Discussion

We believe that this is the first report of an interaction between salicylates and carbonic anhydrase inhibitors causing serious metabolic acidosis in patients with normal renal function. Previous reports of carbonic anhydrase inhibitors causing severe acidosis have been of patients in whom other predisposing factors have been present.¹⁻⁵ In fact, acetazolamide has been used to treat salicylate poisoning.⁶

The mechanism of this interaction, though not clear, may be related to hypocapnia induced by salicylate leading to a reduction in the carbon dioxide available for production of bicarbonate. Carbonic anhydrase inhibitors produce metabolic acidosis by their action on carbonic anhydrase in the proximal and distal renal tubules. This blocks excretion of hydrogen ions, producing an alkali urine. As acidosis develops, however, an increase occurs in the resorption of bicarbonate, which is independent of the activity of carbonic anhydrase; this limits the degree of acidosis that can be attributed to inhibition of carbonic anhydrase alone.⁷ In cases of renal failure the blocking of carbonic anhydrase activity leads to increasing acidosis because the capacity of the tubules to resorb bicarbonate is inadequate. Toxic doses of salicylates that result in metabolic acidosis are likely to have a detrimental effect in combination with carbonic anhydrase inhibitors. Serum salicylate concentrations of over 300 mg/l are required to produce a metabolic acidosis,⁸ and in our two patients salicylate concentrations were below this at the time of presentation. Therapeutic doses of salicylates cause limited respiratory alkalosis, but this fall in carbon dioxide tension has little effect on the production of bicarbonate unless the action of carbonic anhydrase is blocked, when the production of bicarbonate is much lower than if either mechanism were operating in isolation. The

lack of bicarbonate ions would prevent excretion of hydrogen ions, thus causing increasingly severe acidosis.

Therapeutic doses of salicylates and carbonic anhydrase inhibitors given together seem to be capable of inducing potentially fatal metabolic acidosis in patients with normal renal and hepatic function. In such patients the doses should be kept to the minimum or salicylates replaced by an unrelated anti-inflammatory agent. Serum bicarbonate concentrations should be estimated regularly and especially after any increase in the dosage.

These cases have been reported to the Committee on Safety of Medicines.

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Trends in sales of drugs for asthma in New Zealand, Australia, and the United Kingdom, 1975-81

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Abstract

As part of an investigation into the recent epidemic of deaths from asthma in New Zealand, trends in the sales of drugs for asthma in New Zealand, Australia, and the United Kingdom during 1975-81 were examined. Data on sales of drugs were obtained from an international pharmaceutical market research organisation. A striking increase in sales of sympathomimetic aerosols, steroid aerosols, and theophylline per caput occurred in all three countries, with the greatest increase occurring in New Zealand. Sales of sodium cromoglycate also increased in

New Zealand and the UK but fell in Australia. By 1981 New Zealand had the highest sales of all these drugs per caput.

Explanations for the rising mortality from asthma in New Zealand despite large increases in drug sales need to be explored. Although the temporal association between mortality and sales of drugs suggests that direct drug toxicity is unlikely, there may be more subtle adverse effects of drug use.

Introduction

New Zealand is experiencing a new epidemic of fatal asthma that is not occurring in other developed countries.¹ Between 1974 and 1980 the mortality from asthma in people aged 5-34 almost doubled in New Zealand but remained relatively stable in five other countries including Australia and the United Kingdom. Admissions to hospital and sales of drugs for asthma have also increased in New Zealand over the past two decades.² In children under 15 admissions to hospital increased about 10-fold during 1964-80; in people aged 15-44 there was a fourfold increase during this period. The concern that the increasing use of aerosol bronchodilators may have contributed directly or indirectly to an epidemic of deaths from asthma in the 1960s³⁻⁵ led to a sug-

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gestion that recent trends were due to a change in the management of asthma in New Zealand. To explore this possibility we compared trends in the sales of drugs used for the treatment of asthma in New Zealand, Australia, and the UK.

FIG 1—Sales of sympathomimetic aerosols.

FIG 2—Sales of inhaled steroids.

Methods

Data on annual sales of drugs used in the treatment of asthma in New Zealand, Australia, and the UK were obtained from Intercontinental Medical Statistics Ltd, which is a market research company that collects monthly information on purchases of drugs from a representative sample of retail pharmacies. It uses similar methods of data collection in all countries. Estimated annual data on sales of drugs were available from 1975 for the UK, from 1976 for New Zealand, and from 1977 for Australia to 1981 for each country.

Data were obtained for four categories of drugs that are used primarily in the treatment of asthma: inhaled steroids, sodium cromoglycate, sympathomimetic aerosols, and oral theophylline. Only adult doses and presentations were considered: syrups and tablets in paediatric doses were excluded from the analysis, as were all sympatho-

mimetic tablets, because of difficulties in calculating equivalent doses of the different preparations and generic forms.

Sales of drugs were converted into different "units of sales," depending on the type of drug. For sodium cromoglycate the number of units sold equalled the number of sodium cromoglycate capsules plus the equivalent units of nebulised solution and doses of inhaler sold. For steroid aerosols the units sold equalled the number of aerosols (all steroid aerosols contain 200 doses) and equivalent units of rotacaps (100 rotacaps are equivalent to one inhaler) sold. Sales of sympathomimetic aerosols were expressed as doses sold (the number of aerosols sold multiplied by the manufacturer's stated number of doses per aerosol). The equivalent amount of theophylline from sales of aminophylline and choline theophyllinate was calculated and added to the sales of theophylline to give milligrams of theophylline as the units of sales for theophylline drugs. Sales were then expressed as units per 100 000 people for each country.

Results

Figs 1-4 show that there was a pronounced increase in sales per 100 000 people of all drugs examined in each country over the period considered, except for sodium cromoglycate in Australia. Moreover, the greatest increases were seen in New Zealand, which by 1981 had the highest sales of each category of drug per head of population.

Sympathomimetic aerosols—From 1977 to 1981 sales of sympathomimetic aerosols increased by 78% in New Zealand, by 72% in Australia, and 42% in the UK (fig 1). Total sales of sympathomimetic aerosols in New Zealand in 1981 were 2.1 times those in the United Kingdom and 1.3 times those in Australia.

Inhaled steroids—Trends in the sales of inhaled steroids were similar to those for sympathomimetic drugs, with sales almost doubling in New Zealand (96% increase) during 1977-81 and increasing by 80% and 69% in Australia and the UK respectively (fig 2). Again, total sales in New Zealand in 1981 were more than twice those in the UK (2.6 times) and 1.9 times those in Australia.

Oral theophylline—Figure 3 shows the trends in sales of oral theophylline, which also increased in all three countries. From 1977 to

FIG 3—Sales of oral theophylline.

1981 sales more than trebled in New Zealand while in Australia and the UK they increased by 38% and 30% respectively. In 1981 sales of theophylline in New Zealand were 1.6 times those in the UK and 1.3 times those in Australia. In all three countries in the period under consideration sales of the older forms of theophylline declined with a more than compensatory increase in sales of anhydrous and slow release forms.

Sodium cromoglycate—Sales of sodium cromoglycate during 1977-81 increased in New Zealand and the UK by 60% and 20% respectively but declined by 10% in Australia (fig 4). Although between 1977 and

1979 the three countries had comparable sales of sodium cromoglycate, by 1981 New Zealand had the highest sales, which were 1.4 times those in the UK and 1.8 times those in Australia.

Discussion

Stimulated by the recent increase in mortality due to asthma in New Zealand,¹ we carried out this study to compare recent trends in the sales of drugs used in the treatment of asthma in New Zealand, the UK, and Australia, using data collected by Intercontinental Medical Statistics. A striking increase occurred in the sales of these drugs in each of the countries examined, particularly in New Zealand. The size of the increase in such a short time suggests that important changes have occurred in the pattern of the use of drugs for asthma.

An important consideration in a comparison of this type of information is the quality and uniformity of collection of data

FIG 4—Sales of sodium cromoglycate.

in each country. The annual sales data produced by Intercontinental Medical Statistics represent projections made from an analysis of a representative sample of retail pharmacies and are used as market research information by pharmaceutical firms. Collection of data is similar in each of the countries in which the company operates, and there were no major changes in the methods used during the time studied.

The data described here relate only to drugs prescribed through retail pharmacies, and it is possible that hospital prescribing may differ between countries. Intercontinental Medical Statistics now collects information on sales of drugs from hospitals as well as retail pharmacies in New Zealand and the UK (but not in Australia), and examination of these data does indicate differences in levels of hospital prescribing. In 1983 about 9% of all antiasthmatic preparations were dispensed through hospital pharmacies in the UK compared with 4% in New Zealand. Despite these differences, however, the proportion of antiasthmatic drugs prescribed through hospitals is small and would not account for the international differences in sales described here. Furthermore, with the increasing numbers of patients admitted to hospital with asthma in both countries over the past decade,²⁻⁶ it is likely that hospital prescribing for asthma has also increased. Overall sales would therefore probably show a greater increase than this report shows.

The increase in drug sales may represent an increase in the number of patients with asthma who are treated or an increase in the amount of treatment each patient receives, or both. Studies in New Zealand and the UK suggest that the prevalence of asthma has increased over the past 10-15 years.⁷⁻⁸ Moreover, it is possible that New Zealand has a greater prevalence of asthma

than the two other countries examined, though this would explain only a small part of the increase in drug sales. Unfortunately, there appear to be no reported population based studies that have examined trends in the management of asthma with drugs.

A proportion of the increase may be attributable to changes in the prescribing of these drugs to treat other obstructive airways diseases. There are also some differences between the three countries in patterns of prescribing sympathomimetic tablets and syrups, which were not included in the analyses. These differences were examined, however, and were too small to account for the large increase seen in the sale of drugs. It is therefore probable that the management of asthma with drugs has changed.

Data on recent trends in sales of drugs to treat asthma have also been published for the Nordic countries.⁹ From 1975 to 1980 in each of these countries sales of theophylline, inhaled sympathomimetics, and inhaled steroids increased but sales of sodium cromoglycate did not change. Interestingly, the trends of sales in the Nordic countries and in this study are similar. Direct comparisons cannot be made, however, because of different sampling techniques and methods of calculating units of sales.

Despite the recent introduction of new drugs and new formulations for the management of asthma and despite the major increase in sales of these drugs, mortality due to asthma has not declined. Indeed, New Zealand, which in this study had the largest sales of drugs to treat asthma per head of population and the greatest rate of increase in sales in recent years, had also had a recent increase in mortality due to asthma.¹ As it appears unlikely that the increase in mortality due to asthma and sales of drugs to treat asthma in New Zealand can be explained solely by an increase in the prevalence or severity, or both, of asthma, alternative explanations need to be explored.

A previous epidemic of deaths due to asthma occurred in the mid-1960s in New Zealand, Australia, and England and Wales.¹ Although an explanation for this epidemic has never been fully given, several workers have suggested that the introduction of pressurised aerosols containing sympathomimetics was a contributing factor.³⁻⁵ It is therefore possible that the changing pattern of use of drugs to treat asthma in New Zealand could be one factor contributing to the recent increase in mortality due to asthma.

Direct drug toxicity, due to either individual drugs or combinations of drugs, has been implicated by some workers.^{5,10} The temporal association between the recent increase in mortality due to asthma and in sales of drugs to treat asthma in New Zealand suggests, however, that this is unlikely. The current epidemic of deaths appears to have begun in 1975 and, despite an apparent levelling off in mortality since 1979, sales of drugs to treat asthma have continued to increase dramatically. Moreover, since 1977 appreciable increases in sales of drugs to treat asthma have also occurred in Australia and the UK without a concomitant increase in mortality due to asthma. These data of course cannot exclude the possibility of a direct toxic effect in a small group of highly susceptible patients with asthma.

A more likely explanation is that excessive reliance on bronchodilators in severe acute attacks may result in delays in implementing more appropriate treatment such as systemic steroids or using too little, or both. This view is supported by several recent surveys, which indicate that most patients dying from asthma have received insufficient treatment.^{11,12} In addition, prescribing multiple drugs could cause confusion among patients and their doctors as to the most appropriate treatment in acute illness and lead to errors in management.

The excessive use of home nebulisers for delivering sympathomimetic solutions has also been postulated as a cause of increased mortality from asthma.¹³ Until 1980, however, per caput sales of sympathomimetic solutions for use in nebulisers were stable and were lower in New Zealand than in either the UK or Australia. Actual sales data have not been reported here because dose equivalents of sympathomimetic nebuliser solutions repre-

sented less than 1% of total sales of sympathomimetic aerosols. Although this suggests that overuse of nebulisers is unlikely to be a major factor contributing to the current epidemic, the pattern of use may be more important than the total sales, but this cannot be examined in the present study.

One factor that may account in part for the difference in sales of drugs between the countries examined is the cost of prescriptions to the patient. In New Zealand the most frequently prescribed drugs used to treat asthma are free to the patient, whereas the charges for prescriptions in Australia and the UK may act as a financial disincentive. Furthermore, in New Zealand the cost of consultations with general practitioners may discourage patients from seeking the optimum supervision, whereas in the UK there is no financial barrier to consultations with general practitioners. The trends in sales of drugs to treat asthma shown here may reflect international differences in prescribing patterns for all drugs. Indeed, international comparisons of use of drugs per head of population have shown more than two-fold differences between countries.¹⁴

In the absence of comparable data on trends in prevalence and severity of asthma in the countries investigated, the interpretation of our data can only be speculative. Nevertheless, the results of this study show that a dramatic increase in per caput sales of drugs to treat asthma has not been associated with a reduction in mortality due to asthma.

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Diazepam tolerance: effect of age, regular sedation, and alcohol

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Abstract

The dose of intravenous diazepam required for sedation was estimated in a series of 78 patients aged 17-85 years given the drug for dental and endoscopic procedures. Multiple regression analysis showed a significant correlation ($r=0.71$; $p<0.001$) between dose and age, body weight, the taking of regular sedation, and the taking of more than 40 g alcohol daily, but there were no differences in the doses required between men and women, smokers and non-smokers, inpatients and outpatients, or dental and endoscopy patients. Patients aged 80 required an average dose of 10 mg and patients aged 20 an average dose of 30 mg, and the dose required was much higher in those receiving regular sedation or having a high alcohol intake.

Plasma total and free diazepam concentrations were measured in the second half of the series of patients

($n=37$). Plasma concentrations required for sedation fell twofold to threefold between the ages of 20 and 80 and were significantly higher in those taking regular sedation or alcohol. Differences in the acute response to diazepam appeared to be due to differences in the sensitivity of the central nervous system (pharmacodynamic tolerance) rather than to differences in pharmacokinetic factors.

Introduction

The doses of diazepam needed to produce the same degree of sedation varies widely among patients. There is little information about the factors which alter diazepam tolerance and which might be used to predict the dose required. The neurological response to diazepam has been reported to increase with age,^{1 2} but those results may have been influenced by the selection and distribution of patients,¹ and the use of additional premedications.² There is also evidence that patients who take the drug regularly, cigarette smokers,³ and those who take large amounts of alcohol regularly,⁴ may be more tolerant of its effects.

Diazepam is highly bound to plasma proteins and only the unbound fraction is available for distribution in the tissues. Plasma binding decreases with age,⁵⁻⁷ and it has been suggested that the rise in free drug concentration will lead to an increase in the clinical response.⁷ We have studied the relation between the dose of diazepam required for sedation and the factors that have been reported to alter the clinical response. The degree total and free diazepam concentrations were also measured to assess the extent to which the clinical response is determined by pharmacokinetic factors.

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