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Original Article

Questionnaire-based characterization of bronchial asthma in the elderly: Analysis in Niigata Prefecture, Japan

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ABSTRACT

Background: Because the mean lifespan is increasing and the percentage of elderly people among the population as a whole is also increasing, the management of elderly bronchial asthma patients will be an important issue in medicine in the future. In the present study, based on questionnaires given to 3224 asthmatic patients in Niigata Prefecture, the characteristics, management and circumstances of elderly asthmatic patients were investigated.

Methods: Questionnaires were completed by asthmatic patients and their physicians in participating institutions within Niigata Prefecture from September to October 1999. Patients more than 65 years of age were defined as elderly asthmatic patients and a comparison was made between these patients and younger asthmatic patients who were less than 64 years of age and were used as a control group.

Results: In the classification of bronchial asthma, a greater frequency of infectious and mixed-type bronchial asthma was found in the elderly, whereas the use of peak flow meters was lower in this group. Significant differences were found for both selfevaluation of the condition of the asthma and satisfaction with daily life between the two age groups. A lower incidence of ambulance use, emergency room visits and use of inhaled steroids was observed in

Introduction At the end of the 19th century, the number of people over 65 years of age was below 15 million worldwide, less than 1% of the whole population. Now, people over 65 years of age represent 6.2% of the world's popula-

tion. Therefore, the characteristics of some diseases in

elderly people require reconsideration compared with

younger people, including diagnosis and therapy.

Bronchial asthma had been considered a rare disease in elderly patients because of its infrequent onset at this age, although it is a common disorder for respiratory physicians. However, several studies have shown that bronchial asthma in the elderly is not so uncommon. 1-3 Despite the characteristics of elderly asthma reported in several papers, these cases seem to be very complex.⁴

The present study attempts to identify the actual state of bronchial asthma in the elderly. To achieve this, a

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elderly patients, although the incidence of hospitalization and use of oral steroids was higher. The discrepancy between objective and subjective evaluation of asthma control, the incidence of the use of both inhaled and oral steroids and the low use of peak flow meters were problematic in the elderly.

Conclusions: Based on sufficient consideration of the problems specifically related to elderly asthmatic patients, adequate education and careful management of asthma in this group are required, and the accumulation of these steps will result in the achievement of the guidelines final goals.

Key words: bronchial asthma, education, elderly, guidelines, questionnaire.

questionnaire-based investigation was conducted among patients with bronchial asthma and their physicians in cooperation with a number of medical institutions in Niigata Prefecture, Japan. Management for elderly asthmatic patients should be performed under current guidelines.^{5,6}

METHODS

Through questionnaires, patients with adult bronchial asthma who visited the participating institutions were asked their age, duration and onset age of asthma and their asthmatic symptoms in the 2 week period prior to the questionnaire, as well as the usage status of a peak flow meter. The questionnaires also inquired about asthma-related episodes, including ambulance use, emergency room visits, hospitalization, anti-inflammatory agent-induced asthma attacks (aspirin-induced asthma; AIA), unconsciousness during asthma attacks and management of asthma using a respirator. The questionnaire was administered to patients over a period of 2 months, from September to October 1999. At the same time, the patients' physicians answered questionnaires investigating the severity of asthma and the details of treatment. The investigation involved 153 institutions around Niigata Prefecture and information was collected on 3224 cases. The general profile of cases with asthma was understood. In this investigation, patients greater than 65 years of age were defined as elderly asthmatic patients (EAP; n = 1084). After obtaining and analyzing these results, a comparison was made between EAP and

younger asthmatic patients (YAP; n = 2114) as a control group, who were aged less than 64 years.

Student's t-test and the χ^2 -test were performed to compare EPA and YPA. P < 0.001 was considered significant.

RESULTS

Patient background

The baseline characteristics of EAP and YAP are summarized in Table 1. The mean (±SD) age, gender ratio (males/females) and duration of asthma in EAP and YAP were 72.1 ± 5.5 versus 44.5 ± 14.0 years, 1.25 versus 0.94 and 11.8 \pm 13.4 versus 10.4 \pm 11.0 years, respectively. Significant differences were found in age and gender between EAP and YAP. The physicians in charge graded disease type and severity. The rates of atopic, mixed-type and infectious disease, given as percentages, in EAP and YAP were 16.8 versus 49.6%, 38.6 versus 27.5% and 41.6 versus 20.5%, respectively, indicating that the rate of infectious-type disease in EAP was significantly higher than in YAP (P < 0.0001). The rates of mixed- and atopic-type disease were lower (P < 0.0001). As for the severity of the disease, the rates of mild, moderate and severe cases in EAP and YAP, given as a percentage, were 43.0 versus 45.3%, 43.0 versus 44.3% and 12.4 versus 8.7%, respectively. No significant differences were found for severity of disease. Although the use of a peak flow meter is strongly recommended in the guidelines for controlling asthma,^{5,6} such meters were used by 28.5% of EAP, which was

Table 1 Baseline characteristics of the patients

	EAP	YAP	Р
No. patients	1084	2116	
Age (years)	72.1 ± 5.5	44.5 ± 14.0	0.0001
Duration of asthma (years)	11.8 ± 13.4	10.4 ± 11.0	0.0010
Gender (males/females)	602/482	1026/1090	0.0002
Use of peak-flow meter (%)	28.5	38.3	0.0001
Classification			
Atopic (%)	16.7	49.6	0.0001
Mixed (%)	38.6	27.5	0.0001
Infectious (%)	41.6	20.5	0.0001
Severity			
Mild (%)	43.0	45.3	0.2375
Moderate (%)	43.0	44.3	0.5172
Severe (%)	12.4	8.7	0.0010

Where appropriate, data are given as the mean \pm SD.

EAP, elderly asthmatic patients; YAP, young asthmatic patients.

significantly lower (P < 0.0001) than the rate of use by YAP.

For EAP who used a peak flow meter, the peak expiratory flow rate (PEF) value, as a percentage of predicted PEF values (%PEF), was $73.1 \pm 23.0\%$ in the early morning and $76.7 \pm 22.4\%$ at night, which was significantly lower (P < 0.0001) than the figures obtained for YAP users of the peak flow meter (80.0 ± 17.8 and $82.5 \pm 17.8\%$, respectively; Fig. 1).

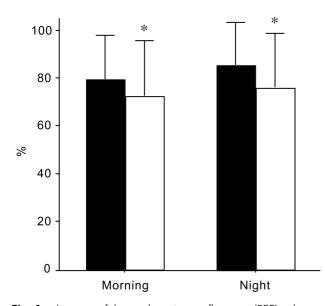


Fig. 1 Average of the peak expiratory flow rate (PEF) value, as a percentage of predicted PEF values (%PEF). Data are the mean \pm SD. (\blacksquare), %PEF in young asthma patients (YAP) in the morning and at night; (\square), %PEF in eldery asthma patients (EAP) in the morning and at night. Significant differences were seen between the two groups (*P < 0.0001).

Asthma attacks during the 2 weeks prior to answering the questionnaire

To investigate the circumstances surrounding asthma attacks, asthma attacks during the 2 weeks prior to answering the questionnaire were analyzed based on the information collected. The percentage of cases who did not experience an attack was 51.0% for EAP and 58.6% for YAP (Table 2). A significant difference was seen in both groups (P < 0.0001). Subjects were asked to rate the condition of their asthma during the 2 weeks prior to the questionnaires by choosing one of five options ('very good', 'fairly good', 'mediocre', 'slightly bad' and 'bad') in order to subjectively evaluate asthma control from the patients' viewpoint. The percentage responses for each of the five levels of 'very good', 'fairly good', 'mediocre', 'slightly bad' and 'bad' were 16.7, 34.5, 33.9, 10.6 and 2.9%, respectively, for EAP and 18.4, 34.9, 25.4, 17.1 and 3.6%, respectively, for YAP (Table 2. Significant differences were found for the 'mediocre' and 'slightly bad' levels between EAP and YAP (P < 0.0001).

Satisfaction with daily life

Another target of asthma treatment according to the guidelines for treatment is to allow patients to live the same life as healthy people. In this context, 'satisfaction with daily life' was used in the questionnaires as an indicator. Subjects were asked to answer the question by choosing one of five options ('very satisfied', 'fairly satisfied', 'mediocre', 'slightly unsatisfied' and 'very unsatisfied'). For EAP, responses of 'very satisfied' and 'fairly satisfied' were recorded in 14.2 and 63.5% of

Table 2					guestionnaires

	EAP	YAP	Р
No. patients	1084	2116	
Percentage without attacks (%)	51.0	58.6	0.0001
Subjective evaluation of asthma			
Very good (%)	16.7	18.4	0.2650
Fairly good (%)	34.5	34.9	0.8123
Mediocre (%)	33.9	25.4	0.0001
Slightly bad (%)	10.6	17.1	0.0001
Bad (%)	2.9	3.6	0.4500

Data show the percentage of subjects without asthma attacks and subjective evaluation of asthma during the 2 weeks prior to answering the questionnaire. Although significantly fewer cases without attacks were found in elderly asthmatic patients (EAP) than young asthmatic patients (YAP), subjective evaluations of asthma were better in EAP than in YAP.

respondents, respectively. Responses of 'mediocre', 'very unsatisfied' or 'slightly unsatisfied' were cited by 10.8, 6.6 and 0.6% of subjects, respectively. There was a significantly higher percentage of responses at the level of 'fairly satisfied' (P < 0.0001) and a significantly lower percentage of 'very unsatisfied' or 'mediocre' (P < 0.0001) for EAP than for YAP (Table 3).

Asthma-related symptoms during the 2 weeks prior to answering the questionnaires

According to the guidelines, it is also important to eliminate asthma-related symptoms, such as coughing and a sense of dyspnea, and to enable satisfactory sleep at night, as well as preventing asthma attacks. Based on

the questionnaire results, the occurrence of a variety of asthma-related symptoms occurring early in the morning, at night and during sleep was examined. With regard to symptoms early in the morning and at night, a significant difference was found in the incidence of sputum early in the morning (P=0.0005) and in the incidence of chest oppression at night (P=0.0003) between the two groups (Table 4). While patients were sleeping, there were no differences in asthma-related symptoms (Table 4).

Emergency events related to asthma attacks

Another obvious objective is to prevent death caused by asthma attacks, as stated in the guidelines. Based on

Table 3 Satisfaction with daily life

	EAP	YAP	Р
No. patients	1084	2116	
Satisfaction with daily life			
Very satisfied (%)	14.2	13.0	0.3612
Fairly satisfied (%)	63.5	54.9	0.0001
Mediocre (%)	10.8	17.4	0.0001
Fairly satisfied (%)	6.6	11.6	0.0001
Very satisfied (%)	0.6	1.8	0.0153

Subjects were asked to answer the question regarding satisfaction with daily life by choosing one of the five answers given above. Significantly better satisfaction with daily life was found in elderly asthmatic patients (EAP) compared with young asthmatic patients (YAP).

Table 4 Asthma-related symptoms during the early morning, at night and during sleep

	EAP $(n = 1084)$	YAP (n = 2116)	Р
Symptoms during the early morning (%)	56.8	53.7	0.2409
Sense of dyspnea (%)	9.5	9.6	0.8805
Wheezing (%)	11.9	13.0	0.3623
Chest oppression (%)	10.5	12.8	0.0608
Sputum (%)	29.7	23.9	0.0005
Coughing (%)	19.1	21.1	0.1664
Symptoms at night (%)	41.9	38.6	0.0603
Sense of dyspnea (%)	5.2	6.4	0.1646
Wheezing (%)	7.3	9.6	0.0250
Chest oppression (%)	6.0	9.7	0.0003
Sputum (%)	11.4	10.0	0.2250
Coughing (%)	9.8	11.8	0.0930
Symptoms during sleep (%)	32.4	29.7	0.1101
Impossible to sleep due to dyspnea (%)	2.1	2.6	0.4608
Too painful to sleep due to dyspnea (%)	6.0	7.3	0.1500
Woke up in night due to chest oppression (%)	11.2	13.9	0.0460

Asthma-related symptoms during the 2 weeks prior to answering the questionnaires are shown. With regard to symptoms during the early morning and at night, significant differences were found in the incidence of both sputum in the early morning and chest oppression at night between elderly asthmatic patients (EAP) and young asthmatic patients (YAP).

the results of the questionnaires, the emergency events experienced by the patients, which included ambulance use, visits to the emergency room and hospitalization (possibly associated with death from asthma), unconsciousness during an asthma attack, management using a respirator (often directly leading to asthma-induced death) and AIA attacks (known to cause severe attacks and death), were examined. Subjects were asked to answer 'yes' or 'no' to the following five questions:

- 1. Have you ever had a respirator due to an asthma attack?
- 2. Have you ever been unconscious due to an asthma attack?
- 3. Have you ever been hospitalized due to asthma?
- 4. Have you ever been taken by ambulance or visited an emergency room due to an attack?
- 5. Have you ever had an attack induced by antiinflammatory drugs, including painkillers, antipyretics or cold medicine?

Figure 2 shows the results of the responses to these questions. Among the EAP respondents, 32.0% had visited or used an emergency room or ambulance, which

was significantly (P < 0.0001) fewer than YAP respondents (43.6%). Furthermore, 49.9% of EAP reported hospitalization due to asthma, which was significantly (P < 0.0001) greater than YAP (43.8%). There was no difference in the incidence of patients who had lost consciousness due to an asthma attack or had managed their asthma with a respirator (Fig. 2). In the EAP group, 6.8% of patients had experienced an attack after taking anti-inflammatory drugs, compared with 9.9% in the YAP group.

Medication

Patients' drug use was examined based on the questionnaire results from their physicians (Fig. 3. Sustainedrelease theophylline was used very frequently in both groups, but a significantly higher incidence of use of sustained-release theophylline was found in EAP compared with YAP (P < 00001). Looking at the rates of use of inhaled steroids, oral steroids and inhaled

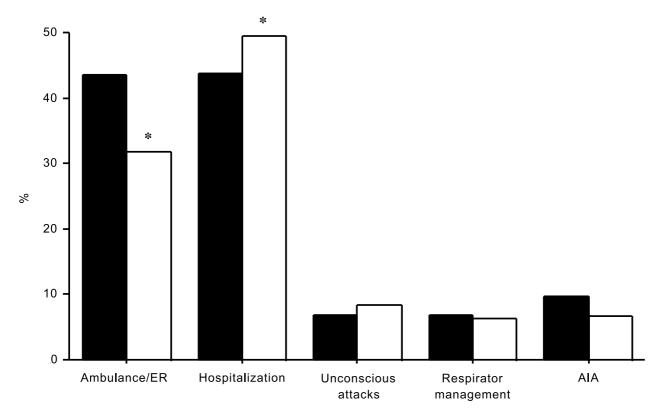


Fig. 2 Rates of visits to an emergency room (ER) or the use of an ambulance, hospitalization due to asthma, loss of consciousness due to asthma attacks and management by a respirator. (\blacksquare), young asthma patients (YAP); (\square), eldery asthma patients (EAP). Significant differences were seen between the two groups (*P < 0.0001). AIA, aspirin-induced asthma attack.

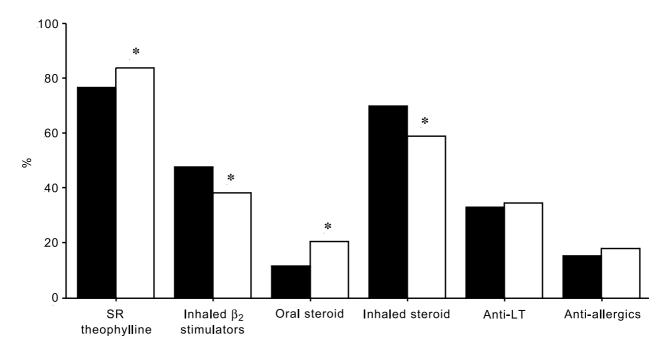


Fig. 3 Summary of the drugs used to control asthmatic patients based on questionnaire results from physicians in charge. (\blacksquare), young asthma patients (YAP); (\square), eldery asthma patients (EAP). Significant differences were seen between the two groups (*P < 00001). SR theophylline, sustained-release theophylline; β_2 stimulators, β_2 -adrenergic agonists; anti-LT, anti-leukotriene compounds.

 β_2 -adrenergic agonists in the EAP group, there were also significant differences compared with the YAP group (all P < 00001), as shown in Fig. 3. However, there was no significant difference in the rate of use of antileukotrienes or anti-allergics.

DISCUSSION

In this questionnaire-based investigation, information was obtained on 2798 cases treated by respiratory physicians and 426 cases treated by general physicians. This means that the majority of patients were from specialist institutions and that the results of the present study may indicate the status of patients managed by specialists more closely than that of patients managed by non-specialists.

In comparing EAP and YAP, there was no significant difference in the duration of asthma between the two groups, which corresponded with the report that high age-onset (after 40 years) asthmatic patients constituted the majority of cases in elderly (over 65 years) subjects with bronchial asthma. Although there were variations in terms of the classification of bronchial asthma, patients

in the present study were divided into atopic-, mixed- and infectious-type disease groups. The percentage of infectious-type disease in EAP was greater than that in YAP, which is consistent with data presented in previous reports.⁷⁻¹⁰ The present investigation found that the rate of use of peak flow meters was 25.8% in EAP, which was significantly lower than that in YAP. However, it should be noted that, even in YAP, only 38.3% of subjects used a peak flow meter. This indicates that this instrument is not widely used in Niigata Prefecture, Japan, and that patient education by physicians for this treatment is not well carried out, although the guidelines strongly recommend it. The advantage of using a peak flow meter for patients was probably not accepted due to both its cost and complexity, although the questionnaire did not address this. With their ability to enable daily evaluation of objective respiratory function, the use of peak flow meters should be more widely introduced in the future.

In assessing PEF, the average %PEF in EAP was under 80% (73.1% in the morning and 76.7% at night, which is comparatively favorable but significantly lower than the figures for YAP; P < 0.0001). This result was not due to more severe remodeling of the bronchial wall, but due to

a larger population of cases of severe asthma and less pulmonary function in the EAP group compared with the YAP group, because no significant difference was found in the duration of asthma, when the remodeling process does not depend upon aging. The differences in %PEF and the percentage of patients without attacks during the 2 weeks prior to answering the questionnaires clearly showed that asthma control in EAP was poorer than in YAP. Nevertheless, other subjective indicators of asthma control, including subjective evaluation of asthma during the 2 weeks and the degree of satisfaction with daily life, were contrary. The tradition of stoicism or 'extreme tolerance' among the elderly in Japan may have influenced these conflicting results. To avoid this, other objective indicators, including an adequate anamnesis and adequate education about self-evaluation of asthma control, are required. These issues are discussed later.

As for preventing death from asthma, the questionnaires found that the patients had experienced ambulance use, visits to the emergency room and hospitalization, unconsciousness during an asthma attack, management by a respirator and AIA attacks. The lower incidence of ambulance use or visits to the emergency room and the higher incidence of hospitalization in EAP are very important. Because EAP are more prone to other diseases, including cerebrovascular or cardiovascular diseases, it is well understood that hospitalization occurs more often in EAP than in YAP. However, this discrepancy, may be partly due to the 'extreme tolerance' mentioned above, resulting in both incomplete self-relief treatment against asthma attacks and a consequent delay in administering medication during an attack. In this respect, adequate education regarding asthmatic attacks will be also required for EAP. In addition, the incidence of an AIA in the EAP group, according to the results of the present study, was lower than in the YAP group, but this difference was not statistically significant, indicating that diagnosis of AIA by anamnesis is not as precise as reported previously¹¹ because of the 10% or greater incidence of AIA in all asthmatic patients. There may be many patients (incorrectly) not diagnosed as having AIA, especially in EAP.

In the present study, some patterns of drug treatment of asthma in EAP were observed. Lower frequency of use of inhaled steroids and β_2 -adrenergic agonists was obvious in the EAP group. Difficulty inhaling medicines and their consequent persistance in oral the and throat cavity in EAP resulted in a lower use of these drugs. Especially with inhalation steroids, any steroid remaining in

the oral cavity can cause oral and throat candidiasis and hoarseness, resulting in decreased compliance with steroid inhalation. In the case of the inhalation of β_2 -adrenergic agonists, their decreased use among EAP is thought to be related to a higher incidence of sideeffects, including palpitation and tremor of the extremities, and a less effective bronchial response¹² than in YAP. The increased use of oral steroid and of sustainedreleased theophylline in EAP partly indicates that these drugs were probably substitutes for inhalation; the former, in particular, was used instead of inhalation steroids. However, the complications associated with systemic steroid administration, including osteoporosis and diabetes mellitus, are known to appear more often and severely in elderly people. It is necessary to reduce the dose of oral steroid in the treatment of EAP using both combinations of other asthma medicines and wellestablished programs for EAP education. In contrast, the high incidence of the use of sustained-released theophylline has been one of the characteristics of drug treatment of asthma in Japan. However, the complications associated with theophylline, including the narrow range of effective serum levels, more interactions with other drugs and a lesser dilator action on the bronchi than β_2 -adrenergic agonists, mean it is not usually used in the USA and European countries. 13 It has been reported that theophylline aided the construction of respiratory muscles, increased tolerance of the long-term use of those muscles and stimulated the central nerve responsible for respiration. 14 Moreover, an anti-inflammatory action for asthma (for activated eosinophils) was recently observed. 15,16 It was reported that the combination of a moderate dose of inhaled steroid and sustained-released theophylline was more effective than a high dose of inhaled steroid.¹⁷ Thus, sustained-released theophylline should be used more frequently worldwide.

Because the mean lifespan is increasing and the percentage of elderly people in the population as a whole is also increasing, the management of elderly patients is expected to become more important in future medicine. In the present study, based on questionnaires given to 3224 asthmatic patients in Niigata Prefecture, the characteristics, management and circumstances of EAP were observed. The discrepancy between objective and subjective evaluation of asthma control, the incidence of the use of both inhaled and oral steroids and the low incidence of the use of peak flow meters are problematic. The differences in the attitudes of asthma patients towards freeing themselves of the disease are very important.

However, it is often difficult for every physician to manage asthma treatment effectively when the strategy in the guidelines cannot be applied to EAP. Thus, based on sufficient consideration of EAP-related problems, adequate education and careful management of asthma among EAP are required and the accumulation of these steps will result in the achievement of the guidelines' final goals.

REFERENCES

- Isoaho R, Puolijoki H, Huhti E, Kivela SL, Tala E. Prevalence of asthma in elderly Fins. J. Clin. Epidemiol. 1994;
 1109–18.
- Parameswaran K, Hildroth AJ, Chadha D, Keaney NP, Taylor JK, Bansal SK. Asthma in elderly: Underperceived, underdiagnosed and underrated. A community survey. Respir. Med. 1998; 92: 573–7.
- 3 Nejjari C, Tessier JE, Letenncur L, Dartigues JF, Barberger Gateau P, Salamon R. Prevalence of selfreported asthma symptoms in a French elderly sample. Respir. Med. 1996; 90: 401–8.
- 4 Quadrelli SA, Roncoroni A. Features of asthma in the elderly. J. Asthma 2001; 38: 377–89.
- 5 National Asthma Education and Prevention Program. Guidelines for the Diagnosis and Management of Asthma, Expert Panel Report 2. Bethesda: National Institutes of Health. 1997.
- 6 Makino S, Furusho K, Miyamoto T, Ohta K. Asthma Prevention and Management Guidelines 1998, Japan (JGL): English version. Int. Arch. Allergy Immunol. 2000; 121: 1–78.
- 7 Quadrelli SA, Roncoroni AJ. Is asthma in elderly really different? Respiration 1998; 65: 347–53.
- 8 Enright PL, Burchette RJ, Peters JA, Lebowitz MD, McDonnell WF, Abbey DE. Peak flow lability: Association with asthma and spirometry in an older cohort. *Chest* 1997; 112: 895–901.

- 9 Barbee RA, Brown WG, Kaltenborn W, Halonen M. Allergen skin-test reactivity in a community population sample: Correlation with age, histamine skin reactions and total serum immunoglobulin E. J. Allergy Clin. Immunol. 1991; 68: 15–9.
- 10 Geraghty R, Foster C, Black D, Roe S. Bronchodiilator response to nebulized salbutamol in elderly patients with stable chronic airflow limitation. Respir. Med. 1993; 87: 375–8.
- 11 Spector SL, Wangaard CH, Farr RS. Aspirin and concomitant idiosyncrasies in adult asthmatic patients. *J. Allergy Clin. Immunol.* 1979; **64**: 500–6.
- 12 Connolly MJ, Crowley JJ, Nielson CP, Charan NB, Vestal RE. Peripheral mononuclear leucocyte beta adrenoceptors and non-specific bronchial responsiveness to methacholine in young and elderly normal subjects and asthmatic patients. Thorax 1994; 49: 26–32.
- 13 Blasis L, Ernst P, Boivin JF, Suissa S. Inhaled corticosteroids and the prevention of readmission to hospital for asthma. Am. J. Respir. Crit. Care Med. 1998; 158: 126–32.
- 14 Murciano D, Aubier M, Lecocguic Y, Pariente R Effects of theophylline on diaphragmatic strength and fatigue in patients with chronic obstructive pulmonary disease. N. Engl. J. Med. 1984; 311: 349–53.
- 15 Sagara H, Fukuda T, Okada T, Ishikawa A, Makino S. Thophylline at therapeutic concentration suppressed PAF-induced upregulation of Mac-1 on human eosinophils. Clin. Exp. Allergy 1996; 26: 16–21.
- 16 Ohta K, Sawamoto S, Nakajima M et al. The prolonged survival of human eosinophils with interleukin-5 and its inhibition by theophylline via apoptosis. Clin. Exp. Allergy 1996; 26: 10–15.
- 17 Evans DJ, Taylor DA, Zetterstrom O, Churg KF, O'Connor BJ, Barnes PJ. A comparison of low-dose inhaled budesonide plus theophylllin and high-dose inhaled budesonide for moderate asthma. N. Engl. J. Med. 1997; 337: 1412–18.