The future of asthma treatment

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In the past few years, significant progress has been made in the treatment of asthma with the development of bronchodilators with longer durations of action, more concentrated inhaled steroid formulations and new modes of administering antiasthma medication. Furthermore, the key role of education in the management of asthma has been emphasized and many educational programs have been established. The recognition of the role of airway inflammation and structural changes in the physiopathology of asthma has led to a re-evaluation of asthma treatment guidelines. Anti-inflammatory drugs are now considered the mainstay of asthma therapy. An unprecedented number of new, potentially helpful agents have been developed and will soon be available. Among other expected developments are the identification and possible correction of genetic abnormalities responsible for the tendency to develop asthma and atopy, and prevention of functional and structural airway changes. This last goal will be achieved by improved environmental control, earlier use of more powerful and safe anti-inflammatory agents, as well as an increased involvement on the part of the asthma patient in treatment.

Key Words: *Airway inflammation, Asthma education and management, Asthma treatment*

IN THE PAST FEW YEARS, ASTHMA TREATMENT HAS IMPROVED with the development of long-acting bronchodilators, more concentrated forms of inhaled steroids and new inhalation devices (1,2). Recognition of airway inflammation as a major mechanism in the development of asthma and airway hyperresponsiveness, and studies suggesting that regular use or overuse of bronchodilators such as short-acting beta₂-agonists may be harmful, have led to a redefinition of the role of these agents in asthma treatment (3,4). Short-acting beta₂-agonists (duration of action 4 to 8 h) are now recommended for acute symptomatic relief of asthma, their need reflecting the level of asthma control.

L'avenir du traitement de l'asthme

RÉSUMÉ : Au cours des dernières années, des progrès importants ont été réalisés dans le traitement de l'asthme grâce à la conception de bronchodilatateurs à longue durée d'action, de formulations plus concentrées de stéroïdes en inhalation et de nouveaux modes d'administration des médicaments antiasthmiques. De plus, on a mis l'accent sur le rôle clé de l'éducation dans la prise en charge de l'asthme et établi de nombreux programmes d'éducation. La reconnaissance du rôle de l'inflammation des voies aériennes et des changements structuraux dans la physiopathologie de l'asthme a conduit à la révision des modalités du traitement de cette maladie. On considère maintenant les médicaments anti-inflammatoires comme la base du traitement de l'asthme. Un nombre sans précédent de nouveaux agents potentiellement efficaces ont été mis au point et seront bientôt disponibles. Parmi les autres progrès attendus se trouvent l'identification et la correction des anomalies génétiques responsables de la tendance à développer de l'asthme et de l'atopie, et la prévention des changements fonctionnels et structuraux dans les voies aériennes. Ce dernier objectif sera atteint avec l'amélioration des conditions environnementales et l'utilisation précoce d'agents anti-inflammatoires plus puissants et plus sûrs accompagnées d'une participation accrue du patient asthmatique à son traitement.

The recent emphasis is on anti-inflammatory treatment, particularly with inhaled steroids. The usefulness of cromoglycate and nedocromil has also been recognized (5). The possibility of using other agents with anti-inflammatory properties such as methotrexate, gold salts or antimalaria drugs has been considered in severe asthma, although their use is limited by variable effects and toxic properties (6,7). New devices providing easier administration of aerosols, powder inhalers and different types of spacers have been developed (8,9). Finally, the major role of education in managing asthma has been recognized, and different educational programs have been developed (10,11).

TABLE 1
New investigational agents potentially useful in asthma treatment

Bronchodilators

Long-acting beta₂-agonists:

salmeterol*, formoterol

Specific antagonists of muscarinic receptors

Selective inhibitors of phosphodiesterase isoenzymes

Potassium channel activators

Nitroprusside, atrial natriuretic factor

Bronchial anti-inflammatory agents

Inhaled steroids: fluticasone, mometasone, etc

Specific mediator antagonists for:

leukotrienes

5 lipoxygenase

PAF

phospholipase A₂

Inhibitors of neurogenic inflammation:

opioids

neurokinin antagonists

Adhesion molecule antagonists

Immunomodulators:

cyclosporine A

FK506, rapamycin

cytokine inhibitors (IL-4, IL-5)

anti-immunoglobulin E antibodies

*Recently made available in Canada; PAF Platelet activating factor

Recent improvements in our knowledge of the physiopathological mechanisms of asthma and identification of the cells and key mediators involved in asthmatic airway inflammation have led to the development of new substances with promising antiasthmatic properties. We are presently at a turning point in asthma therapy and an unparalleled number of therapeutic agents are currently on trial or soon will be (Table 1). Excellent reviews of these recent developments have been published (12-15).

This article reviews promising developments in asthma therapy in terms of pharmacotherapy, modes of administration of medications, immunotherapy, gene therapy, changes in the therapeutic scheme and asthma education.

PHARMACOTHERAPY

Long-acting beta₂-agonists: A new generation of beta₂-agonists has been developed, represented by drugs such as salmeterol and formoterol (16). These medications have powerful bronchodilator effects of prolonged duration (more than 12 h), and bronchoprotective effects that can last 36 to 48 h in some asthma patients (17). Long-acting beta₂-agonists are considered most useful for controlling asthma symptoms in subjects using anti-inflammatory treatment, particularly when they have nocturnal symptoms.

Theophylline and derivatives, phosphodiesterase inhibitors: Theophylline is an excellent bronchodilator but its use is limited by toxicity. It would be of interest to find derivatives with the same therapeutic efficacy but fewer side effects. In this regard, enprophylline has shown no antagonist effect on adenosine, and it is a good bronchodilator. Unfortunately, its use has been impeded by toxic effects.

Recently, it has been suggested that theophylline could produce bronchial anti-inflammatory effects when given in low doses (18). These observations remain to be confirmed and the long term effects of this mode of administration of theophylline have yet to be explored.

Different phosphodiesterase isoenzymes have been recognized and selective inhibitors have been synthesized (19). Theophylline inhibits different phosphodiesterase isoenzymes in a nonspecific fashion but specific inhibitors seem to be more promising. Type III and IV isoenzymes are involved in bronchial smooth muscle relaxation and are potentially useful bronchodilators. Selective inhibitors of type IV isoenzymes seem to have anti-inflammatory properties such as inhibiting inflammatory cell activation and recruitment, increase in pulmonary capillary permeability, generation of superoxides, cytokines and leukotrienes, and release of mediators from some inflammatory cells (12,20). However, their toxicity profile seems to be problematic, with the class III inhibitors showing some cardiovascular side effects, and class IV gastrointestinal or central nervous system side effects and electrolyte disturbances.

Selective anticholinergic agents: Vagal tone is increased in asthma, and anticholinergic agents have bronchodilator effects. Recently, different types of bronchial muscarinic receptors were described (21). Ipratropium is a nonselective inhibitor of these receptors. The synthesis of more selective inhibitors could probably increase their efficacy. Unfortunately selective anti-M1 agents cause mucosal dryness after systemic administration, and the development of other types of antagonists seems to be difficult.

Potassium channel activators: Potassium channels take part in the recovery of the basic state of cells after activation and help to maintain their stability. The opening of these channels causes bronchial smooth muscle relaxation. Different types of channels have been described and medications that selectively activate bronchial smooth muscle potassium channels, such as cromakalim, which was initially developed for the treatment of hypertension, could also have some spasmolytic effects useful in asthma treatment (22,23). Their usefulness, however, remains to be confirmed. They occasionally cause side effects, such as headache or postural hypotension from vasodilation. They are presently available in oral form, and it is possible that an aerosol might prevent some of the side effects.

Other agents: Calcium antagonists, such as nifedipine, verapamil and diltiazem, that block the calcium entry via voltage-dependent channels, have not been as useful as predicted in asthma. Agents that work on calcium entry via receptor-operated channels may be more efficient (24).

Others agents that have been suggested as potentially useful in the treatment of asthma include inhibitors of phosphoinositol hydrolysis (25), atrial natriuretic factor (26) and nitrite derivatives (27). Nitrous oxide has been described as a neurogenic endogenous bronchodilator agent, but its effect seems weak (28). Vasoactive intestinal peptide is a powerful bronchodilator agent in vitro, but is not effective in humans through inhalation (29). Finally, prostaglandins such as PGE₂

stimulate adenylyl cyclase and have bronchorelaxing effects *in vitro*. The search for specific antagonists of PGE receptor subtype is ongoing.

Inhaled steroids with weak systemic activity: Inhaled corticosteroids have become the mainstay of asthma treatment and are the most effective antiasthma medication. They inhibit many inflammatory mechanisms, particularly inflammatory cell activation and cytokine synthesis (30). Some efforts have been made to improve the local bronchial antiasthmatic effect of inhaled steroids and to reduce potential systemic effects. This has led to the synthesis of new molecules, such as fluticasone, mometasone, butixicort, tipredane and 'lazeroids' (13).

The mode of action of steroids involves interaction with either a cytosolic steroid receptor, which acts at the level of the genes to increase or reduce the level of transcription, or interaction with some activation factors of transcription, such as activating protein 1 (31). The search for new medications that will act on the transcription of the same genes or on other factors influencing transcription will probably lead to new useful compounds.

Nedocromil sodium: Nedocromil sodium has some effects similar to cromoglycate although they seem more intense (32). Its effects and indications are discussed in this issue by Gaudreault (pages 24A-31A) and Rouleau (pages 19A-23A).

Inflammatory mediator antagonists: We may consider the inflammatory process to be so complex that medications that act on only one mediator are less efficacious than those acting at different levels such as the steroids. The usefulness of specific antimediators has yet to be demonstrated, but they could be particularly useful in subgroups of asthmatics in whom physiopathological mechanisms depending on these mediators are predominant. Many mediators involved in the inflammatory cascade have been considered as potential targets for the development of anti-inflammatory medications. Antihistamines have not been very effective in the treatment of asthma, but they may help to treat associated conditions, such as rhinitis (33). The antiasthmatic effects of leukotriene and 5-lipoxygenase inhibitors are presently under study, and it will be interesting to see not only their efficacy as bronchodilators but also their potential as anti-inflammatory drugs, as some have shown both bronchodilator and broncho-protector effects (34,35). Inhibitors of phospholipase A₂, the enzyme that is responsible for the synthesis of arachidonic acid and phosphodiesterase-activating factor (PAF), may also be useful (36). Antagonists have been developed for PAF and thromboxanes but they seem to be of variable efficacy (37,38).

Antineuropeptides: Neuropeptides are released by neural sensory endings in the asthmatic airway via an axonal reflex and may increase airway inflammation through neurogenic pathways. Sensory neuropeptide antagonists such as substance P and neurokinin A, mediators of the nonadrenergic, noncholinergic excitatory system and of calcitonin gene-related peptide are presently on trial (39,40). Until now, these agents have shown protective effects against some bronchoconstrictor stimuli such as exercise, acetylsalicylic acid and

allergens. Long term clinical trials will be decisive. Neurokinin 1 receptors seem to be responsible for the anti-inflammatory effects of tachykinins and inhibitors of these receptors are currently being developed. The recent discovery of nonpeptidic neurokinin antagonists is promising.

Adhesion molecule inhibitors: The transfer of inflammatory cells from blood to tissue depends on their adhesion to the endothelium under the influence of glycoprotein-type adhesion molecules present on leukocytes and some endothelial cells. They may be expressed by the presence of stimuli such as cytokines, or mediators such as PAF and leukotrienes (41,42). Antagonists of adhesion molecules such as intercellular adhesion molecule-1 (ICAM), vascular cell adhesion molecule and late factor of activation, can block the recruitment of these inflammatory cells. It has been shown that an anti-ICAM-1 can block the eosinophil infiltration induced by the inhalation of antigens at the level of the airways in a primate model (43). The different tissue responses to adhesion molecules remain to be documented, and we do not know if their expression varies according to the type of ongoing inflammation. We still have to find agents that will not simultaneously inhibit the immune response to infectious agents.

Immunomodulators: The inhibition of activation and recruitment of lymphocytes at the inflammatory site can counteract the inflammatory process. Cyclosporine A, which inhibits the expression of interleukin-2 (IL-2) by lymphocytes and inhibits the response of T lymphocytes to IL-2, has shown some usefulness, although toxicity limits its use (44). Some other immunomodulators may be more effective and less toxic (13,45). The development of cytokine inhibitors would also be interesting, particularly those that inhibit their synthesis, or antagonists for IL-3, IL-4 and IL-5. The possible results of such intervention could be inhibition of the growth and differentiation of mast cells, a possible suppression of the synthesis of immunoglobulin (Ig) E, and a potential inhibition of activation and migration of eosinophils into the airway following, for example, allergen exposure (46,47). However, specific receptor antagonists for cytokines seem to be difficult to synthesize.

Other possibilities for suppressing immune responses include immunotoxins to eliminate IgE-bearing B lymphocyte, and the development of synthetic peptides that can inhibit both the bridging between IgE and antigens, and the interactions between T and B lymphocytes (48).

MODE OF ADMINISTRATION OF MEDICATION

Liposomes: Liposomes are lipid microparticles in which drugs can be incorporated (49). Liposomes can be used to direct an antiasthma medication towards a specific target, such as macrophages or lymphocytes. This is a promising possibility in treatment.

New inhalation devices: The past decade has seen a more frequent use of devices such as spacers to facilitate the use of aerosol. Powder devices have also been developed, stimulated in part by the progressive elimination of chlorofluorocarbons (CFCs). New products to replace CFCs are being sought.

SPECIFIC IMMUNOTHERAPY

The role of immunotherapy in the treatment of asthma is controversial and is considered as marginal by many (50). This is partly due to its limited efficacy, because of a lack of specificity of antigens, as well as potential side effects, duration of treatment and cost. It will probably be possible in the near future to use desensitization with more specific antigens and fewer side effects.

GENE THERAPY

The presence of genetic determinants for atopy on chromosome 11 has been suggested (51). However, other studies could not reproduce the results, as discussed in a recent editorial (52). The possibility of influencing genetic predisposition to the development of atopy or the synthesis of high levels of IgE, both of which are considered to be important factors in the development of asthma, is probably still many years away.

MODIFICATION OF THE THERAPEUTIC SCHEME

It is possible that not only the synthesis of new products but also the way they are administered will change, as they have changed in the past few years. Asthma is considered a long term process with remodelling of the airways under the influence of an inflammatory response (53). Descriptions of the natural history of occupational asthma have determined that the longer the sensitizing exposure and the more significant it is, the less reversible the asthma (54). The influence of the stage of the disease at which anti-inflammatory drugs are given on the chronicity of the disease should be more extensively studied.

Medications can be more effective when given at an early stage of the disease than when structural and functional abnormalities have become irreversible (55). It is possible that in the near future anti-inflammatory treatment for asthma will be advocated even before symptoms occur, to prevent its development. The recent international consensus on asthma treatment suggests that bronchial anti-inflammatory agents should be started as soon as bronchodilator need occurs more than three times a week (3).

Regarding another aspect of treatment, chronopharmacological studies will allow us to determine the optimum time for administering medications to maximize antiasthma effect and reduce potential side effects, as well as reducing the number of doses required. Inhaled steroids, for example, seem to be more efficient when given at the end of the day (56).

Finally, improvement in environmental control, particularly in reducing smoking and antigenic exposure in children, should help to prevent asthma and reduce its severity.

ASTHMA EDUCATION: THE QUEBEC NETWORK

Teaching asthmatic subjects about asthma and its treatment, in order to increase their autonomy in controlling the disease and their self-management skills, is essential to achieve adequate asthma control. This aspect of asthma treatment has long been neglected and we have to make up for lost time. Educational models and teaching programs have been

developed recently (10,11,57). There are still, however, few integrated multidisciplinary structures to make effective and uniform asthma education available to most asthmatic subjects. Studies over the past two decades have shown an increase in asthma mortality and morbidity that might have been prevented. Teaching should therefore cover the essentials, with practical applications aimed at changing behaviour instead of merely increasing knowledge; ideally, it should be implemented by specialized educators.

It became apparent to us that we needed a joint effort between the different groups offering or willing to offer teaching programs to asthmatic patients in the province of Quebec, to increase their availability, make the approach more uniform and avoid wasting energy and resources by duplicating tools, while attempting to offer a coherent approach to asthma treatment.

A model of a provincial asthma education network has been developed with the help of the Quebec Lung Association, the Quebec Ministry of Health, the pharmaceutical industry, professionals involved in asthma care, and the public. The content of the program is based on national and international recommendations on asthma evaluation and treatment. The objectives of the network are to offer asthmatic patients high quality and uniform teaching to increase their self-management abilities and, with the help of their physician, to reduce the consequences of their disease, while improving their quality of life and reducing health care costs.

The activities of the network include training the professionals responsible for asthma education. Their knowledge and skills are updated through training sessions and courses at established asthma clinics. Teaching materials are being developed and a liaison newsletter is regularly published by the Quebec Asthma Education Network. Four 'regional' committees of experts from Laval University, McGill University, the University of Montreal and the University of Sherbrooke are in charge of educator training. Education of asthmatic patients is the responsibility of education centres located in selected institutions of the provincial health network, as determined by the regional boards. They make a specialized educator available to their asthmatic clients, supervised by a designated physician. Educators and supervising physicians are not involved in asthma care directly; they offer only educational services. If problems are detected, the information is communicated to the referring physician. The network also helps to establish asthma education programs in clinics and institutions, to look at local needs. Finally, it promotes the formation of support groups through the Quebec Lung Association.

The network infrastructure includes a scientific committee, comprising chest physicians, allergists, general practitioners, pediatricians and other related health professionals involved in asthma care and responsible for the program's content and evaluation. An advisory committee is made up of representatives from different professional associations and the pharmaceutical industry. It provides technical and administrative advice on the network's activities. A user's committee provides feedback from those receiving the educational

service. The network is directed by a team comprising the director of the Quebec Lung Association and the chairperson of the scientific committee. A provincial administrative coordinator oversees all the details of the network's activities. An evaluation and research program has been developed to verify the effectiveness of the program. Finally, the Quebec Asthma Education Network is an active member of the Canadian Network for Asthma Care.

CONCLUSION

Effective prevention and a cure for asthma is still a long way off, but many preventive tools are presently available, such as environmental control measures and early use of anti-inflammatory agents when bronchodilator need be-

comes regular (58). Gene therapy and averting structural and functional abnormalities before the symptomatic stage of asthma are potential avenues in the prevention of the disease, but many studies are needed to assess them. Many new drugs will soon become available; among the more welcomed are new steroids with increased antiasthma properties and less potential for side effects, and the development of effective nonsteroidal anti-inflammatory drugs. We should also work at improving the availability and quality of asthma education with the aim of optimizing asthma treatment through increased self-management skills, improving intervention when asthma worsens, and ensuring the adequate use of preventive measures. More studies are also needed to determine which educational interventions are the most effective.

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