Overreliance on bronchodilators as a risk factor for life-threatening asthma

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OBJECTIVE: To assess the potential impact on the risk of life-threatening asthma of current recommendations in pharmacotherapy, which emphasize the early use of steroids and the avoidance of beta-agonist overuse.

DESIGN: Nested case-control study.

SETTING: Province of Saskatchewan.

POPULATION STUDIED: From a cohort of 12,301 subjects dispensed 10 or more asthma medications from 1980 to 1987, 129 case patients were identified who had experienced an episode of fatal or near fatal asthma and 129 control patients matched to the cases on age, time period at risk and severity of asthma (as judged by the need for hospitalization for asthma in the preceding two years).

METHODS: Two clinicians reviewed the therapy these 258 subjects had been dispensed over the prior two-year period and classified their treatment as 'incompatible' or 'compatible' (at least partially compatible) with current pharmaco-

therapeutic guidelines. In addition to this classification a treatment evaluation score was also applied to each study subject. This score was based on the use of anti-inflammatory therapy (oral and inhaled) in conjunction with the regular use of bronchodilators, as well as the use of oral corticosteroids for patients recently discharged from hospital following an attack of asthma.

RESULTS: At least one of the two clinician reviewers judged therapy to be incompatible with current standards in 49% of the case patients compared with 20% of the subjects who had not experienced a life-threatening episode. The mean $\pm$ SD treatment score was 3.5 ± 1.7 in cases compared with 0.8 ± 1.4 in controls, suggesting quality of pharmacological treatment was worse in cases ($P < 0.001$).

CONCLUSIONS: Pharmacological therapy incompatible with current recommendations was more common among cases of fatal and near fatal asthma in Saskatchewan from 1980 to 1987. (*Pour résumé, voir page 35*)

Key Words: Adverse effects, Beta-agonists, Corticosteroids, Drug therapy, Morbidity, Mortality

La confiance excessive dans les bronchodilatateurs comme facteur de risque pour un épisode d'asthme mettant la vie du patient en danger

OBJECTIF : Évaluer l'impact potentiel des recommandations en vigueur en matière de pharmacothérapie, qui rappellent d'utiliser précocement des stéroïdes et d'éviter la surutilisation des bêta-agonistes, sur le risque d'un épisode d'asthme mettant la vie du patient en danger.

MODÈLE : Étude cas/témoins emboîtés

CONTEXTE : Province de la Saskatchewan.

POPULATION ÉTUDIÉE : D'une cohorte de 12 301 sujets à qui on a prescrit 10 médicaments anti-asthmiques et plus, de 1980 à 1987, 129 patients-cas ont été identifiés qui avaient subi un épisode d'asthme fatal ou presque fatal, et 129 patients-témoins étaient appariés aux cas pour l'âge, la durée du risque et la gravité de l'asthme (jugé par le besoin d'hospitalisation causée par l'asthme dans les deux années précédentes).

MÉTHODES : Deux cliniciens ont passé en revue le traitement qui avait été prescrit à ces 258 sujets pendant les deux

années précédentes et l'ont classifié comme « incompatible » ou « compatible » (du moins partiellement compatible) avec les lignes directrices en vigueur de la pharmacothérapie. En plus de cette classification, une cote d'évaluation du traitement a également été appliquée à chaque sujet participant à l'étude. Cette cote était basée sur l'utilisation d'agents anti-inflammatoires (par voie orale ou par inhalation) en conjonction avec l'utilisation régulière de bronchodilatateurs, de même que sur l'utilisation de corticostéroïdes pour les patients qui venaient de quitter l'hôpital après avoir souffert d'une crise d'asthme.

RÉSULTATS : Au moins un des deux réviseurs cliniciens a jugé le traitement incompatible avec les normes en vigueur chez 49 % des patients-cas comparativement à 20 % des sujets qui n'avaient pas subi un épisode mettant leur vie en danger. La moyenne $\pm$ écart-type de la cote du traitement était de $3,5 \pm 1,7$ pour les cas comparativement à $0,8 \pm 1,4$ pour les témoins, indiquant que la qualité du traitement pharmacologique était plus mauvaise chez les cas ($P < 0,001$).

CONCLUSIONS : Un traitement pharmacologique incompatible avec les recommandations en vigueur était plus courant chez les cas d'asthme fatal et presque fatal en Saskatchewan, de 1980 à 1987.

ASTHMA MORBIDITY AND MORTALITY HAVE BEEN INCREASING in a number of countries despite recent scientific advances that have improved the understanding of this chronic lung condition (1-3). The treatment of asthma has been identified as a potential contributing factor to this increasing morbidity and mortality (4-6). In the past, pharmacological treatment of asthma focused on bronchodilator therapy, but the more recent recognition that chronic asthma involves a characteristic inflammatory response in the airways has changed the therapeutic management of asthma (7-9). This greater emphasis on anti-inflammatory therapy and decreased reliance on bronchodilators alone is reflected in the revised guidelines for the treatment of asthma disseminated to the medical community in written reports as well as scientific journals (10-13).

The primary objective of the present study was to estimate the potential impact that this change in emphasis might have by comparing pharmacotherapy in asthmatics with or without a life-threatening episode in Saskatchewan from 1980 to 1987. This was accomplished in two ways: first, by having two clinicians review clinical and drug treatment information on all cases of life-threatening asthma and a similar number of control patients with asthma who had not had a life-threatening episode, and subsequently classify their pharmacotherapy as 'incompatible' or 'partially compatible' with current pharmacotherapeutic recommendations, as first formalized in the Canadian Asthma Guidelines (12); and second, by applying an 'Asthma Management Score' to each of the cases and selected controls to obtain a numerical index of the degree of 'incompatibility'. A further objective of this study was to determine whether fenoterol was more likely

than albuterol to have been prescribed in subjects who over-rely on bronchodilators.

PATIENTS AND METHODS

Overall study design: As previously reported (14), a nested case-control design was used to examine the relationship between the use of beta-agonists and the risk of death and near death from asthma. Briefly, linked health insurance databases of the province of Saskatchewan were used to identify a cohort of 12,301 patients who were dispensed 10 or more prescriptions for an asthma medication between January 1, 1978 and April 30, 1987. These medications were not available without a prescription and a dispensing record was required for the pharmacist to be directly reimbursed by the government, which pays for all prescribed medications. Subjects had to be between the ages of five and 54 years during the study period (January 1, 1980 to April 30, 1987) to be considered at risk. Predetermined criteria were used to identify case patients who died of asthma during the study period (44 patients) or, for those who survived, experienced a near-fatal asthmatic episode (85 patients). A near-fatal event was defined as intubation, mechanical ventilation, or PCO_2 greater than 45 mmHg during a hospitalization for asthma. Up to eight controls were selected from among the cohort of 12,301 and were matched to each case patient on the basis of age at entry into the cohort, date of entry, the occurrence of a hospitalization for asthma in the prior two years, region of residence and receipt of social assistance at any time during the study. In addition, the controls were required to have been at risk for the outcome at the time of the event in the case patient, referred to as the index

TABLE 1
Asthma management score

Criteria	Points
Average number of beta-agonist inhalers per month (prior 12 months)	
>3	3
>2 ≤3	2
≥1.5 ≤2	1
<1.5	0
Anti-inflammatory therapy* (number of prescriptions dispensed during prior 12 months)	
none	3
<3	2
≥3 ≤11	1
>11	0
Use of contraindicated drugs†	
within 1 month of index event or hospitalization for asthma	2
2 to 12 months before index event or hospitalization for asthma	1
Most recent acute attack requiring hospitalization within 12 months before index event not adequately treated	
no corticosteroids	2
inhaled corticosteroids only	1
Maximum score	10

*Includes oral corticosteroids, inhaled corticosteroids, and inhaled cromolyn; †Includes beta-blockers, sedatives and parasympathomimetics

date. A total of 655 controls were matched to the 129 case patients.

Clinical information was obtained for all 129 cases and their 655 matched controls from two sources – hospital medical records and physician questionnaires (15). First, hospitalizations with a primary discharge diagnosis of asthma during the two years preceding the index event or matching index date (not the hospitalization which might have occurred at the time of the life-threatening episode) were identified from the computerized databases. Abstractors, blind to the study hypothesis and unaware of the case/control status of the subjects, visited hospital medical record departments and, using a standard form, obtained information from the patients' charts on precipitating factors, presenting respiratory symptoms and their duration, past history, signs of a life-threatening attack, lung function and arterial blood gases.

Second, the computerized out-patient physician datafile was used to identify physician visits by study subjects. Eligible visits were those in which a general practitioner, pediatrician, internist, allergist or respirologist had seen the study subjects in the two years before the index date or event. Questionnaires were hand delivered by research personnel to these physicians and were subsequently picked up on completion. Clinical information similar to that gathered from hospital medical records was sought from the physicians. Ethical approval was obtained from the appropriate agencies of Saskatchewan Health.

Study subjects for management classification: The subjects were the 129 cases of fatal and near-fatal asthma pre-

TABLE 2
Characteristics of study subjects

	Case patients	Controls
Number of subjects	129	129
Male (%)	54	12
	Mean ± SD	
Age (years) at index event	30±15	28±14
Number of office visits*		
to specialists	10±11	6±10
to nonspecialists	35±30	29±25
Number of hospitalizations†	2.1±3.4	1.1±1.3

*Visits were those made during the two years before the index event or date. Specialists included pulmonary medicine, allergology, pediatrics and internal medicine; †In which there was a primary or secondary diagnosis of asthma

viously identified, as described above. From the controls who were matched to each case, the first control per case was selected in whom similar clinical information (ie, hospital record information) was or was not available. This was undertaken to ensure that cases and controls were classified according to comparable information. A total of 258 subjects were therefore included in the analysis. Because controls were listed by sex with females appearing first, they were more likely to be selected as controls for the present analysis.

Methods for management classification: For each case and matched control a dossier of information was assembled. For the fatal case patients this included a copy of the death certificate, as well as autopsy and coroner reports when available. If the death occurred in hospital, a copy of the hospital discharge summary associated with the event was also obtained. For the near-fatal case patients, a copy of the hospital discharge summary associated with the near-fatal episode was retrieved. In addition to the information surrounding 'the event', additional clinical information was obtained from the hospital medical records for each case and matched control who were hospitalized for an asthma-related episode during the two years before the index event, as described above.

Detailed exposure information regarding medication dispensed each month for the 12-month period before the index event or matching index date was also obtained for each case patient and matched control from the Prescription Drug Data Base of Saskatchewan Health. One unit of an inhaled beta-agonist was equivalent to the dispensing of one metred dose inhaler (MDI). For other medications a unit represented the dispensing of one prescription, usually a one-month supply. For the physician review, beta-agonists were identified by class only, and not by individual generic names.

Each of the dossiers for the cases and their matched control was reviewed independently by two clinicians experienced in the treatment of asthma. On the basis of the information available the clinicians classified the management of each subject as either 'incompatible' or 'at least partially compatible' with the current emphasis in pharmacotherapy. These classifications were then collated to determine the number of cases and controls classified as

TABLE 3
Frequency of management classified as incompatible with current treatment guidelines in 129 matched pairs following clinician review

Classification	Cases (%) (n=129)	Controls (%) (n=129)	P value*
At least one clinician classified treatment as incompatible	63 (48.8)	26 (20.2)	<0.001
Both clinicians classified treatment as incompatible [†]	15 (11.6)	10 (7.8)	>0.05

*McNemar χ^2 statistic; [†]These subjects were included in the 63 cases and 26 controls classified as treatment incompatible by at least one clinician

TABLE 4
Correspondence between classification by clinicians and asthma management score

Classification by clinicians	Number (n=258)	Mean score
Classified as incompatible by		
both clinicians	25	4.9
one of the two clinicians	64	4.0
neither of the clinicians	169	2.6

'incompatible' as judged by both reviewers, as well as the number classified as 'incompatible' as judged by at least one of the reviewers. No attempt was made to have the two clinicians judge the adequacy of pharmacotherapy in an equivalent way, and their assessments were carried out without knowledge of the other clinician's judgement. Only general instructions were given as to the factors to be considered. These were the use of high or increasing doses of bronchodilators, especially inhaled beta-agonists, the underuse of inflammatory drugs and the use of contraindicated drugs, especially in relation to clinical events such as hospitalizations. It was felt that greater sensitivity to inadequacies in pharmacotherapy might be obtained by keeping the clinical evaluations independent in this way, though at the price of a less adequate demonstration of the validity of such a clinical assessment.

To validate the subjective assessments made by the two clinicians and to provide a more objective measure of the quality of pharmacotherapy, an asthma management score was developed based on current pharmacological treatment guidelines (Table 1). This was considered necessary since the clinicians could not be blinded to the case control status, i.e. the occurrence of a life-threatening event, and such knowledge may have resulted in their being more critical of the management in this group. The potential range for the management score was 0 to 10, with 0 reflecting pharmacological treatment most compatible with current guidelines, and 10 indicating treatment considered least compatible. This management score was applied to each of the cases and controls by another member of the research team, who was blind to the case and control status of each subject, using the same information the clinicians had reviewed. The weight given to

the different elements of the score are somewhat arbitrary. This is necessarily so, since it is difficult to equate the prescription of a contraindicated medication, for example, a beta-blocker, which occurred in one case, with a given level of overuse of beta-agonists. However, the weights given for the different levels of use of beta-agonists and anti-inflammatory agents are compatible with the dose-response relationships observed in the cohort of 12,301 subjects with asthma. **Analysis:** The frequency of management incompatible with current pharmacotherapy, as classified by the two clinicians, was compared in the cases and controls using the McNemar χ^2 statistic for matched pairs. The mean asthma management score was calculated for cases and controls, and the paired *t* test was used to determine whether there was a significant difference in the mean scores. In determining the association between exposure to fenoterol and albuterol and management classified as incompatible, an unmatched odds ratio and 95% confidence interval were calculated. This was undertaken since the outcome of interest was now the management classification in cases and controls combined.

RESULTS

Characteristics of study subjects are presented in Table 2. While the case patients and the controls were similar with respect to age, consequent to the way controls were selected a larger percentage of the cases were males (54%) than in the controls (12%). When examined in the cohort of 12,301 patients as a whole, sex was not associated with outcome (life-threatening episode of asthma). Furthermore, in the study sample, there was no sex difference in the type or quantity of pharmacotherapy received. The present authors are, therefore, confident that the sex difference between cases and controls did not bias the results presented here. The case patients used the services of physicians and were hospitalized more frequently than the controls.

The frequencies of management classified as incompatible with the current emphasis in pharmacotherapy, as determined by the two clinician reviewers, are presented in Table 3. A significantly higher proportion of cases (subjects who had died of asthma, or experienced a near-fatal asthmatic episode) than controls from each matched pair were classified as receiving treatment incompatible with current guidelines by at least one of the two clinician reviewers ($P<0.001$). For the situation in which both the clinicians classified the subject as receiving treatment incompatible with current guidelines, the difference between the cases and controls did not achieve statistical significance ($P>0.05$), at least in part due to the small number of subjects classified in this way. Note that the 63 cases and 26 controls classified as having incompatible treatment by at least one clinician included the 15 cases and 10 controls classified as such by both clinicians.

The results of the asthma management score that was applied to each of the case and control subjects revealed a score ranging from 0 to 8 for cases, and 0 to 7 for controls, with 10 being the maximum score possible. The cases had a statistically significant higher mean score (3.5) than did the

TABLE 5
Association between clinical classification of overreliance on beta-agonist and being dispensed fenoterol or albuterol in the prior 12 months

		Overreliance on beta-agonists*				Overreliance on beta-agonists*	
		Yes	No			Yes	No
Fenoterol	Yes	9	47	Albuterol	Yes	16	168
	No	16	186		No	9	65
		Odds ratio 2.2				Odds ratio 0.69	
		95% CI 0.94 - 5.13				95% CI 0.29 - 1.62	

*As judged by both clinicians. CI Confidence interval

controls, (2.8; $P < 0.0002$, 95% confidence interval 0.3 to 1.1), with a higher score reflective of pharmacological treatment less compatible with current pharmacotherapy. The correspondence between the classification of treatment by clinician review and that of the asthma management score is provided in Table 4. The average scores are consistent with the clinicians' classification – a higher mean score (reflective of pharmacological treatment less compatible with current guidelines) corresponding to subjects who were classified as incompatible with current guidelines by both clinician reviewers, or by one alone compared with subjects whose treatment was classified as at least partially compatible with the current emphasis in pharmacotherapy.

Table 5 examines the relationship between the likelihood of a subject's treatment being classified as incompatible with current pharmacotherapy by both clinicians and whether they had been dispensed fenoterol rather than albuterol in the prior 12 months. The small number of subjects precludes achieving statistical significance. The trend towards a positive association between being dispensed fenoterol and being classified as overreliant on bronchodilators as opposed to the possible negative association between albuterol and appropriateness of drug therapy suggests, however, that these two inhaled beta-agonists were used in patients in whom the quality of therapy was different. It may also suggest, in accordance with the results of Sears (5), that prescribing fenoterol may worsen the severity of the disease, which in turn would lead to a greater need for, or reliance on, bronchodilators.

DISCUSSION

In response to increasing asthma morbidity and mortality in many parts of the world, various organizations have brought together experts in the treatment of asthma to develop guidelines for asthma management in the hope of favourably influencing prognosis in this common disorder (10-13). An important aspect of these guidelines is the greater emphasis placed on early use of anti-inflammatory therapy and less reliance on bronchodilator therapy. This current emphasis in pharmacotherapy is based on several long term studies recently demonstrating the efficacy of inhaled steroids in decreasing asthma morbidity (9,16-18), suggestive evidence that regular use of bronchodilators may actually make asthma worse (5,6,19-21) and the strong association

between overuse of inhaled beta-agonists and life-threatening asthma (14). In an attempt to estimate the impact on asthma morbidity that might result from this change in emphasis in the pharmacotherapy of asthma, we evaluated the drug therapy received by asthmatic subjects who had experienced a life-threatening attack and compared it with subjects of the same age and asthma severity who had not experienced a life-threatening episode. Nearly half of the cases of life-threatening asthma were judged by at least one clinician experienced in the treatment of asthma to have received treatment that did not at least partially meet currently recommended therapy, compared with 20% of study subjects who did not experience such a life-threatening event. The most common pattern observed was the increasing use of various bronchodilators over time without any dispensing of preventive or anti-inflammatory therapy (22).

To render the evaluation of therapy more objective, we developed a management score that was then applied to the treatment regimens by an observer not experienced in the treatment of asthma. The score was formulated to reflect the hypothesis that excessive therapy with inhaled beta-agonist bronchodilators without concomitant use of anti-inflammatory therapy is ill-advised. Again, according to this score, cases of life-threatening asthma demonstrated greater divergence from current recommendations than subjects who had not experienced such attacks. As one would expect, since both the score and the clinical assessment are based on current standards of therapy, the score is higher among subjects in whom clinicians thought the therapy did not meet these standards. This provides some validation of the clinical assessments.

We and others (23) have reported a stronger association between fenoterol, as opposed to albuterol, use and fatal asthma. Such a difference might be explained if subjects who were prescribed fenoterol were at a greater baseline risk of an adverse event. Inasmuch as not being dispensed therapy that reflects current recommendations is a marker of increased risk, subjects dispensed fenoterol appear to be at greater risk. Such channelling of therapy to different risk groups has been found for fenoterol in another population (24). Our evidence for such differential prescribing can only be considered as preliminary given the low statistical power available for such an analysis. This study was based on the examination of computer and clinical records of information collected in the past. This limits the amount of detail available on nonpharmacological therapy as well as on environmental risk factors for life-threatening asthma. If such factors were associated with the pharmacotherapy dispensed in a different way in patients with a life-threatening episode of asthma than in those without such a history, these factors could partly explain the relationships described.

CONCLUSIONS

The results presented show that cases experiencing fatal or near-fatal asthma were more likely than controls to have received inadequate therapy as judged by current treatment guidelines (specifically less anti-inflammatory and more

beta-agonist treatment). From this evidence, we suggest that less reliance on bronchodilators and greater use of anti-inflammatory therapy may have a positive impact on asthma morbidity.

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