Comparison of potency of inhaled beclomethasone and budesonide in New Zealand: retrospective study of computerised general practice records

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BMJ 1998;317:986–90

Abstract

Objective To determine whether inhaled budesonide and beclomethasone are equipotent in the treatment of asthma in primary care.
Design Retrospective study of computerised clinical records from 28 general practices in New Zealand.
Subjects 5930 patients who received 16 725 prescriptions for inhaled budesonide or beclomethasone from 1 July 1994 to 30 June 1995.
Setting General practices on the database of the Royal New Zealand College of General Practitioners Research Unit. Linked information from secondary care was available for a subset of the practices.
Main outcome measure Mean prescribed daily inhaled corticosteroid dose.
Results The daily prescribed dose was higher for patients receiving inhaled budesonide (mean 979 µg) than beclomethasone (mean 635 µg), a difference of 344 µg (95% confidence interval 313 to 376 µg). This difference was consistent in all age bands and with different types of inhalation device. Evidence of systematic prescribing of higher doses of budesonide to patients with more severe asthma was not found.
Conclusions In primary care in New Zealand evidence suggests that budesonide is less potent than beclomethasone. Consideration of validated, established, and other possible markers of asthma severity did not support confounding by severity as a reason for the higher prescribed doses of budesonide. Pending further epidemiological evaluation, international asthma guidelines may need to be modified on the equivalence of inhaled corticosteroid doses. Furthermore, the comparative potency of newly developed inhaled steroids in clinical trials will need to be confirmed in appropriately designed epidemiological studies based in general practice.

Introduction

International guidelines for the treatment of asthma regard inhaled budesonide and beclomethasone as equipotent.[1] This view is based on the results of randomised clinical trials comparing inhaled beclomethasone and budesonide which have mostly failed to detect differences in potency.[2–5] However, these studies have been limited by the small numbers of patients studied, the mild to moderate nature of their asthma, differences in inhaler devices used, differing end points and duration of treatment, crossover designs with carryover effects, previous use of inhaled corticosteroids, concomitant drug treatment, and the difficulties resulting from the flat dose-response relation for inhaled corticosteroids in the therapeutic range for provocation and lung function end points.[2 6 7] Other problems include the uncertain size of any differences when calculating sample sizes at the design stage of a clinical trial and the variability of asthma within and between patients. These limitations illustrate the difficulties in designing a definitive randomised clinical trial to further explore the relative potency of different inhaled corticosteroids in asthma. However, the topic remains of substantial interest not only for clinical reasons such as helping practitioners with anticipated inhaled corticosteroid dose equivalencies, advancing the debate about appropriate doses of inhaled corticosteroids,[1] and possibly explaining the anecdotal variability in usual prescribed doses in different countries, but also because of the costs entailed if these drugs are not equipotent.

The existence of primary care computerised databases containing standardised prescription and clinical information provides an opportunity to study relative potency of drugs in a pragmatic way using epidemiological methods. We used such an approach in this study accessing the database of the Royal New Zealand College of General Practitioners Research Unit, which includes patient identifier codes (all data are anonymised), consultation dates and free text, prescribing dates, and prescription details.[8 9]

Subjects and methods

Twenty eight general practices from the database were specified in the study protocol for this study as their computerised documentation of consultations and prescribing were known to be complete. In these 28 practices computers are the sole source of complete patient records. The study protocol was approved by the Southern Regional Health Authority (Otago) Ethics Committee in August 1996. The main objective was to use the inhaled corticosteroid prescribing data to compare the potency of budesonide and beclomethasone in general practice. All patients prescribed inhaled budesonide or beclomethasone formulations

Table 1 Characteristics of prescriptions for beclomethasone dipropionate or budesonide alone over one year in 28 general practices in New Zealand

	Mean (SD) dose (μg)		No of patients		No of prescriptions	
Age group (years)	Beclomethasone	Budesonide	Beclomethasone	Budesonide	Beclomethasone	Budesonide
0-2	263 (224)	582 (260)	133	11	304	30
3-4	248 (122)	485 (295)	192	34	517	60
5-6	294 (164)	436 (266)	221	87	566	194
7-8	315 (147)	583 (438)	164	68	382	150
9-10	384 (228)	564 (283)	176	53	435	115
11-12	436 (255)	588 (314)	164	65	376	147
13-14	484 (254)	673 (475)	147	45	359	91
15-19	567 (386)	946 (622)	350	101	830	228
20-24	632 (362)	1052 (647)	323	91	784	187
25-29	665 (422)	914 (567)	263	88	590	200
30-34	665 (403)	988 (540)	254	97	618	222
35-39	708 (437)	1239 (856)	216	86	572	187
40-44	698 (492)	1108 (788)	236	75	592	168
45-49	767 (476)	1047 (571)	217	82	715	206
50-54	743 (492)	1179 (624)	182	79	457	232
55-59	939 (692)	1130 (719)	175	69	636	208
60-64	857 (540)	1230 (650)	209	78	719	230
65-69	925 (618)	1049 (564)	234	86	1005	275
70-74	910 (539)	1360 (961)	194	94	811	306
⩾75	878 (529)	1212 (795)	245	143	1037	521
All patients	635 (476)	979 (686)	4295	1532	12 305	3957

available in New Zealand from 1 July 1994 to 30 June 1995 were identified in the database.

A dataset was prepared including patient identifier code, date of birth, sex, consultation data, and prescribing date and information, including other drug treatment. The protocol specified age bands of two years up to the age of 14 and then bands of five years for analyses of inhaled corticosteroids by dose. Tabulations and histograms showing the proportions receiving one or more prescriptions above 800 μg per day (age to 14 years) or above 1500 μg per day (for age 15 years or over) in each age group were also defined in the protocol.

Prescribed daily doses of corticosteroids were calculated from the number of micrograms per inhalation for each drug and the number of inhalations indicated per day. Prescribed daily doses were based on the minimum dose indicated in the prescribing notes when a flexible regimen was prescribed. For example, if 2-4 puffs 2-4 times daily was prescribed the daily dose was calculated using 2 puffs twice daily. Qualifications on a few prescriptions that stipulated changing the dose when peak flow rate dropped below a given value were not taken into account. Corticosteroids that are inhaled through a metered dose inhaler and are available in New Zealand are Becotide (beclomethasone, Glaxo Wellcome; 50 μg, 100 μg, 250 μg), Respocort (beclomethasone, 3M; 100 μg, 250 μg), Atomide (beclomethasone, Douglas; 50 μg, 100 μg, 250 μg), and Pulmicort (budesonide, Astra; 200 μg). The breath activated devices are Becodisk (beclomethasone, Glaxo Wellcome; 100 μg, 200 μg, 400 μg), Pulmicort Turbuhaler (budesonide, Astra; 100 μg, 200 μg, 400 μg), Respocort (beclomethasone, 3M; 50 μg, 100 μg, 250 μg).

A scatter plot of the daily dose prescribed by age for patients receiving beclomethasone or budesonide alone showed higher doses and greater variation in the average daily dose with increasing age. These characteristics suggested that a log transformation of the data might be appropriate for subsequent analyses of the average daily dose of inhaled corticosteroids. Linear regression was therefore used to analyse the log data incorporating extra sum of squares techniques to determine whether the addition of a set of explanatory variables significantly improved the regression model. A search for evidence of bias towards usage of budesonide in patients with known or potential markers of more severe asthma was undertaken. This covered the number of courses of oral corticosteroids and antibiotics, the amount of oral corticosteroids prescribed, and admissions, outpatient consultations, emergency room visits, and overall consultation rates. Analyses for secondary care were based on linkage to hospital data whenever possible because data on hospital contacts in the database of the Royal New Zealand College of General Practitioners Research Unit are incomplete. We also analysed the doses of inhaled corticosteroids for patients changing from budesonide to beclomethasone and from beclomethasone to budesonide treatment.

Results

The computerised records of 128 585 patients and their 626 744 prescriptions were covered in this study. During the study period 6582 patients received 18 168 prescriptions for inhaled corticosteroids; 5930 (90.1%) of them who received 16 725 prescriptions (92.1%) had computer records that included dosing instructions. These 5930 patients were the focus of the subsequent analysis. In all, 4295 (72.4%) were exclusively prescribed beclomethasone and 1532 (25.8%) budesonide. Of the other 103 (1.7%) patients, 61 changed from beclomethasone to budesonide treatment and 32 from budesonide to beclomethasone treatment, with 10 changing more than once. The proportion changing in one direction was not significantly different from the proportion changing in the other (difference 0.65% (95% confidence interval –0.2% to 1.4%); P = 0.08).

Prescribed daily doses

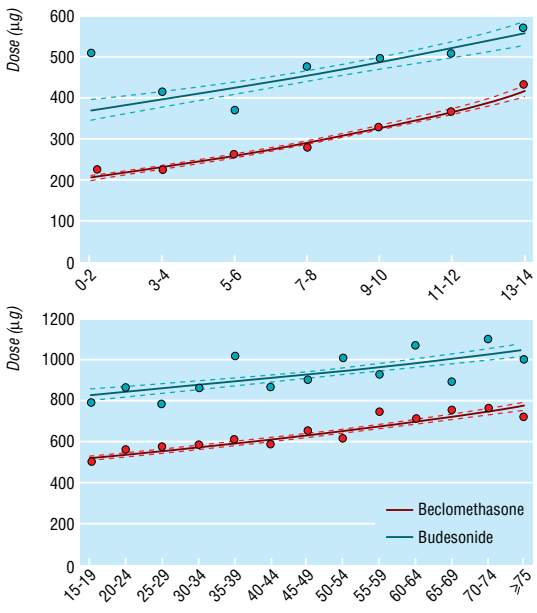
Table 1 shows the average daily dose in the prespecified age categories in patients who were exclusively prescribed budesonide or beclomethasone. Overall, the

Table 2 Characteristics of prescriptions for prednisone to patients also prescribed budesonide or beclomethasone diproprionate

	Budesonide		Beclomethasone	
	No (%) of patients	Mean dose (µg)	No (%) of patients	Mean dose (µg)
All patients				
No of patients	1532		4295	
No of prednisone prescriptions:				
0	1231 (80.4)	907	3533 (82.3)	582
1	163 (10.6)	1089	459 (10.7)	754
2	65 (4.2)	1273	140 (3.3)	935
3	25 (1.6)	1609	67 (1.6)	979
⩾4	48 (3.1)	1728	96 (2.2)	1335
Patients ⩽35 years old				
No of patients	760		2414	
No of prednisone prescriptions				
0	649 (85.4)	757	2114 (87.6)	465
1	76 (10.0)	894	229 (9.5)	602
2	23 (3.0)	1051	45 (1.9)	717
3	9 (1.2)	1063	18 (0.7)	781
⩾4	3 (0.4)	1067	8 (0.3)	1214

daily prescribed dose was higher for patients taking budesonide (mean 979 µg) than for those taking beclomethasone (mean 635 µg), a difference of 344 µg (95% confidence interval 313 to 376 µg). Further investigations using multiple regression analysis confirmed the significance of this difference ($P<0.001$) and its consistency across age bands, with some increase in doses with age for both corticosteroids (figure). The higher doses of budesonide prescribed were evident whether mean or geometric mean data were compared.

In all, 5731 patients received 15 802 prescriptions exclusively for beclomethasone or budesonide given only by metered dose inhaler or breath activated devices during the study. In this analysis we excluded 96 patients who changed from metered dose inhaler to breath activated devices or the other way round. Of the patients given beclomethasone, 1537 received 4312 prescriptions for breath activated devices and 2680 received 7598 prescriptions for metered dose inhalers. Of the patients given budesonide, 1396 received 3553 prescriptions for breath activated devices and 118 received 339 prescriptions for metered dose inhalers.



Relation between age and average daily prescribed dose of beclomethasone and budesonide. Regression lines and geometric mean doses with 1SE (dotted lines) are shown

For prescribed daily doses using breath activated devices the mean for beclomethasone was 616 µg and for budesonide 988 µg, a difference of 372 µg (328 to 416 µg). For metered dose inhalers the mean for beclomethasone was 644 µg and for budesonide 887 µg, a difference of 243 µg (173 to 313 µg). The significance of these differences was confirmed using multiple regression analysis (both $P<0.001$).

Asthma severity analyses

A total of 1063 patients received 2221 prescriptions for prednisone (table 2). We performed specific analyses focusing on patients aged 35 years or under to limit confounding from patients with chronic bronchitis or emphysema.

The length of course of oral corticosteroids prescribed was similar in the budesonide and beclomethasone groups. No significant differences were found in the proportions of patients receiving prednisone between the two groups in any analysis.

Linkage of the database to information from secondary care was available for 1409 of the patients, all of whom were in the Otago region of the South Island of New Zealand. Table 3 shows the number of inpatient admissions, outpatient consultations, and emergency room visits for asthma in these patients. A significantly higher proportion of patients receiving budesonide accessed hospital services (7% *v* 4%, $P=0.008$).

The proportions of patients who had received two or more prescriptions for high doses of inhaled corticosteroids were similar in the two groups, and the event rate was higher with beclomethasone (table 3). Any increased use of secondary care services was therefore by patients receiving lower doses of budesonide. Systematic prescribing of budesonide to patients with more severe asthma as an explanation for the higher doses of budesonide prescribed was not supported by these analyses of secondary care use.

Of the 4295 patients receiving beclomethasone alone, 843 (19.6%) received at least two prescriptions for antibiotics for conditions related to asthma. A similar proportion was found for those taking budesonide (286 (18.7%)). The proportions were similar whichever delivery device was used. None of the analyses of antibiotic prescribing supported the presence of a severity bias. Overall consultation rates with general practitioners were not significantly different for patients taking budesonide (9.96 per annum) or beclomethasone (9.27 per annum) during the calendar year.

Ninety three patients switched from beclomethasone to budesonide or from budesonide to beclomethasone. An important result of the analysis of this group is that the average daily dose for patients changing from beclomethasone to budesonide was 756 µg before and 1110 µg after the change (difference 354 µg (133 µg to 575 µg)) and for patients changing from budesonide to beclomethasone 1069 µg and 729 µg per day (difference 340 µg (3 µg to 677 µg)). The crossover doses are consistent with the overall data showing average prescribed beclomethasone doses to be lower than budesonide doses.

Table 3 Numbers of events in secondary care for respiratory reasons among 1409 patients prescribed inhaled corticosteroids

Secondary care events	No of events (No of patients) among all patients		No of events (No of patients) among 155 patients who received two or more high dose prescriptions*	
	Budesonide alone (n=501)	Beclomethasone alone (n=908)	Budesonide alone (n=77)	Beclomethasone alone (n=78)
Inpatient admissions	8 (8)	10 (10)	0	2 (2)
Outpatient consultations	72 (22)	52 (23)	11 (5)	19 (7)
Emergency room visits	28 (21)	30 (21)	5 (4)	6 (5)
No (%) of patients with any secondary care event†	37 (7)	37 (4)	8 (10)	8 (10)

*Daily dose >800 μg (to age 14 years) or >1500 μg (15 years and over).
†Patients may have had events in more than one department, so total numbers of patients are not sums of the numbers of patients in each department.

Discussion

This epidemiological study has taken advantage of the opportunity provided by the database of the Royal New Zealand College of General Practitioners Research Unit to examine the relative potency of inhaled budesonide and beclomethasone in clinical practice. We found that the average prescribed daily dose of budesonide was about 50% higher than the average prescribed daily dose of beclomethasone. However, several potential sources of bias need to be addressed before budesonide is accepted as having a lower potency.

Potential sources of confounding

The main question is whether the findings are confounded by severity of asthma. We evaluated the recognised[10–12] and other possible markers of asthma severity. A detailed analysis which included the number of prescriptions for oral corticosteroids, number of inhaled corticosteroid prescriptions per patient, and antibiotic use did not show evidence of severity bias. Likewise, the increased rate of secondary care events in patients prescribed lower but not higher doses of budesonide did not support preferential prescribing of high dose budesonide to patients with more severe asthma.

A separate question is whether the prescribing practices of the general practitioners included in this study are different from those of other general practitioners in New Zealand because they had expended considerable effort computerising their medical records. This was necessary to provide standardised data for the purposes of this study and would not be expected to influence the differential prescribing of inhaled corticosteroids. Both beclomethasone and budesonide were well established drugs in New Zealand at the time of the study, with stable market shares. Survey of the contributing general practitioners at the end of the study found that they all believed that beclomethasone and budesonide were dose equivalent as described in the current New Zealand guidelines.

Another issue is whether the study had sufficient power to reliably detect a difference in potency between two inhaled corticosteroids using the delivery devices which are in widespread use. We are confident that with 5930 patients and 16 725 prescriptions our conclusions are not weakened by a type 2 statistical error.

Titration of dose according to response

The interpretation of our findings is based on the established clinical practice in New Zealand of general practitioners adjusting the dose of inhaled corticosteroid according to changes in the severity of their patients' asthma. This practice was formally recommended by the Department of Health in asthma guidelines sent to all medical practitioners in New Zealand in 1991[13] and reinforced as part of a major initiative by the Asthma Foundation of New Zealand in 1992.[14] It was also strongly promoted by the academic profession and pharmaceutical companies and, as a result, had become common practice for general practitioners before our study began.

General practitioners are therefore likely to have titrated the doses of inhaled steroids so that patients achieved satisfactory control as recommended in the national and international asthma treatment guidelines and that a higher average dose of budesonide was required for such control to be achieved. The difference in dose of the two inhaled corticosteroids was consistent in all age groups and with different inhalation devices, suggesting that it is probably not the result of undetected severity bias. Furthermore, the low rate of switching drugs and the observation that similar differences in doses between the two inhaled steroids were present after switching adds confidence to this interpretation of the findings.

Systemic effects and potency in vitro

Our findings are consistent with comparative studies investigating adverse systemic effects, which have fewer limitations than the comparative efficacy studies. Budesonide has been reported to cause less suppression of the pituitary axis[15] and less suppression of serum markers for bone and collagen turnover[16] than beclomethasone. Our findings are also consistent with in vitro data in which receptor affinity of 17-beclomethasone monopropionate (the active metabolite of beclomethasone dipropionate) is 1.4 times greater than that of budesonide.[17]

Conclusions

In conclusion, our results suggest that a higher dose of inhaled budesonide should be advised in the various asthma guidelines to give a treatment effect similar to a lower dose of inhaled beclomethasone. Confirmation of our results using similar computerised databases in other countries would not be difficult and is now required. Pending such epidemiological evaluation, international asthma guidelines may need to be modified. In addition, the fact that equipotency of these inhaled corticosteroids was generally accepted on the basis of clinical trials with low statistical power and results showing no difference raises new questions about the way in which clinical potency of inhaled steroids is assessed. We suggest that assessment of the potency of

Key messages

- Important limitations of the randomised clinical trials comparing beclomethasone and budesonide have usually resulted in failure to detect differences in potency
- In this study using a computerised database in primary care inhaled budesonide had about two thirds of the potency of inhaled beclomethasone
- Asthma treatment guidelines may need to be modified concerning the dose equivalence of inhaled corticosteroids
- The relative potency of newly developed inhaled corticosteroids needs to be assessed in primary care

newly developed inhaled steroids in clinical trials will require confirmation in appropriately designed epidemiological studies based in general practice.

Contributors: BDP had the idea for the study, developed the protocol, analysed and interpreted the data, and wrote the manuscript. AP developed the protocol, submitted the proposal for ethical consideration, planned the analysis, coordinated the project, and wrote reports for the study. DMacK performed the statistical analyses and wrote reports for the study. JH prepared the database, analysed data, and wrote reports for the study. RB analysed and interpreted the data and wrote the manuscript. MT developed the protocol, oversaw the study, edited the manuscript, and is guarantor for the study.

Funding: This study was supported in part by Novartis New Zealand, but the main costs were borne by the Royal New Zealand College of General Practitioners Research Unit. Over the past five years the research unit has received research funds for asthma research from Glaxo, 3M New Zealand, and Novartis New Zealand. The Researched Medicines Industry Association, an organisation representing the research based pharmaceutical industry operating in New Zealand, provided some core funding. The member companies of the association are: Abbott Laboratories NZ, Allergan Australia, Astra Pharmaceuticals (New Zealand), Baxter Healthcare NZ, Bayer New Zealand, Boehringer Ingelheim NZ, Boehringer Mannheim NZ, Bristol-Myers Squibb NZ, Ciba-Geigy New Zealand (now Novartis New Zealand), CSL (NZ), Eli Lilly and Company (NZ), Faulding Pharmaceuticals, Glaxo Wellcome NZ, ICI Pharmaceuticals, Janssen Cilag, Knoll Australia, Merck Sharp and Dohme (NZ), Pfizer Australia, Pharmacia and Upjohn Inter-American Corporation, Pharmaco NZ, Rhone-Poulenc Rorer NZ, Roche Products (New Zealand), Sandoz Pharma, Sanofi Winthrop (NZ), Schering NZ, Schering-Plough, Searle (a division of Monsanto NZ).

Competing interests: BDP is a medical director of Novartis New Zealand; this company markets no inhaled corticosteroids at present, but it does market a long acting β_2 agonist. In the past five years RB has received research grants from Astra Draco, Glaxo Wellcome, Novartis, 3M Pharmaceuticals; RB has received fees for consulting and reimbursement for attending a symposium from Astra Draco and Glaxo Wellcome; RB has received a fee for speaking from Astra Draco and Glaxo Wellcome.

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(Accepted 7 August 1998)

One hundred years ago

The Collins case

The recent trial of Dr. Collins will be read by the profession with interest, and with mingled feelings of satisfaction and regret—with interest, on account of the medico-legal questions involved, and the ability with which they were handled by the able counsel who defended Collins; with satisfaction, because a scoundrel has been stopped in his evil trade; with regret, that a career which began with such bright promise should end in such a ruin of disgrace.

The case was simple. Mrs. Uzielli, a fashionable lady, found herself pregnant. She did not want any more children, so she went to Collins, who induced abortion. Fatal peritonitis followed. Collins was put upon his trial for murder, but the jury found him guilty of manslaughter, No one could suppose that he wanted to kill the poor lady; and this consideration doubtless prevented the jury from finding him guilty of wilful murder … .

… We imagine that the only doctors who are never asked to procure abortion are those who are known not to practise midwifery. The medical profession has in this matter a very sacred duty: to make their patients not merely recognise that maternal duties exist, but that those duties are their highest privileges. Those who regard their children as a "heritage of the Lord" will not rush to imperil their health and their lives when menstruation fails to appear.

A marriage in which pregnancy is habitually either prevented or interrupted is one from which the strongest tie that binds together husband and wife is absent; in which worldly pleasures, which soon pall, are preferred to duties which if accepted and faithfully discharged, add greater interest and delight to life than anything else: in which love often waxes cold, and old age becomes a dreary solitude. The husband very possibly sets up an establishment somewhere else, and the wife, as a great novelist puts it, "relapses upon religion and little dogs." The Hebrew Poet-king was right when he said: "Happy is the man that hath his quiver full of them; he shall not be afraid of his enemies in the gate." (*BMJ* 1898;ii:103)