Use of anti-asthma drugs in New Zealand

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ABSTRACT Increased sales of anti-asthma drugs, and a second “epidemic” of asthma mortality, raised concerns about the management of asthma in New Zealand. To study this, prescriptions were obtained from randomly selected pharmacies to identify 235 patients receiving one common anti-asthma drug, 175 of whom were willing to be interviewed. The authors considered that 80% had asthma, and only 20% suffered primarily from chronic bronchitis or emphysema. The increased sales of anti-asthma drugs could not therefore be explained by their increasing use in treatment of other respiratory disorders. One third of the identified asthmatic subjects experienced daily symptoms despite regular drug treatment. Inhaled corticosteroids were used by only 42% of this group with persistent symptoms. Regular or short course oral corticosteroids, with or without inhaled steroids, had been required by 49%. All patients with domiciliary nebulisers appeared to use these appropriately, and most had peak expiratory flow meters. Despite the increased sales of anti-asthma drugs, corticosteroids appear to be as much underused in patients with chronic asthma in the community as in those who die of their disease.

During 1975–81 sales of anti-asthma drugs in New Zealand increased substantially and at a greater rate than in the United Kingdom and Australia. Possible explanations for this were that there was an increase in the severity or the prevalence of asthma or a change towards more intensive pharmacological management that was greater in New Zealand than in other countries. The increase in drug sales could also have been due to increased use of these drugs by patients with other types of airflow obstruction, such as chronic bronchitis and emphysema.

There is little published information about the management of asthma in New Zealand, and the way in which combinations of drugs are used. Speculation that the use of inhaled β2 agonists in combination with oral theophylline may have contributed to increased mortality from asthma has been debated vigorously, as has criticism of the delivery of high doses of β2 agonists by air driven home nebulisers. In New Zealand and elsewhere, however, fatalities have been associated more often with undertreatment of acute asthma. We have studied the range of illnesses of patients prescribed one common anti-asthma drug, salbutamol, and examined some aspects of the pharmacological management of asthma in the community.

Methods

A list of all pharmacies in Dunedin (population 95,000) was obtained from the Geographical Directory of Retail Pharmacies in New Zealand. Consecutive numbers were assigned to the pharmacies, and a random number table was used to select the pharmacies used in the study. All prescription records written during two specified weeks during July–September 1984 that ordered any form of salbutamol were obtained from these pharmacies. Repeat prescriptions were not included, neither were the same patients recorded twice. After the approval of the general practitioner concerned had been obtained, an explanatory letter and initial questionnaire were mailed to all the patients requesting information on age and sex; whether they thought they suffered from asthma, bronchitis, emphysema, heart problems, or other conditions; whether they suffered from hayfever, eczema, or hives; the symptoms for which the doctor had prescribed salbutamol; and whether they were willing to be interviewed.

At a later interview one of us (BS) obtained a detailed clinical history, including the onset, frequency, and characteristics of wheeze, cough, sputum production, and dyspnoea, and the smoking history.
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using a structured questionnaire. Asthma was diagnosed if one or more of the following ordered criteria were fulfilled: (1) an early age of onset with a characteristic history of episodic wheeze and dyspnoea; (2) episodic wheeze and dyspnoea in lifetime non-smokers; (3) objective evidence of variable airflow obstruction (greater than 20% improvement in forced expiratory volume in one second or in peak expiratory flow rate occurring spontaneously or with treatment); (4) subjective evidence of variable airflow obstruction—namely, wide fluctuations in symptoms and exercise tolerance with time.

Subjects with earlier asthma who subsequently smoked were accepted as asthmatic only if symptoms had been more or less continuous from childhood or early adult life and there was clear objective or subjective evidence of reversibility of airflow obstruction. On the other hand, subjects whose symptoms of wheeze and dyspnoea began or recurred in later adult life only after many years of heavy smoking (at least 20 pack years) were not regarded as primarily asthmatic, even if symptoms were episodic, but were considered to have chronic bronchitis or emphysema. Chronic bronchitis was diagnosed if there was a lengthy smoking history (>20 pack years), and symptoms of recurrent cough and sputum production preceded the development of wheeze and dyspnoea. Emphysema was diagnosed if a heavy smoker (>20 pack years) developed progressive dyspnoea on exertion without appreciable cough, sputum, or wheeze. Mixed chronic bronchitis and emphysema and also acute bronchitis were recognised in addition. The case history was discussed in detail with a respiratory physician (MS), and any previous pulmonary function tests were reviewed before a final diagnosis was assigned to each patient.

In patients considered to have asthma, factors provoking wheezing, the frequency and intensity of episodes, and all drugs prescribed and used were documented. Asthma was classified as intermittent if the patient had wheeze or dyspnoea less often than once a week, frequent if episodes occurred once or more per week but not daily, and persistent if wheezing or dyspnoea occurred every day or on most days.

A pilot study to test the questionnaires was carried out in 20 patients obtained from records of five randomly selected pharmacies; these patients were not used in the main study. The study was approved by the Otago Hospital Board ethical committee.

Data were recorded for computer coding and analysed with a standard statistical package (SPSS) on a Burroughs B5900 computer.

Results

Of 41 pharmacies in Dunedin city, 18 were randomly selected for this study. One used a record system unsuitable for information retrieval, and four declined to participate, one because of inconvenience and three because of concern about confidentiality of prescription records despite ethical approval. Full records of 13 pharmacies were made available to the investigators, and all subjects whose prescriptions met the entry criteria were approached.

Of 235 subjects who were sent the letter and initial questionnaire, 26 refused to participate, 11 were no longer at the recorded address, and 23 did not reply to the initial letter or to a follow up letter, leaving 175 patients who agreed to be interviewed. Of these, four subsequently could not be contacted and one was excluded as salbutamol was prescribed for treatment of premature labour. Thus, of the 234 patients eligible for study, 170 (72.6%) were interviewed. All but three were caucasian. Patients lived throughout a wide area of Dunedin city. The sex and age distribution of the 170 subjects interviewed is shown in table 1.

Diagnosis

Of the 170 interviewed, 135 (79.4%) were considered by the authors to have asthma, 32 (18.8%) chronic airflow obstruction due to chronic bronchitis or emphysema or both, and two (1.2%) acute bronchitis. One individual could not be classified from the information available. Results of previous lung function tests performed at the hospital laboratory were available for 75 (44%) of the 170 cases. Most of the non-asthma diagnoses were made in patients aged over 60 years and were more common in men. Asthma was diagnosed in 94% of the 119 patients under the age of 60 years; 55% of all identified asthmatic subjects were aged 10–39 years (table 1). The male:female ratio was 1.3:1 for asthma and 4.8:1 for other respiratory conditions.

Characteristics of Asthma

Forty seven subjects (35% of the sample diagnosed as asthmatic) had intermittent asthma, 43 (32%) frequent, and 45 (33%) persistent asthma as defined above. There was no significant variation in sex ratio among the different groups. Intermittent asthma was more common in patients under 30 and over 60 years, whereas in only 14% of 30–59 year old patients was asthma so classified. A history of allergic rhinitis or conjunctivitis was noted in 58% of patients, eczema in 42%, and urticaria in 9%. Overall, 73% had a history of one or more of these conditions.

Aetiological factors that patients thought provoked their asthma ranged from infections (93%) and exercise (90%) to dusty and smoky atmospheres, temperature changes, excitement, and allergen exposure (particularly grass or hay, flowers, pets, and foods). There was no pattern in the distribution of the season
of greatest severity of symptoms. Wheezing was worse at night in 60% of patients. Typical attacks lasted less than one hour in 67% of patients, one or more hours in 21% and one or more days in 18%. In only 17% of cases was a doctor consulted for a typical wheezing attack. Forty nine patients (36%) had been admitted to hospital for asthma, 15 in the last 12 months. Most admissions resulted from nocturnal attacks.

**Drug Treatment**

Because of the selection criteria used, all patients had used at least one form of salbutamol. Pressurised aerosols were included in 70% of prescriptions used for patient selection, slow release salbutamol tablets in 23%, dry powder salbutamol capsules in 11%, standard tablets in 8%, syrup in 7%, and respirator solution in 4%. When interviewed 2–4 weeks after selection for the study, all but 10 patients were continuing to take treatment for asthma. Half of these patients were taking one or two treatments for asthma but 22% were on four or more asthma treatments (excluding antibiotics and cough mixtures).

The frequency of use of different types of treatment by patients with asthma on the day before interview is shown in table 2. In all, 93% used a $\beta_2$ agonist preparation, 8% ipratropium bromide, and 23% theophylline as bronchodilator treatment. Seven of 31 patients taking theophylline were not currently prescribed sodium cromoglycate or inhaled corticosteroids. Of 11 patients using oral corticosteroids, two were not prescribed inhaled steroids. The distribution of use of $\beta_2$ agonists, theophylline, and inhaled corticosteroids did not differ significantly among the three groups. Oral corticosteroids, either continuously or in a short course, were used currently by 11 patients; 30 patients (22%) had previously had short courses of prednisone.

The patterns of drug combinations encountered are summarised in table 3. Almost one third of all asthmatics used only a $\beta$ sympathimmetic agent, while another third used bronchodilators combined with inhaled corticosteroids; four of these 39 patients also used cromoglycate. The use of bronchodilator drugs within each subgroup is shown in table 4. The distribution of use of oral and inhaled preparations did not differ significantly among the groups.

Treatments were taken as a regular routine by 50% of those using any drugs on the day before interview, partly as a routine and partly on demand for symptoms by 28%, and solely for symptoms by 22%.

One patient was taking a $\beta$ adrenergic blocking

### Table 1  Sex and age distribution of all patients who were prescribed any form of salbutamol and were available for interview, and of those considered to have asthma

| Age (y) | Males | | | | Femalettes | | | | Both sexes | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | All* | Asthma† | | | All* | Asthma† | | | All* | Asthma† | | |
| n | n | % | n | n | % | n | n | % | n | n | % |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| <10 | 12 | 11 | 92 | 4 | 4 | 100 | 16 | 15 | 94 | 31 | 31 | 100 |
| 10–19 | 21 | 21 | 100 | 10 | 10 | 100 | 31 | 31 | 100 | 24 | 24 | 100 |
| 20–29 | 10 | 10 | 100 | 14 | 14 | 100 | 31 | 31 | 100 | 24 | 24 | 100 |
| 30–39 | 13 | 11 | 85 | 8 | 8 | 100 | 21 | 19 | 90 | 11 | 11 | 100 |
| 40–49 | 6 | 6 | 100 | 5 | 5 | 100 | 11 | 11 | 100 | 16 | 12 | 75 |
| 50–59 | 9 | 5 | 56 | 7 | 7 | 100 | 16 | 12 | 75 | 23 | 10 | 43 |
| 60–69 | 17 | 7 | 41 | 6 | 3 | 50 | 23 | 10 | 43 | 28 | 13 | 46 |
| 70+ | 18 | 6 | 33 | 10 | 7 | 70 | 28 | 13 | 46 | 170 | 135 | 79 |

*All: all patients prescribed any form of salbutamol.
†Asthma: patients considered by authors to have asthma.

### Table 2  Regular drug treatment used by patients with intermittent, frequent, and persistent symptoms of asthma at time of interview

<table>
<thead>
<tr>
<th>Drug Type</th>
<th>No (% of patients with intermittent symptoms(n = 47)</th>
<th>frequent symptoms(n = 43)</th>
<th>persistent symptoms(n = 45)</th>
<th>Total (n = 135)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\beta$ sympathomimetic</td>
<td>39 (83)</td>
<td>41 (95)</td>
<td>45 (100)</td>
<td>125 (93)</td>
</tr>
<tr>
<td>Theophylline</td>
<td>9 (19)</td>
<td>9 (21)</td>
<td>13 (29)</td>
<td>31 (23)</td>
</tr>
<tr>
<td>Ipratropium bromide</td>
<td>3 (6)</td>
<td>4 (9)</td>
<td>4 (9)</td>
<td>11 (8)</td>
</tr>
<tr>
<td>Sodium cromoglycate</td>
<td>6 (13)</td>
<td>10 (23)</td>
<td>9 (20)</td>
<td>25 (19)</td>
</tr>
<tr>
<td>Inhaled corticosteroid</td>
<td>12 (25)</td>
<td>17 (40)</td>
<td>19 (42)</td>
<td>48 (36)</td>
</tr>
<tr>
<td>Systemic corticosteroid</td>
<td>3 (6)</td>
<td>1 (2)</td>
<td>7 (16)</td>
<td>11 (8)</td>
</tr>
</tbody>
</table>
Table 3  Combinations of drug treatment prescribed for patients with asthma

<table>
<thead>
<tr>
<th>Drug Combination</th>
<th>No (%) of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>β sympathomimetic only</td>
<td>40 (30)</td>
</tr>
<tr>
<td>β sympathomimetic with other bronchodilators only</td>
<td>8 (6)</td>
</tr>
<tr>
<td>Bronchodilators with cromoglycate only</td>
<td>21 (16)</td>
</tr>
<tr>
<td>Bronchodilators, cromoglycate, and inhaled corticosteroids</td>
<td>4 (3)</td>
</tr>
<tr>
<td>Bronchodilators with inhaled corticosteroids</td>
<td>35 (26)</td>
</tr>
<tr>
<td>Bronchodilators with oral and inhaled corticosteroids</td>
<td>9 (7)</td>
</tr>
<tr>
<td>Bronchodilators with oral corticosteroids only</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Other regimens</td>
<td>6 (4)</td>
</tr>
<tr>
<td>No current treatment</td>
<td>10 (7)</td>
</tr>
<tr>
<td>Total</td>
<td>135 (100)</td>
</tr>
</tbody>
</table>

A peak expiratory flow meter—six (13%) with intermittent asthma, 13 (30%) with frequent asthma, and 15 (33%) with persistent asthma. Written records were kept by only 18 patients, and only 19 of the 34 recorded peak flows during an exacerbation of wheezing.

Discussion

Among the reasons suggested for the occurrence in New Zealand during 1977–82 of a second “epidemic” of deaths from asthma, especially in young people, were a more severe form of the disease, changing environmental factors, and changing management of the disease in this country. The New Zealand national asthma mortality study showed that, although inaccuracies in death certification and higher mortality rates in non-caucasian populations each played a part, these factors did not explain the excess mortality adequately. Sears et al. found that underuse of effective treatment, particularly with corticosteroids, and overreliance on bronchodilators were common in the patients who died. Because of the retrospective nature of the national mortality study, it was not possible to determine whether undertreatment occurred more frequently in patients who died than in those who did not. A concurrent regional case-control study of asthma mortality suggested, however, that management was poorer in fatal cases than in community controls matched for age and severity of disease.

International comparisons of trends in sales of drugs commonly used for treatment of asthma showed a substantial rise in sales in New Zealand from 1975 to 1981, greater than that seen in Australia and the United Kingdom. Some of the increase could have been due to greater prescribing of these drugs for chronic bronchitis, acute bronchitis, or emphysema. The fact that the reported increase in sales of inhaled sodium cromoglycate, which is used almost exclusively for asthma, was less than that of anti-asthma medications sometimes useful in these other respiratory disorders lent support to that hypothesis. In our community sample of 170 patients prescribed salbutamol, however, we found that 80%
had asthma, and only 19% had chronic bronchitis or emphysema or both. As no like study has previously been undertaken in this country, we cannot determine whether prescribing of anti-asthma drugs for other respiratory disorders increased over the years 1975–81. But a rise in sales of sympathomimetic aerosols of over 75% during those years could scarcely be explained by increased prescribing for conditions that even now account for only some 20% of sales. We conclude that the increased sales of anti-asthma drugs must be explained by increased use in patients with asthma.

Only 13 of 18 randomly selected pharmacies were willing or able to participate in the study, but we do not believe that this introduced any systematic bias. Three potential sources of bias that could affect the relative proportion of patients considered to have asthma do require comment. Only 11% of patients refused interview, but a further 16% were unable to be located or did not reply to two letters. The letters did not specify our interest to be solely asthma, but also mentioned bronchitis and emphysema. If older patients were less inclined to respond, the proportion of patients with chronic bronchitis or emphysema may have been underestimated. Even if half of the non-respondents did not have asthma, however, the proportion of the sample with chronic bronchitis and emphysema would still be only 28%. Diagnoses for non-respondents were not sought from general practitioners, as the accuracy of such diagnosis could not be validated.

Secondly, the study was undertaken in mid to late winter, when chronic bronchitis and emphysema may be more likely than asthma to undergo exacerbation requiring treatment. While we cannot quantify any bias introduced by the season of the study, any such bias would act in a direction opposite to that of the first potential bias. There is no evidence for appreciable seasonal variation in morbidity from asthma or hospital admissions for asthma in New Zealand.

Thirdly, patients were selected because they were prescribed salbutamol. This may have allowed inclusion of a greater proportion of asthmatic rather than bronchitic patients than would selection on the basis of theophylline or ipratropium bromide prescriptions. Nevertheless, $\beta_2$ sympathomimetics comprise the most widely used group of drugs in all forms of obstructive lung disease, and had shown a considerable increase in sales during 1975–81. Selection by prescription of a $\beta_2$ agonist may have allowed inclusion of better treated asthmatics (for example, by not detecting those given antibiotics only) than would be encountered in a community questionnaire survey of asthma management. If so, our concerns about inadequacies of treatment are increased.

The New Zealand national asthma mortality study suggested that patients with severe asthma were often undertreated with corticosteroids. In this study of treatment of asthma in the community, corticosteroids (oral or inhaled) were used by only 42% of those with persistent asthma. As this group all had daily symptoms despite some form of regular treatment, this suggests substantial undertreatment of chronic asthma. Despite the considerable increase in aerosol corticosteroid sales in New Zealand during 1975–81—to levels (per capita) exceeding those in Australia and the United Kingdom—many patients who should benefit are not yet prescribed this treatment. The use of multiple bronchodilator drugs appears to be preferred to the addition of inhaled corticosteroid as the second drug.

Only 19% of patients were prescribed sodium cromoglycate, a proportion similar to the 16% in the national mortality study and 12% in a general practice survey. Some patients had previously used cromoglycate and found it was less effective, but the low usage is consistent with the underusage noted in children in the North Tyneside study. Prescribing indications for theophylline are still variable, and its exact place in asthma management is arguable. In this study 77% of patients taking theophylline were also prescribed inhaled corticosteroids or sodium cromoglycate, an important finding in view of Grant’s hypothesis that overreliance on theophylline or other bronchodilator drugs to the exclusion of prophylactic treatment was a particular problem in New Zealand.

Concern has been expressed that use of domiciliary nebulisers could lead to overreliance by patients on high dose inhaled bronchodilators during a severe attack, with resultant delay in seeking medical assistance. Possible toxicity of high doses of $\beta$ adrenoceptor agonists and tolerance to high doses of $\beta$ agonist have been reported. Laroche et al found that 12 of 53 patients using nebulisers had not received instructions on proper use of the apparatus, and less than half the patients had been given a peak flow meter. In contrast, we found that Dunedin patients with nebulisers used them correctly, and that 10 of 14 used a peak flow meter. Grant noted in 1982 that 6000 home nebulisers had been purchased in New Zealand in two years, but only 2000 peak flow meters had been bought in the same time. That position may have changed over subsequent years; recent removal of the cost to the patient of peak flow meters in New Zealand should increase the frequency of home monitoring of serious asthma.

In summary, 80% of all patients who had prescriptions for salbutamol identified in randomly selected pharmacies and who were willing to be interviewed were found to have asthma and only 20% suffered non-asthmatic respiratory disorders. Despite
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substantial increases in anti-asthma drug sales in New Zealand, inhaled and perhaps oral corticosteroids still appear to be underused in persistent asthma. Peak expiratory flow rate was monitored by only 25% of all asthmatics, although most patients with domiciliary nebulisers had a peak flow meter. This survey of community use of anti-asthma drugs suggests that deficiencies in management of asthma are not confined to those who die of their disease.

The cooperation of the pharmacists, general practitioners and especially the patients involved in this study is gratefully acknowledged. The study was supported by the Mackie Estate Trust Fund, May and Baker NZ Ltd., and the Pharmaceutical Society of New Zealand. Statistical help was given by Mr G Spears, Department of Preventive and Social Medicine, University of Otago Medical School.

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