Recent trends in the use of inhaled β_2-adrenergic agonists and inhaled corticosteroids in Saskatchewan

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Abstract • Résumé

Objective: To examine recent trends in the use of inhaled β_2-adrenergic agonists and inhaled corticosteroids for the treatment of asthma among Saskatchewan residents and to determine whether these trends are in keeping with widely publicized guidelines recommending a reduction in the use of agents to treat symptoms (i.e., inhaled β_2-adrenergic agonists) and increased use of prophylactic agents (i.e., inhaled corticosteroids).

Design: Descriptive pharmacoepidemiologic study conducted with the use of data from the computerized database of the Saskatchewan Prescription Drug Plan.

Setting: Saskatchewan.

Patients: Saskatchewan residents 5 to 54 years of age who received one or more outpatient prescriptions for drugs to treat asthma (inhaled drugs, ingested β_2-adrenergic agonists and ingested methylxanthines) from 1989 to 1993.

Outcome measures: Epidemiologic trends, calculated for each year: number of prescriptions per 1000 persons; number of patients who received prescriptions for inhaled corticosteroids, inhaled β_2-adrenergic agonists and any type of drug to treat asthma; mean number of such prescriptions per patient; and weighted mean amount of salbutamol, fenoterol and beclomethasone dispensed per patient.

Results: There has been an increase in the proportion of the population receiving prescriptions for drugs to treat asthma. The number of patients receiving these drugs per 1000 people rose during the study period from 33.38 to 46.59 for any drug to treat asthma, from 24.70 to 33.77 for inhaled β_2-adrenergic agonists and from 6.1 to 19.9 for inhaled corticosteroids. The mean number of prescriptions per patient decreased steadily for all drugs to treat asthma (from 5.34 in 1989 to 3.88 in 1993), for inhaled β_2-adrenergic agonists (from 4.35 to 3.09) and for inhaled corticosteroids (from 2.98 to 2.25). The weighted mean amount of inhaled salbutamol dispensed per patient per year decreased by 40%, from 178.08 mg in 1989 to 109.14 mg in 1993. The weighted amount of fenoterol dispensed per patient per year declined even more, by 58%, from 387.91 mg in 1989 to 164.00 mg in 1993. Conversely, the weighted amount of inhaled beclomethasone dispensed per patient per year increased by 35% from 46.95 mg in 1989 to 63.50 mg in 1992, then dropped to 56.17 mg per year in 1993.

Conclusion: These data demonstrate a substantial change in Saskatchewan in the prescribing of drugs to treat asthma; they suggest that many physicians responded to current guidelines advocating increased attention to prevention of airway inflammation in the treatment of asthma.

Objectif : Analyser les tendances récentes de l'utilisation d'agonistes β_2 adrénergiques inhalés et de corticostéroïdes inhalés pour le traitement de l'asthme dans la population de la Saskatchewan et déterminer si ces tendances sont conformes aux lignes directrices générales où l'on recommande d'utiliser moins d'agents de traitement des symptômes (c.-à-d. agonistes β_2 adrénergiques inhalés) et davantage d'agents prophylactiques (c.-à-d. corticostéroïdes inhalés).

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← For prescribing information see page 1522

Conception : Étude pharmaco-épidémiologique descriptive effectuée à l'aide de données provenant de la base de données informatisée du régime des médicaments prescrits de la Saskatchewan.

Contexte : Saskatchewan.

Patients : Habitants de la Saskatchewan âgés de 5 à 54 ans à qui l'on a prescrit, en service externe, à une ou plusieurs reprises, des antiasthmatiques (médicaments inhalés, agonistes $ß_2$ adrénergiques ingérés et méthylxanthines ingérées) de 1989 à 1993.

Mesures des résultats : Tendances épidémiologiques, calculées pour chaque année : nombre d'ordonnances par 1 000 personnes; nombre de patients à qui l'on a prescrit des corticostéroïdes inhalés, des agonistes $ß_2$ adrénergiques inhalés et n'importe quel type d'antiasthmatique; nombre moyen d'ordonnances par patient et volume moyen pondéré de salbutamol, de fénotérol et de béclométhasone dispensé par patient.

Résultats : Le nombre des patients à qui l'on a prescrit des antiasthmatiques a augmenté en pourcentage de la population. Au cours de la période d'étude, le nombre de patients qui ont reçu ces médicaments par 1 000 personnes est passé de 33,38 à 46,59 dans le cas de n'importe quel antiasthmatique, de 24,70 à 33,77 dans celui des agonistes $ß_2$ adrénergiques inhalés et de 6,1 à 19,9 dans celui des corticostéroïdes inhalés. Le nombre moyen d'ordonnances par patient a diminué régulièrement dans le cas de tous les antiasthmatiques (de 5,34 en 1989 à 3,88 en 1993), dans celui des agonistes $ß_2$ adrénergiques inhalés (de 4,35 à 3,09) et dans celui des corticostéroïdes inhalés (de 2,98 à 2,25). Le volume moyen pondéré de salbutamol inhalé dispensé par patient par année a diminué de 40 % pour tomber de 178,08 mg en 1989 à 109,14 mg en 1993. Le volume pondéré de fénotérol dispensé par patient par année a diminué encore plus, soit de 58 %, pour passer de 387,91 mg en 1989 à 164,00 mg en 1993. Par ailleurs, le volume pondéré de béclométhasone inhalé dispensé par patient par année a augmenté de 35 % pour passer de 46,95 mg en 1989 à 63,50 mg en 1992, pour retomber ensuite à 56,17 mg par année en 1993.

Conclusion : Ces données indiquent que la prescription d'antiasthmatiques a changé considérablement en Saskatchewan et que beaucoup de médecins ont réagi aux lignes directrices en vigueur qui préconisent d'accorder une attention accrue à la prévention de l'inflammation des voies aériennes pour traiter l'asthme.

During the past 7 to 8 years guidelines for the management of asthma have changed strikingly, primarily as a result of a clearer understanding of the pathophysiologic aspects of the disease. As recently as 1987, asthma was still defined as a primarily bronchospastic disease, in which hypersensitive airways led to bronchoconstriction.[1] First-line therapy was aimed at reducing bronchoconstriction and the resulting symptoms through the use of bronchodilators such as inhaled $ß_2$-adrenergic agonists or orally ingested theophylline. Inhaled corticosteroids were relegated to third-line or fourth-line therapy; they were mainly used to treat severe cases of asthma in which $ß_2$-adrenergic agonists, theophylline and cromoglycate had failed to control symptoms.[1,2]

Recently, however, it has become widely recognized that asthma involves a significant inflammatory component, which causes the airways to be hyper-responsive.[3] As a result, asthma management now focuses on controlling inflammation as well as treating bronchospasm.[4–6] Current guidelines recommend that inhaled corticosteroids be used as first-line or second-line therapy and that inhaled $ß_2$-adrenergic agonists be used only as needed. Furthermore, these agents should not be used regularly without concomitant regular use of inhaled corticosteroids.[7,8]

In addition to these guidelines, articles published during the past 5 years have raised concerns about the safety of some $ß_2$-adrenergic agonists. A study conducted in New Zealand in 1989 found that the use of inhaled fenoterol was associated with an increased risk of death from asthma.[9] There has been considerable controversy over the methods used in that study and a subsequent one, also conducted in New Zealand.[10–14]

In 1992 Spitzer and associates[15] reported the results of a study of these uncertainties (the Saskatchewan Asthma Epidemiology Project), conducted with the use of data from Saskatchewan. The investigators showed that the risk of death and near-death from asthma was positively associated with increasing use of inhaled $ß_2$-adrenergic agonists[15–18] and negatively associated with regular use of inhaled corticosteroids[19] by patients with asthma 5 to 54 years of age.

The purpose of our study is to describe trends in the use of inhaled $ß_2$-adrenergic agonists and inhaled corticosteroids by Saskatchewan residents 5 to 54 years of age for the years 1989 to 1993 and to determine whether the use of these agents reflects current recommendations.

Methods

This study is based on outpatient prescriptions for drugs to treat asthma claimed through the Saskatchewan Prescription Drug Plan (SPDP) from 1989 to 1993. All drugs used for the treatment of asthma and listed in the Saskatchewan formulary or covered under Exceptional Drug Status (EDS) were reviewed. The primary focus of our study was to examine the use of inhaled $ß_2$-adrenergic

agonists (fenoterol, salbutamol, terbutaline, procaterol, metaproterenol [also known as orciprenaline] and isoproterenol) and inhaled corticosteroids (beclomethasone, budesonide, flunisolide and triamcinolone). However, to gain a perspective on the use of these two drug classes vis-à-vis overall use of drugs to treat asthma, we also reviewed ingested β_2-adrenergic agonists, ipratropium, cromoglycate, ketotifen, nedocromil and methylxanthines. Ingested corticosteroids were excluded because we were unable to determine the indication for their use from the database. Topical nasal agents (such as corticosteroids and ipratropium) were also excluded.

All Saskatchewan residents between 5 and 54 years of age who received drugs through the SPDP were included. The age range 5 to 54 years was used both in this study and in the previous Saskatchewan Asthma Epidemiology Project[18] because these drugs are more likely to be used for conditions other than asthma in children less than 5 years of age and in people older than 55. The number of eligible residents in this age group remained relatively constant during the 5-year study period: there were 681 793 eligible residents in 1989, 673 418 in 1990, 656 652 in 1991, 659 885 in 1992 and 660 682 in 1993. In the calculation of rates, the data for each study year were adjusted in relation to the 1989 Saskatchewan population 5 to 54 years of age.

Data source

The database maintained by the SPDP includes the generic and brand names of the drug, strength, form, quantity, the date on which the drug was dispensed, and the patient's age and sex, for every prescription claimed through the plan. All prescriptions for drugs listed in the Saskatchewan formulary or under EDS and dispensed to eligible Saskatchewan residents in ambulatory care are included in the database. Of the approximately 1 million people in Saskatchewan, 94% are eligible for benefits under the drug program. Only residents whose prescriptions are covered by other agencies, such as the Workers' Compensation Board or the federal government (i.e., status Indians, members of the Royal Canadian Mounted Police or the Canadian Armed Forces and inmates in federal penitentiaries) are ineligible for coverage. Prescription drugs dispensed in hospitals and most nonprescription drugs are also excluded from the database.

The SPDP is a basic insurance program that makes a percentage copayment on the portion of the prescription cost that exceeds a deductible amount. During the 5-year study period, the deductible amounts and copayment rates changed several times, as described in detail in Appendix 1.

Definitions

In this article "patient" means a person who received one or more prescriptions for a drug to treat asthma in a calendar year. "Inhaled" drugs include all forms intended for pulmonary inhalation: aerosols, inhalation solutions, disks, rotacaps, nebulas and so on.

Results

To examine the use of inhaled β_2-adrenergic agonists and inhaled corticosteroids from the perspective of all drug management of asthma, we looked at the rate of prescriptions for various classes of drugs for asthma per 1000 people per year (Table 1). The rate of prescriptions dispensed for any type of drug to treat asthma increased from 178.22 prescriptions per 1000 people in 1989 to 202.22 in 1991, then declined to 180.66 in 1993. There was a similar trend in the rate of prescriptions dispensed

Table 1: Prescriptions for drugs to treat asthma in people 5 to 54 years of age, Saskatchewan, 1989 to 1993

	Year; mean no. of prescriptions per 1000 people				
Drug	1989	1990	1991	1992	1993
β_2-adrenergic agonists	115.15	122.25	127.36	119.43	110.97
Ipratropium	2.23	2.72	2.83	2.59	2.53
Inhaled corticosteroids	18.19	25.79	34.71	42.08	44.67
Methylxanthines	25.60	22.24	18.38	13.25	10.38
Cromoglycate	17.06	18.17	18.88	15.69	11.12
Ketotifen*	NA†	NA	0.04	0.69	0.71
Nedocromil*	NA	NA	0.02	0.31	0.24
Total	178.22	191.16	202.22	194.08	180.66

*Added to the Saskatchewan formulary in 1991.
†NA = not applicable.

for β_2-adrenergic agonists (inhaled and ingested), ipratropium and cromoglycate. There was a steady decline in the rate of prescriptions for methylxanthines during the 5-year period, from 25.60 prescriptions per 1000 people in 1989 to 10.38 in 1993. Conversely, the rate of prescriptions for inhaled corticosteroids increased steadily, from 18.19 prescriptions per 1000 people in 1989 to 44.67 in 1993. The rate of prescriptions for ketotifen and nedocromil, both added to the Saskatchewan formulary in 1991, also increased.

As shown in Table 2, there has been a steady increase in the proportion of the population eligible for coverage through the SPDP receiving prescriptions for any form of drug to treat asthma, including inhaled and ingested forms. In 1989 33.38 patients per 1000 people received at least one prescription for a drug to treat asthma; by 1993 this rate had increased by 40%, to 46.59. Some patients received more than one type of drug. The rate of patients receiving inhaled β_2-adrenergic agonists showed a similar trend, increasing by 37%, from 24.70 patients per 1000 people in 1989 to 33.77 in 1993. The increase in the use of inhaled corticosteroids was the most striking: the rate of patients receiving these drugs increased more than three-fold during the 5 years studied. Most of the increase involved patients taking beclomethasone, the rate of which increased from 5.90 patients per 1000 people in 1989 to 18.05 in 1993. The rate of patients taking fenoterol was the only rate of patients taking a β_2-adrenergic agonist that showed a consistent decline, from 1.31 patients per 1000 people in 1989 to 0.92 in 1993.

There was a decrease in the mean number of prescriptions dispensed per patient per year for most inhaled β_2-adrenergic agonists (except procaterol), inhaled corticosteroids (except flunisolide) and for drugs to treat asthma in general (Table 3). A consistently higher mean number of prescriptions were dispensed for patients taking inhaled fenoterol than for those taking salbutamol.

We then analysed the mean amount of drug dispensed per patient during each year. This calculation was weighted to account for variations in the strength of the drug in formulations dispensed. In 1993 salbutamol and fenoterol accounted for more than 98% of prescriptions for inhaled β_2-adrenergic agonists dispensed in Saskatchewan and beclomethasone accounted for more than 90% of prescriptions for inhaled corticosteroids dispensed. Therefore, in this part of the analysis we assessed use of only these three drugs.

There was a marked, progressive decrease in the weighted mean amount of salbutamol dispensed per patient per year (from 178.08 mg to 109.14 mg) during the 5-year study period (Table 4). For fenoterol, the mean amount per patient per year increased between 1989 and 1990 (from 387.91 mg to 393.39 mg), then declined to 164.00 mg in 1993. A striking decrease in the amount of this drug prescribed between 1992 and 1993 was due mainly to a change in the formulation of this drug in January 1993; a "puff" of the aerosol, which had contained 200 μg, was changed to 100 μg. Conversely, the mean amount of beclomethasone dispensed per patient

Table 2: Patients 5 to 54 years of age taking drugs for asthma, Saskatchewan, 1989 to 1993

	Year; no. of patients per 1000 people				
Drug	1989	1990	1991	1992	1993
Inhaled β_2-adrenergic agonists					
Salbutamol	23.62	26.43	30.89	31.02	32.37
Fenoterol	1.31	1.21	1.15	1.01	0.92
Terbutaline	0.12	0.24	0.53	0.52	0.50
Procaterol	0	0.24	0.54	0.40	0.30
Metaproterenol (orciprenaline)	0.01	0.01	0.01	0.01	0
Isoproterenol	0.01	0.01	0.01	0	0
Total*	24.71	27.66	32.52	32.56	33.77
Inhaled corticosteroids					
Beclomethasone	5.90	8.90	13.27	15.67	18.05
Budesonide	0.12	0.33	0.86	1.60	2.11
Flunisolide	0.17	0.16	0.17	0.13	0.11
Triamcinolone	0	0.01	0	0	0
Total*	6.11	9.26	14.09	16.95	19.85
All forms of drugs to treat asthma*	33.38	37.59	44.38	44.14	46.59

*The total may be lower than the sum because some patients received more than one drug within a class during the year.

per year increased from 46.95 mg in 1989 and to 63.50 mg in 1990, then dropped to 56.17 mg in 1993.

Discussion

During the 5 years covered in our study, there was a steady increase in the number of patients who received at least one prescription per year for a drug used in the treatment of asthma, from 3% of the population to almost 5% (Table 2). This increase may be explained by an increase in the prevalence of asthma, or an increase in its severity and, subsequently, the need for drug therapy, or both. However, it may also be due, at least in part, to health care professionals' increased recognition in recent years of the diverse symptoms associated with asthma, as a result of the findings of the Saskatchewan Asthma Epidemiology Project.[15,18]

Our data cannot provide a valid estimate of the prevalence of asthma in the province, since not all patients with asthma receive a prescription or even visit a physician every year.

In contrast with those taking other inhaled β_2-adrenergic agonists, the number of patients taking fenoterol consistently declined during the 5-year period. This trend away from fenoterol use may stem from awareness of studies conducted in New Zealand that implicated fenoterol, but not other β_2-adrenergic agonists, in death or near-death from asthma.[9,10] Despite the decline in the number of patients receiving fenoterol, patients using this drug consistently received more prescriptions and a greater amount per patient than those taking salbutamol. In fact, those taking fenoterol were still receiving a greater mean amount of the drug than those taking salbutamol after the formulation was changed from 200 µg to 100 µg per puff in January 1993. The reasons why patients taking fenoterol used such a large amount are uncertain. The drug may actually lead to symptoms, and therefore to greater need for therapy.

Table 3: Prescriptions for drugs to treat asthma per patient 5 to 54 years of age, Saskatchewan, 1989 to 1993

	Year; mean no. of prescriptions per patient receiving that drug				
Drug	1989	1990	1991	1992	1993
Inhaled β_2-adrenergic agonists					
Salbutamol	4.19	3.99	3.53	3.36	3.02
Fenoterol	6.13	6.14	5.68	5.39	4.74
Terbutaline	2.67	2.00	2.10	1.93	1.89
Procaterol	0	1.96	2.77	3.25	3.57
Metaproterenol (orciprenaline)	13.50	15.00	9.40	6.40	3.00
Isoproterenol	17.00	11.33	3.75	0	0
Total	4.35	4.12	3.64	3.44	3.09
Inhaled corticosteroids					
Beclomethasone	2.96	2.73	2.42	2.43	2.22
Budesonide	2.26	2.86	2.35	2.26	1.97
Flunisolide	2.61	3.46	2.84	3.26	3.35
Triamcinolone	0	1.75	2.00	3.50	2.00
Total	2.98	2.78	2.46	2.48	2.25
All forms of drugs to treat asthma	5.34	5.09	4.56	4.40	3.88

Table 4: Amount of three most common drugs dispensed per patient per year, Saskatchewan, 1989 to 1993

	Year; weighted* mean amount of drug dispensed per patient per year, mg				
Drug	1989	1990	1991	1992	1993
Inhaled salbutamol	178.08	170.01	145.22	129.93	109.14
Inhaled fenoterol	387.91	393.39	359.54	328.04	164.00
Inhaled beclomethasone	46.95	55.39	59.63	63.50	56.17

*For explanation of weighting, see text.

It is hypothesized that all β_2-adrenergic agonists have this effect,[20] but fenoterol may cause symptoms in patients to a greater extent than other such drugs. Also, patients who are prone to abuse β_2-adrenergic agonists may find fenoterol more potent than other drugs in this class, and, therefore, it may be more liable to abuse. A third possibility is that physicians reserve this drug for severe asthma, and the higher dosage is accounted for by the severity of the disease in patients taking it.

Our results show a marked change in the patterns of prescriptions for drugs to treat asthma in Saskatchewan during the past 5 years. There has been a shift toward the use of inhaled corticosteroids, evinced by an increase in the proportion of patients receiving these agents and an increase in the mean amount of beclomethasone dispensed per patient. In 1989, 18% of patients receiving any type of drug for asthma received at least one prescription for an inhaled corticosteroid; by 1993 this proportion had risen to 43%. Similarly, the mean amount of beclomethasone dispensed per patient per year increased by 35% between 1989 and 1992; however, it dropped by 12% in 1993. In contrast the percentage of patients receiving β_2-adrenergic agonists remained fairly constant during the 5-year period. Of patients receiving drugs to treat asthma in 1989, 74% received a prescription for a β_2-adrenergic agonist, as compared with 72% of patients who received a prescription for one of these drugs in 1993. The mean amount of salbutamol and fenoterol dispensed per patient declined steadily, suggesting that lower dosages were prescribed or that these drugs were used less often.

These trends suggest that the recommendations of various authorities[7,8] are being followed in Saskatchewan. One limitation of our analysis, however, stems from the restricted information we gained concerning trends in the use of other drugs to treat asthma. If current consensus guidelines for the management of asthma are indeed being adhered to in Saskatchewan, we would expect to see an increase in the use of other preventive agents such as cromoglycate, nedocromil and ketotifen. However, the rate of prescriptions for cromoglycate declined by 35% (Table 1) during the study period. This may represent a true decline in the use of cromoglycate, or it may simply result from an increase in the amount of drug dispensed per prescription, as occurred in the case of beclomethasone. For the same reason, it is difficult to interpret the decline in the number of prescriptions per patient for methylxanthines and the lack of change in the number of prescriptions per patient for ipratropium. Nedocromil and ketotifen are relatively new to the Saskatchewan market — they have been covered as controlled drugs under the plan since 1991. In all likelihood, the increase in the rate of prescriptions per 1000 people for these drugs represents a true increase in use.

An additional limitation of our study is that it deals with aggregated data. It would be useful to look at the prescribing of these drugs for individual patients in order to assess the appropriateness of dosages and concomitant drug use.

We cannot claim that the shift in the use of inhaled β_2-adrenergic agonists and inhaled corticosteroids shown in this study was due entirely to changes in physicians' prescribing patterns resulting from knowledge gained about the risks and benefits of different classes of drugs. Successive changes in the provincial drug plan (Appendix 1), which have caused significant increases in costs for many patients, may be another major influence on prescribing patterns in Saskatchewan. The steady decline in the use of β_2-adrenergic agonists may be a direct result of these changes. However, as we have shown, the decrease in the use of these drugs has been accompanied by an increase (except in 1993) in the use of inhaled corticosteroids, which tend to be more expensive than β_2-adrenergic agonists. The most significant change in the drug plan occurred in March 1993, when deductible levels for a family were increased from $190 to $850 semiannually. The sudden decrease in the amount of beclomethasone dispensed per patient in 1993 may have reflected this change. However, drug-plan data show that the March 1993 increase in deductible levels had very little effect on the overall number of prescriptions dispensed in the province.

The trends in Saskatchewan that we have shown here suggest that physicians are responding to new information about the management of asthma. Further studies are needed to ascertain whether these shifts in prescribing patterns are associated with a decline in rates of death or near-death from asthma among Saskatchewan residents.

We thank Andrea Laturnas, Rhonda Schappert and Deborah Rieb for help with data retrieval and analysis, and Jacquie Bramley and Helene Christensen for their assistance in the preparation of the manuscript.

Funding and data for this project were provided by Saskatchewan Health; however, the interpretations and conclusions of the authors do not necessarily represent those of the Government of Saskatchewan or Saskatchewan Health.

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Appendix 1: Deductibles and copayments, Saskatchewan Prescription Drug Plan, 1989 to 1993*

Jan. 1, 1989
For regular family, annual deductible of $125, copayment of 20%
For senior family, annual deductible of $75, copayment of 20%
For single senior, annual deductible of $50, copayment of 20%
Mar. 8, 1991
Annual deductibles same as 1989, copayment of 25%
May 19, 1992
For regular family, semiannual deductible of $190, copayment of 35% to a maximum of $375, then copayment of 10%
For single senior and senior family, deductibles at 1989 level, but becoming semiannual, with a copayment of 35% to a maximum of $375, then copayment of 10%
Mar. 19, 1993
Family units subject to a deductible are eligible for the Special Support Safety Net Program, in which the subsidy level is based on family income. Copayment is based on the subsidy level in relation to drug cost
For Family Income Plan recipients and Saskatchewan Income Plan recipients, semiannual deductible of $100, copayment of 35%
For Guaranteed Income Supplement recipients in special care homes, semiannual deductible of $100, copayment of 35%
For family units not covered under the Family Income Plan, Saskatchewan Income Plan or Guaranteed Income Supplement, semiannual deductible of $850, copayment of 35%

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