Various drugs and methods have been used in the treatment of asthma in Japan. The basic treatment in Japan is presumably similar to other countries.

For symptomatic treatment, bronchodilators which include β-agonists and xanthine derivatives, are considered to be the first choice drugs. Steroids are used for intractable or life-threatening asthma. Other medications include anticough preparations, expectorants, and anti-cholinergic drugs.

For prophylaxis, disodium cromoglycate or similar anti-allergic drugs are used. β-agonists, steroids and anti-cholinergic drug inhalation are also used for the prevention of asthma. Chinese herb medicines, calcium antagonists, hyposensitization therapy, gold salt, histaglobin, acupuncture, and moxibustion have also been used to some extent in Japan.

β-AGONISTS

Many β-agonists have been used in Japan. For instance, epinephrine, isoproterenol, metaproterenol, trimetoxinol, terbutaline, salbutamol, tulobuterol, and procaterol are available. Trimetoxinol was discovered in 1967 and other Japanese products, namely tulobuterol and procaterol, have been used in the last several years. The available β-agonists are long acting and specific to β-receptors, resulting in fewer side effects. Oral preparations are the most commonly used form of beta-agonist in Japan (Fig 1).

Inhalation of β-agonists has been used for acute asthma attacks and is considered the first choice in such a condition. The number of inhalation puffs should be limited to several times in a day. Recently, there has been a trend to use inhalers for prophylaxis. For instance, the inhalation of β-agonists has been used three to four times in a day for chronic asthmatic patients, even though no wheezing or shortness of breath is clinically experienced. The mild airway obstructive changes may not be recognized by the patients, but, if not treated, may precipitate an acute asthmatic attack. Consequently, the prophylactic use of cartridge inhalers is quite popular in Japan.

Injection of β-agonists is limited in Japan. Only epinephrine has been injected during an acute asthmatic attack. Susphrine provides rapid and sustained action of epinephrine, but has not been adopted in Japan. The sublingual route of isoproterenol and rectal suppository of salbutamol or other forms of β-stimulants are not used in Japan.

XANTHINE DERIVATIVES

Aminophylline is available for intravenous, oral and rectal administration. Intravenous aminophylline is widely used to control the acute attack. Rectal use has only very limited value, since Japanese people are not accustomed to using suppositories. Overall, the use of xanthine preparations is still quite limited (Fig 2).

At the present time, the number of xanthine derivatives available is limited in Japan, although long-acting

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drugs such as Theodur are available. The use of a β-agonist or xanthine derivative alone is appropriate if effective. In many situations, however, a combination of both drugs is necessary to achieve adequate effectiveness, and combined usage of β-agonists and xanthine derivatives is common practice in Japan as in many other countries. Long-acting theophyllines have been adopted in Japan and the dose is monitored according to the clinical response and blood level. Measurement of theophylline blood levels has become popular in Japan.

**STERIODS**

In life-threatening asthma, use of corticosteroids are essential. Their potentially serious side reactions, when used systemically, limit such use to those situations when other measures do not provide sufficient control of symptoms. Repository injectable preparations of steroids such as triamcinolone are available and convenient in some acute cases, as asthmatic symptoms subside for several weeks following the single injection of 20-40 mg. However, these preparations should be used cautiously since profound and long-lasting adrenal suppression is observed.

Aerosol steroids such as beclomethasone dipropionate have been used in Japan for more than ten years and have proved quite effective in controlling asthma. While useful in reducing the need for systemic corticosteroids, there is no place for this aerosol in the treatment of an acute attack. Because of the general prejudice against using steroids, steroid inhalation has not been popular among general practitioners in Japan; however, there is an increasing frequency of use of aerosolized steroids. The number of steroid-dependent patients in Japan is estimated to be less than 1 percent.

**DISODIUM Cromoglycate AND SIMILAR DRUGS**

Disodium cromoglycate is effective in asthma and has been used clinically for the last 20 years in Japan. Children tend to respond better than adults and some Japanese pediatricians feel disodium cromoglycate is the first choice drug in children's asthma. Perennial asthmatics without definable allergens may also respond. Exercise-induced asthma can often be prevented by therapy with disodium cromoglycate. Oral preparations of disodium cromoglycate-like drugs such as ketotifen (a Swiss product) and tranilast (from Japan) lead to a reduction in both the frequency and the intensity of asthma attacks. More money is spent on anti-allergic drugs than on any other preparation to treat asthma in Japan (Fig 2). Many similar drugs are coming into clinical use in Japan, including inhibitors of the lipoxygenase pathway and leukotriene antagonists.

**OTHER DRUGS**

In asthma, there is increased production of highly viscid mucus. If mucus flow and removal by ciliary action is impaired, additional airway obstruction may occur, and bronchial infection often is superimposed. Therefore, it is imperative to institute measures to keep the mucus liquefied and thin. Increased fluid intake and use of expectorants and mucolytic agents are used in conjunction with other antiasthmatic treatment. It is unwise to suppress the cough in asthmatic patients unless it is irritative, fatiguing, and non-productive. In patients with yellow or green sputum and an exacerbation of asthma, a broad spectrum antibiotic such as tetracycline, ampicillin or oleandomycin may be of considerable value.

Tranquilizers and sedatives have in the past enjoyed some popularity in the treatment of asthma because the dyspneic patient is anxious. However, verbal reassurance and relief of bronchospasm using bronchodilators is the treatment of choice for anxiety.
Atropine is not approved for use in asthma because of drying effects on mucous membranes. However, anti-cholinergic aerosols such as ipratropium bromide (SCH 1000) block vagal irritant receptors in airways and have been used to some extent in Japan, since these new drugs have much less drying effect. Calcium transport antagonists such as nifedipine have some clinical value in the elderly asthmatic with hypertension or angina pectoris.

Histaglobin, the conjugate of γ-globulin and histamine, has been used in the treatment of asthma to some extent in Japan. After 10 to 15 weekly injections of 1 to 3 ampules of histaglobin, monthly injection is recommended as maintenance therapy for an extended period.

IMMUNOTHERAPY

Immunotherapy has been used fairly widely in the last 30 years. In spite of good environmental control and use of proper medications, asthma sometimes cannot be well controlled. For such cases, immunotherapy is considered. Because of other effective drugs and methods, however, the number of cases under immunotherapy has decreased. Moreover, immunotherapy with molds, especially Candida albicans, occasionally causes a severe systemic reaction following an injection. In addition, the possibility of immune-complex diseases was raised with immunotherapy. Therefore, the use of molds has been largely deleted from therapy. Consequently, immunotherapy has been confined to house dust and pollens in many institutes in Japan. There is a trend, however, to use purified allergens in immunotherapy. This may change the current use of immunotherapy. Denatured allergen, polymerized allergen and conjugated allergen to innate materials have been tested in animal experiments with encouraging results. Oral hyposensitization is also under investigation. More studies are needed before clinical use can be recommended.

GOLD (CHRYSTHERAPY)

Gold has been used as a medicine off and on for the last several hundred years. Indications for gold therapy include chronic infection, rheumatoid arthritis and other chronic diseases. Because of its side effects, however, it has not been used widely except for rheumatoid arthritis. In the last 50 years, gold has been adopted in the treatment of intractable asthma in Japan, with beneficial effects. Gold has not been used to relieve acute symptoms of asthma, but rather for a slow amelioration of symptoms and to decrease the need for other medications, especially steroids. Gold therapy can cause some asthmatic patients to go into remission for months and even years. The typical regimen for asthma is a weekly intramuscular injection of 10 mg for ten weeks, followed by 25 mg per week for ten weeks, if no adverse reactions are noted. If needed, the dose is increased to 50 mg. In the past, doses of 100 mg or even 150 mg were used; however, recently 25 mg or 50 mg was considered the maximum dose. After 25 mg or 50 mg for ten injections, the same dose was given every two weeks for ten weeks or more, and then every four weeks for months or years. According to the clinical response, the dose is reduced to 25 mg, then 10 mg. Injection of 10 mg monthly will then be given for prolonged periods. As a result of such therapy, improvement in asthmatic symptoms will be seen after about 30 injections. A considerable anti-asthmatic effect was usually achieved when a total of 1,000 mg had been administered after years of therapy. The effectiveness of gold was proved by a double-blind study. Because of side effects such as skin eruption, proteinuria, bone marrow suppression, and liver dysfunction, gold is only used in severe and intractable cases. Recently, oral gold (auranofin) has been used in the treatment of rheumatoid arthritis. The clinical effectiveness of auranofin in asthma is currently under investigation in Japan.

CONCLUSION

Nonspecific measures such as protection from meteorologic factors, control of the internal environment in the home, and discouraging smoking, are important in the treatment of asthma. In the last 20 years, asthma has become much easier to treat as a result of the development of more effective drugs and forms of therapy.

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