths registered during asthma attacks in the sixties. An overdose, especially in connection with hypoxia, may thus be the cause of death. Here it should be borne in mind that hypoxia

Table 2
Effects of adrenergic receptor stimulation¹

	Alpha	Beta ₁	Beta ₂
Bronchial muscle	(contraction) ²	0	relaxation
Release of mediators	(increase)	0	decrease
Ciliary function			increase
Mucosal oedema	decrease	0	0 (or decrease? ³)
Peripheral vessels	contraction	0	dilatation
Tendency of arrhythmias	0	increase	0
Tendency of finger tremor	0	0	increase
Urinary retention	increase	0	0

¹ With the permission of N. Svedmyr (20).

² With infectious asthma the use of alpha-stimulating drugs (adrenaline and ephedrine) should be avoided, since there exists a possibility of an enhancement of alpha-mediated bronchoconstriction (20).

³ Persson et al. (12).

increases the sensitivity of the heart to β_1 -stimulation, thus increasing the tendency to cardiac arrhythmias.

The new selective β_2 -stimulating drugs, rimiterol, salbutamol, isoetharine (etyiprenalin), terbutaline, and fenoterol (Table 1) should be the first choice of sympathomimetics. These drugs represent the great advance within the group of sympathomimetic agents. The drugs have an almost selective, bronchorelaxing effect and can thus be designated "selective" β_2 -stimulators. No α -stimulating (pressor) effect is seen, and in current doses hardly any β_1 -stimulating effect. The risk of cardiac stimulation is therefore considerably smaller, although not entirely abolished. A modest increase in pulse rate can occur. This is due to a moderate vasodilatation by stimulation of β_2 -receptors of the vessels in the skeletal muscles followed by compensatory reflexes. The drug causes little change in the blood pressure.

Also other advantages are obtained by the β_2 -stimulating drugs: they are chemically stable and are metabolized or excreted rather slowly because of their resistance to the catecholamine-inactivating enzymes, monoamine oxidase and catechol-O-methyltransferase, which rapidly inactivate adrenaline and isoproterenol in the gut wall and in the liver before reaching the systemic circulation. Many of the β_2 -stimulating drugs are therefore effective when given orally, and they act for a long period. The duration of the bronchorelaxing effect is given in Table 1. By inhalation the bronchodilating effect will set in almost as fast as for adrenaline and isoproterenol, i.e. in the course of a few minutes, whereas peroral administration will not be effective until after 15–30 min.

The drugs may give rise to an unpleasant side effect, namely skeletal muscle tremor. This is a β_2 -effect which is characteristic for β_2 -stimulating drugs. Tremor of the fingers is often seen after peroral administration, but hardly ever after inhalation where a local effect is obtained with fewer systemic side effects.

Sympathomimetics are our most important drugs in the management of asthma. However, refractoriness to sympathomimetic agents is not uncommon after protracted therapy in severe cases and in status asthmaticus, especially when bronchospasm is associated with the presence of inflammation and viscid mucus plugs in the bronchi. In these cases a supplementary treatment must be instituted immediately, including steroids and methylxanthines. With status asthmaticus the condition can be life-threatening and here immediate intensive treatment in the hospital is required.

Sympathomimetics should in general not be used in patients suffering from heart diseases or thyrotoxicosis, or in connection with anaesthetics (cyclopropane and halogenated anaesthetics), which increase the sensitivity of the heart to β_1 -stimulation. However, it is obvious that the risk of cardiac arrhythmias is considerably less with the selective β_2 -stimulating drugs. Adrenaline and ephedrine imply a risk of hypertension and vascular diseases, and ephedrine may cause exacerbations in patients with prostatic hypertrophy, since a long-lasting contraction of the sphincter of the bladder may lead to urinary retention. Furthermore, adrenaline and isoproterenol elevate the blood sugar, and in diabetic patients the hyperglycaemia calls for an increased administration of insulin or other antidiabetics.

Hypertensive crisis and cardiac arrhythmias are the most serious drug interaction risks, which might appear in connection with treatment with tricyclic antidepressant drugs such as imipramine. These drugs potentiate the α - and β_1 -stimulating effects of sympathomimetics by counteracting their inactivation. Therapy with β -receptor blocking agents like for instance propranolol (Inderal®) and pindolol (Viskén®) will abolish the bronchorelaxing effect of both sympathomimetic drugs and the sympathetic neurotransmitters, and hereby provoke asthma attacks in the asthmatic patient. However, the risk is less when using cardio-selective β_1 -blockers (metoprolol and atenolol), which

possess a relatively smaller β_2 -blocking effect. In addition, a combination of optimal therapy with β_2 -stimulating drugs is used to minimize the risk.

Methylxanthines

Like sympathomimetics, methylxanthines have a general bronchorelaxing effect (Fig. 1). This might be due to an increase in the cyclic AMP level of the smooth muscle cell, since the drugs inhibit the breakdown of cyclic AMP by inhibiting the phosphodiesterase. To obtain a sufficient bronchodilating effect, the plasma concentration should be rather high, corresponding to 10-20 μg of theophylline per ml (17, 24). In this therapeutic plasma range serious side effects are avoided, but not gastrointestinal symptoms like nausea and vomiting. It would be desirable and ideal if the plasma concentration could be provided by monitoring, since the elimination of theophylline is of great individual variation, and this makes conventional dosing difficult. The variation is due to diseases, genetic factors, food, smoking, and to drug interactions (11). The new sympathomimetics (selective β_2 -stimulating drugs) must in general be preferred to methylxanthines. However, methylxanthines still have an important place in the therapy. The main indications for theophyllines include severe asthma attacks and status asthmaticus, where the patient responds badly to sympathomimetics. Therapeutic plasma concentrations are rapidly obtained when aminophylline is given intravenously, and a high percentage of patients experience almost immediate relief. To avoid the risk of an acute fall in blood pressure, cardiac arrhythmias, and convulsions, a slow intravenous injection is given. Combination therapy with peroral methylxanthines is also used when tremor impedes the oral use of selective β_2 -stimulating drugs (17, 18).

Theophylline and its various salts, aminophylline and choline theophyllinate (Chophyllin® and Choleydyl®) are all absorbed well after oral administration and show on the

whole the same bronchodilating effect (17, 24). However, the problem is the gastrointestinal symptoms. Previously, it was assumed that the symptoms were due to a local effect, but a systemic effect might also be involved, since similar symptoms appear after intravenous administration. The theophylline derivatives hydroxypropyl-theophylline (proxiphylline) and dihydroxypropyl-theophylline (glyphylline) have become popular, since they cause fewer gastrointestinal symptoms, but they are, however, less potent bronchodilators (17, 18). Nuelin®, a microcrystalline theophylline preparation, which is rapidly dissolved, does not seem to imply considerable absorptive advantages over conventional theophylline and its salts (24), but it has not yet been clarified whether the gastrointestinal symptoms are reduced.

Glucocorticoids

In severe asthma the mucus plugging and oedema is an important factor in airway obstruction, and the obstruction due to bronchial inflammation is largely refractory to the bronchodilators. Glucocorticoids are often life-saving drugs in the treatment of severe asthma. The effect of the glucocorticoids probably depends on several different mechanisms. The most important property of the steroids is probably their antiinflammatory effect, which counteracts the oedema of the mucous membrane (Fig. 1.) *In vitro* experiments with human bronchial segments have shown that corticosteroids improve the bronchodilating effect of sympathomimetics, and it is suggested that this effect may be a mechanism of action for steroids in asthma (1, 23). The effect may be due to an improved β_2 -receptor function and/or to a direct change in the cyclic AMP metabolism leading to an increased level of cyclic AMP (1). It is possible that this effect of the steroids could be valuable, especially in severe asthma, where a reduction in the beta-receptor function has been suggested as a pathogenic mechanism in asthma, or as the result of a β_2 -receptor tolerance due to long-term treatment with

sympathomimetics (19, 21) Glucocorticoids also seem to affect the mucus, perhaps by reducing the high viscosity in severe cases of asthma (6).

All these effects probably explain the favourable effect of the glucocorticoids, when the other types of asthma remedies fail. However, it is well known that glucocorticoids imply the risk of a long series of adverse effects. Therefore, treatment with these drugs should not be instituted until it is no longer possible to control the asthma with other anti-asthmatic drugs. In principle, treatment with beclomethasone aerosol (Becotide®) should always be tried first, since this treatment does not imply the risk of serious complications with normal dosage. In more severe cases systemic glucocorticoid therapy will be necessary, since higher plasma concentrations and a more rapid onset of the effect are required. Thus, intravenous administration of hydrocortisone is used in status asthmaticus, and relief is mostly obtained after 5 h.

Previously, treatment of chronic, steroid-requiring asthma was a problem, since the side effects with long-term treatment implied restrictions in the use of systemic glucocorticoids, whereby the patient was often insufficiently treated. With beclomethasone inhalation therapy it is now in many cases possible to control the asthma without any systemic side effects (3). This is the consequence of a rapid metabolic inactivation of the absorbed part of the drug. The favourable effect of beclomethasone does not set in until after several days of treatment. The daily aerosol dose is usually 0.4 mg, the effect of which equates approximately 7.5 mg of prednisone. Not until daily doses of 0.8 mg beclomethasone are being given, can systemic side effects be demonstrated in the form of a poor depression of the adrenocortical function. The only local side effect observed is oropharyngeal candidiasis (oral thrush) (22). The thrush is seldom seen with low dosage, but can become a problem with higher doses. Another disadvantage seems to be worsening of eczema and allergic rhinitis on

discontinuation of systemic steroids. With periodic aggravation of the asthma, occasional recourse to systemic steroid therapy, or a combination, cannot be avoided.

With systemic glucocorticoid therapy the side effects appear especially if administration of higher doses is continued for more than 2–3 weeks. The serious side effects include reduced resistance to infections, hyperglycaemia, possible aggravation of an already existing peptic ulcer, osteoporosis, muscle atrophy, possible hypertension and oedema, adrenal atrophy, psychotic manifestations and growth retardation in children. Therefore, the contraindications are infections (especially tuberculosis), diabetes mellitus, peptic ulcer, osteoporosis, hypertension, cardiac and renal failure, psychosis and pregnancy. Therapy with glucocorticoids in these cases must be carried out with special caution.

Sodium cromoglycate

Sodium cromoglycate (Lomudal®) has neither bronchodilatory nor antiinflammatory effect. The mechanism of action may be a blockade at the mast cell membrane of the antigen antibody-induced calcium uptake (4). It thus prevents the development of asthma at an early stage by inhibiting the release of histamine and SRS-A from the mast cell, i.e. agents which cause bronchoconstriction, oedema and mucus secretion. The action of sodium cromoglycate is therefore entirely preventive, and it must be administered before the patient is exposed to antigen or exercise. Not all types of asthma respond to sodium cromoglycate. The best effect is obtained in extrinsic (exogenous) asthma, as for instance pollen-induced asthma, and also in exercise-induced asthma. It has proved to be especially valuable in the management of childhood asthma, but is often ineffective in adults. Optimal effect is obtained if the treatment is initiated a fortnight before the start of the pollen season, whereafter daily treatment is continued throughout the season.

Sodium cromoglycate is administered by inhalation, since peroral administration is ineffective due to the poor absorption. The drug is atoxic and gives rise to only a few side effects such as airway irritation, which might result in coughing or transient bronchospasm. No interactions or contraindications are known.

Anticholinergic drugs

The bronchodilatory effect of anticholinergic drugs (parasympatholytics) is due to a blockade of cholinergic (muscarinic) receptors in the bronchial smooth muscle (Fig. 1). Hereby the reflex-induced bronchospasm is counteracted, but the local effect of allergic-inflammatory mediators is not prevented. Previously, atropine and related drugs (stramonium cigarettes) were used, but today they are obsolete because of the side effects, especially the tendency to a reduced ciliary activity and mucus secretion, resulting in less but more viscous secretion, which may be difficult to cough up (5, 8). A rational utilization of the favourable effect of the drugs has not been achieved until recently by the introduction of a quaternary atropine-related compound, ipratropium bromide (Atrovent®), (5, 15, 16). By inhalation therapy with the recommended doses an effective bronchodilating effect is obtained without causing any subjective or objective side effects. The onset of action occurs within 5 min of inhalation and the bronchodilating effect is maintained for 4 to 5 h (2, 5).

Antihistamines

Antihistamines are of little benefit in asthma. The drugs block the H_1 -receptor in the smooth muscles of the bronchi and hereby counteract the local effect of histamine, but the local effect of other allergic-inflammatory mediators is not affected, nor is the reflex-induced bronchospasm.

CONCLUDING REMARKS

Several drugs are now available for the treatment of bronchial asthma and the choice between them is based on considerations which involve an understanding of the basic pharmacological mechanisms and the pathophysiology of asthma. The severity of asthma is generally determined more by the inflammatory component than by the bronchospasm. Bronchospasm is reversed by the bronchodilators, but treatment of the inflammation in severe asthma needs the use of steroids. Among the bronchodilators, sympathomimetics and methylxanthines exert a general broncho-relaxing effect, whereas anticholinergics only prevent reflex-induced bronchospasm. The selective β_2 -stimulating drugs should be the first choice of bronchodilators in the treatment of asthma. A prophylatic effect is obtained with sodium cromoglycate by an inhibition of the release of mast cell-derived mediators, whereas antihistamine drugs, which block only the local effect of histamine on the bronchi, are of little therapeutic value.

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