

The Clinical Effects and Cost-Avoidance of a Change in Perioperative Bronchodilator Use

Brian Zimmer, A.C. Casson, Charles D. Bayliff and C.F.P. George

ABSTRACT

The clinical effects and financial impact of a change in prescribing habits from routine to occasional use of perioperative bronchodilators, following the presentation of drug information, were assessed retrospectively by comparing the outcomes of patients admitted for major thoracic surgery.

Eighteen of 24 (75%) patients in Period A (prior to change) received salbutamol bronchodilator therapy versus 10 of 17 (59%) in Period B (following the change) ($p=.448$). Of the patients who did receive salbutamol aerosols, the mean dose in grams per patient was greater in Period A than in Period B (6.85 ± 5.96 vs. 2.64 ± 4.44 respectively $p<0.05$). Two patients from Period A and one from Period B were receiving digoxin prior to admission. In the remaining patients, 5 of 22 (23%) in Period A and 1 of 16 (6%) in Period B developed atrial fibrillation requiring digoxin ($p=.36$). The proportion of patients with obstructive airways disease (OAD) who developed an arrhythmia was not different between the two groups. However, in those patients without OAD an arrhythmia was reported in 9 of 16 patients (56%) receiving salbutamol, versus only 1 of 11 (9%) of those not receiving it ($p=0.032$). The number of days patients were hospitalized during Period A and Period B were 10.2 ± 4.97 and 9.4 ± 3.68 respectively ($p=0.85$). A potential average cost-avoidance of \$68.46 per patient could be realized with this new practice. We conclude that a change in prescribing habits had no adverse clinical outcome and resulted in a considerable cost-avoidance.

Key words: *cost-avoidance, prescribing change, salbutamol*

Can J Hosp Pharm 1994;47:149-53

RÉSUMÉ

On a évalué rétrospectivement les effets cliniques et l'incidence financière d'une modification des habitudes de prescription, à savoir passage de l'usage régulier à l'usage occasionnel de bronchodilatateurs périopératoires, après présentation de la documentation sur les médicaments, en comparant l'état des malades au terme d'une importante intervention chirurgicale à la cage thoracique.

Dix-huit patients sur 24 (75 p. 100) de la période A (avant le changement) ont reçu du salbutamol, un bronchodilatateur, contre 10 sur 17 (59 p. 100) lors de la période B (après le changement) ($p=0,448$). La dose moyenne en grammes de salbutamol par personne était plus élevée pour les malades qui en avaient reçu sous forme d'aérosol durant la période A que durant la période B ($6,85 \pm 5,96$ contre $2,64 \pm 4,44$ respectivement; $p<0,05$). Deux patients de la période A et un de la période B prenaient de la digoxine avant l'admission à l'hôpital. Par ailleurs, cinq patients sur 22 (23 p. 100) durant la période A et un sur 16 (6 p. 100) durant la période B ont souffert de fibrillation auriculaire, ce qui a exigé l'administration de digoxine ($p=0,36$). La proportion de malades atteints du syndrome respiratoire obstructif qui ont par la suite développé une arythmie était similaire pour les deux groupes, mais pour les autres, on a observé de l'arythmie chez neuf des 16 patients (56 p. 100) qui prenaient du salbutamol, contre un patient seulement sur 11 (9 p. 100) pour ceux à qui on n'avait pas administré le médicament ($p=0,032$). Les patients ont respectivement été hospitalisés $10,2 \pm 4,97$ jours durant la période A et $9,4 \pm 3,68$ jours durant la période B ($p=0,85$). La nouvelle pratique permettrait une économie moyenne de 68,46 \$ par malade. On en conclut qu'une modification des habitudes de prescription ne nuit en rien à l'issue clinique du traitement et permet une économie considérable au niveau des coûts.

Mots-clés : *modification de la pharmacothérapie, réduction des coûts, salbutamol*

Brian Zimmer, B.Sc.Pharm., is a staff pharmacist in the Department of Pharmacy Services at Victoria Hospital in London Ontario.

A.C. Casson, M.B., Ch.B., FRCPS, is a staff member of the Department of General Surgery at Victoria Hospital.

Charles D. Bayliff, Pharm.D., is Clinical Coordinator of Pharmacy Services in the Department of Pharmacy Services at Victoria Hospital.

C.F.P. George, M.D., FRCPC, is a staff member of the Department of Medicine at Victoria Hospital.

Address Correspondence to: Brian Zimmer, B.Sc.Pharm., Department of Pharmacy Services, Victoria Hospital, 375 South Street, London, Ontario N6A 4G5.

Acknowledgements: The authors wish to thank Dr. R. Inculc of the Department of Surgery, Victoria Hospital for his assistance in patient recruitment and Mrs. Jan Butler for her secretarial assistance.

INTRODUCTION

Patients undergoing thoracotomy receive a number of therapies in the perioperative period to minimize complications. Treatments include agents such as analgesics and antibiotics as well as pulmonary physiotherapy. Beta₂-agonists are often included to facilitate pulmonary physiotherapy by enhancing sputum mucociliary clearance (MCC). These agents also provide relief from obstructive airways disease that may be present in many of these patients.

While the role of beta₂-agonists in relieving bronchospasm is well established in obstructive airways disease (OAD), there is considerably more controversy regarding the ability of these agents to facilitate MCC. *In vitro* testing has repeatedly demonstrated that beta₂-agonists produce an increased ciliary beat frequency.¹⁻³ *In vivo* information, however, is somewhat limited and has produced contradictory findings.⁴⁻⁸ Sutton et al compared the effects of nebulized saline to that of nebulized terbutaline prior to chest physiotherapy.⁴ Although both therapies resulted in a significant increase in sputum yield compared to physiotherapy alone, no significant difference between the two nebulized regimens was observed. A study done by Lafortuna and Fazio demonstrated that enhanced MCC could be observed with nebulized salbutamol, but the effect was transient lasting less than one hour.⁵ Pavia et al were unable to detect any effect on MCC following chronic inhalation of nebulized terbutaline, the last dose of which was administered two hours prior to the study.⁶ In a study of 42 patients, Isawa et al were unable to demonstrate an improvement in MCC using metered dose inhaler (MDI) procaterol as measured using radiolabelled aerosol particles⁷, although the drug did produce bronchodilation.

It appears that based on these limited studies the beneficial effect of beta₂-agonists on MCC may be limited nebulized solution. However, current practice at our institution as well as others, results in routine conversion of nebulized aerosol to MDI immediately post-operatively.

While the benefits of beta₂-agonist therapy in patients who do not have OAD remains to be elucidated, there is some evidence that this therapy may be toxic. The beta₂-agonists administered orally⁹, by nebulizer solution¹⁰, and by MDI¹¹, have been implicated in the development of several cardiac side effects. One study showed that oral terbutaline resulted in a significant increase in heart rate and development of PVCs, as well as an increased prevalence of ventricular tachycardia⁹. In another report, Higgins calculated 26.3% of patients receiving nebulized salbutamol developed an arrhythmia.¹⁰ Furthermore, a recent case has described a young patient who developed atrial fibrillation subsequent to use of a salbutamol MDI equipped with a spacer device.¹²

In light of these observations, special considerations regarding the use of a beta₂-agonist in a population already at high risk of developing arrhythmias, such as those undergoing thoracic surgery, must be taken. It has been shown that patients undergoing a pneumonectomy have a high risk of further morbidity and mortality.^{13,14} In one instance, 22% of such patients developed tachydysrhythmias following surgery. Of these, it appears that atrial fibrillation occurs most frequently.^{14,15} The role of agents which may aggravate arrhythmias in this setting is not well studied but one would anticipate that agents such as beta₂-agonists would be contributory.

Following the provision of this information to the thoracic surgeons, we observed a subsequent change in prescribing habit whereby routine beta₂-agonist use declined in terms of both frequency and duration and we wished to quantify and describe the impact of this change. Therefore, the objective of this study was to evaluate the clinical effects and economic impact of the change in prescribing habit. Specifically, we wished to assess beta₂-agonist use, cost and clinical endpoints including development of arrhythmia and hospital stay.

METHODOLOGY

All patients admitted to the thoracic surgery service who underwent thoracotomy during two, eight-week periods were identified retrospectively from hospital admission lists.

The first eight-week period, from March 1992 to April 1992, occurred prior to the provision of drug information and the subsequent change in prescribing habit (Period A). The second eight-week period, from August 1992 to September 1992, followed the educational intervention (Period B). The educational intervention consisted of a letter complete with references to each of the two thoracic surgeons and two fellows. The letter reviewed the risks and benefits of inhaled beta₂-agonist use and provided similar information as that found in the introduction.

The records identified each of the patients who underwent thoracotomy retrospectively and without exclusion for age or admitting diagnosis. Each record was reviewed and the data collected on a pre-developed data sheet included demographic information (age, sex, drug therapy on admission), medical history, baseline electrocardiogram, and pulmonary function test results. For the purposes of this study, a

patient was considered to have OAD if FEV₁ was less than 66% predicted and Forced Expiratory Ratio (FER) was less than 66%, or the patient had been receiving bronchodilator therapy prior to admission. Beta₂-agonist utilization, namely route, dose, frequency, and duration of therapy during the hospital admission was recorded. All patients received perioperative continuous ECG monitoring for at least 48 hours and were observed for the development and treatment of cardiac arrhythmias including atrial fibrillation, sinus tachycardia (which is defined as a heart rate greater than 110 bpm for at least one hour duration) or bigeminy. These ECG endpoints were also recorded.

Data were analyzed using the Epistat computer program. Student's t-test, Fisher's Exact test with probability being converted to a two tailed test, and Wilcoxon Rank Sum test were used as appropriate. A p value of less than 0.05 was considered to be significant. All data are expressed as means +/- SD unless otherwise indicated.

RESULTS

Over a period of 16 weeks, the medical records of 41 patients were reviewed and included in the study. Twenty-four patients were included in Period A and 17 in Period B. There were no significant differences between these two patient samples in terms of age, sex, history of OAD, or risk factors for the development of an arrhythmia (Table I). All patients received salbutamol via MDI format.

During the two periods, a similar proportion of patients received perioperative salbutamol, 18 of 24 in Period A and 10 of 17 in Period B (p=0.448). The average total salbutamol dose received per patient during Period A (6.85 ± 5.69 g) was greater than in Period B (2.64 ± 4.44 g) (p<0.05) (Table II).

Two patients from Period A and one from Period B were receiving digoxin prior to admission. In the remaining patients, 5 of 22 (23%) in Period A subsequently developed atrial fibrillation requiring digoxin as compared to only 1 of 16 (6%) in Period B (p=.36) (Table III).

During Period A, a total of 545 treatments were administered, an average of approximately 23 treatments per patient. At a cost of \$4.89 per treatment, this equates to a cost of \$112.47 per patient. During Period B, a total of 153 treatments (or approximately nine treatments per patient) were administered. This equates to \$44.01 per patient. Hence,

the potential cost-avoidance per patient would be \$68.46.

The length of hospital stay was not affected by salbutamol utilization (p = 0.85) The average length of hospital stay during Period A was 10.2 ± 5.0 days and averaged 9.4 ± 3.7 days in Period B.

DISCUSSION

This retrospective review has demonstrated that a change in prescribing habits occurred following the provision of drug information. The significant reduction in salbutamol utilization was associated with a reduction in medication expenditure and a trend

Table I: Demographic Data of Patients Surveyed

	PERIOD A	PERIOD B	p value
Number of Patients	24	17	
Age (yrs)	60.0 ± 17.6	62.2 ± 10.7	0.65
Sex (M/F)	15/9	10/7	0.53
OAD*	5/24	9/17	0.12
CRF*	0.71 ± 1.04	0.47 ± 0.62	0.41

* OAD -Obstructive Airways Disease defined as FER < 66% and FEV₁ <66% predicted or beta₂-agonist use prior to admission
 * CRF - Mean number of Cardiac Risk Factors expressed per patient for arrhythmias including myocardial infarction, hypertension, ischemic heart disease, previous arrhythmias

Table II: Salbutamol Utilization

	PERIOD A	PERIOD B	p value
No. of patients receiving salbutamol(%)	18/24 (75)	10/17 (59)	p=0.45
mean total salbutamol dose (g) per patient (n)	6.85 ± 5.69 (24)	2.64 ± 4.44 (17)	p<0.05
total number of treatments received	545	153	

Table III: Clinical Outcome Indicators

	PERIOD A	PERIOD B	p value
No. patients receiving digoxin prior to admission	2	1	
No. patients requiring digoxin (%)	5/22 (22.7)	1/16 (6.25)	p=0.36
Length of Hospital Stay (days)	10.2 ± 5.0	9.4 ± 3.7	p=0.85

to reduced toxicity without altering hospital stay.

The reduction in toxicity was observed only upon subgroup analysis in those patients without OAD. This subgroup analysis may explain, in part, why there was no overall reduction in hospital stay. Alternatively, it may be other aspects of postoperative recovery such as ability to ambulate, removal of chest tubes and intravenous catheters following surgery and not the development of arrhythmias per se that are the rate-limiting steps to discharge. Nonetheless, toxicity may be important in some patients though our data do not confirm this. Even if the stay was not prolonged, the need for antiarrhythmic therapy (i.e., digoxin) that is often continued for up to three months has the potential to cause morbidity.

Of note, the proportion of patients receiving aerosol bronchodilators was not different between the two periods, but the amount of beta₂-agonist use was. It was likely that infrequent conventional doses of beta₂-agonists could be tolerated by most patients, but as frequency and dose increase so, in all likelihood, does the risk of arrhythmia. The use of the spacer device, described in literature and used here, increases deposition and may increase toxicity as already described.¹² Furthermore, the postoperative patient who is beta₂-agonist naive may be at increased risk of toxicity in this setting.

The literature would suggest that the incidence of atrial dysrhythmias ranges from 6% to 29% in patients undergoing pneumonectomy.¹³ Over the 16-week period of our study, six (15%) patients developed new onset atrial fibrillation requiring digoxin. Three of these patients

had undergone a pneumonectomy. Of interest, 83% (5/6) of these cases occurred during Period A.

This study was limited by the small size and retrospective design. The power of such a review does not demonstrate whether an association between perioperative bronchodilators and arrhythmia development exists. This, of course, would require further recruitment of patients. Although the difference between the two groups in this respect was not significant, the apparent trend may warrant caution in using beta₂-agonists perioperatively and the need to observe these patients more closely. As well, because of the retrospective nature of the study, the documentation, particularly of arrhythmias, may be incomplete. While we do not know if this was an issue in our study, the fact that neither the nursing staff nor the location were altered during the relatively short time between periods favours consistent documentation.

Another limitation was that the information was presented to the thoracic fellows prior to the change in prescribing habits that occurred coincidentally with the change in the fellows. Even during those periods prior to the change, the liaison pharmacist periodically encountered patients who developed dysrhythmias while on salbutamol therapy and intervened on their behalf. Theoretically, this may have biased the study in a negative fashion in that some of the patients in Period A did not receive beta₂-agonists. This would diminish the differences between the groups, further supporting our findings.

There are, however, situations where the beta₂-agonists should be used. Their safety profile in patients is well established and the drug may be indicated in

patients with OAD. Although not one of our original objectives, subgroup analysis revealed an interesting observation in those patients without OAD who received salbutamol. While in patients with OAD there was no difference in the proportion of patients who received perioperative salbutamol and who developed arrhythmias, there was a difference in those patients without OAD with 9/16 (56%) of those who received the drug developing an arrhythmia versus only one of 11 (9%) in those who did not receive beta₂-agonists ($p=0.032$). While the conclusions that can be drawn from subgroup analysis are limited, this may offer further support to the fact that in the absence of proven benefit, that the drug should not be given.

The benefit from beta₂-agonists in improving MCC shown in past studies may well be due to the utilization of nebulized saline. Sutton et al showed no improvement in sputum clearance when terbutaline was added to a regimen of nebulized saline accompanied by chest physiotherapy.⁴ Whether this translates into a reduction of complications such as atelectasis or pneumonia was not assessed. Further support for this lack of beta₂-agonist effect comes from Isawa et al who showed that MDI administered bronchodilator provided no benefit to sputum clearance.⁷ On the basis of this, it would appear that beta₂-agonists have a limited role in this area.

Studies of prescribing changes may also look at cost-effectiveness or cost-avoidance.¹⁶ If we conclude from this study that the effectiveness of perioperative bronchodilators is equivocal, then a potential cost-avoidance may be realized. With perioperative bronchodilators being admini-

stered by respiratory therapists, there is a substantial cost associated with therapy, both in terms of drug and personnel costs. Currently, the average cost per treatment at Victoria Hospital is \$4.89. This study illustrated that the change in prescribing habit resulted in a potential average cost-avoidance of \$68.46 per patient. If only 10 patients per month (41 having been studied over a four-month trial) were to be managed utilizing this new practice, a yearly cost-avoidance of approximately \$8200.00 would be realized. A number of other surgical disciplines also use this therapy for perioperative care. In our institution last year, approximately 550 adult surgical patients received bronchodilator therapy. Assuming only one-half of those patients' therapies were altered, a cost-avoidance of more than \$18,000 per annum could be realized.

In conclusion, this study has illustrated that a reduction in the use of perioperative bronchodilators following the provision of information occurred without deleterious effects on patient outcome. Additional patient recruitment would be necessary

to identify whether there is an association between the use of these bronchodilators and arrhythmia development. As well, a considerable cost-avoidance may be realized with this new practice. ☒

REFERENCES

1. Van As A. The role of selective beta₂-adrenoceptor stimulants in the control of ciliary activity. *Respiration* 1974;31:146-51.
2. Verdugo P, Johnson NT, Taur PY. Beta-adrenergic stimulation of respiratory ciliary activity. *J Appl Physiol* 1980;48:868-71.
3. Iravani J, Melville GN. Mucociliary function of the respiratory tract as influenced by drugs. *Respiration* 1974;31:350-7.
4. Sutton PP, Gemmell HG, Innes N, et al. Use of nebulized saline and nebulized terbutaline as an adjunct to chest physiotherapy. *Thorax* 1988;43:57-60.
5. Lafortuna CL, Fazio F. Acute effect of inhaled salbutamol on mucociliary clearance in health and chronic bronchitis. *Respiration* 1984;45:111-23.
6. Pavia D, Bateman JR, Sheahan NF, et al. Clearance of lung secretion in patients with chronic bronchitis; effect of terbutaline and ipratropium bromide aerosol. *Eur J Resp Dis* 1980;61:245-53.
7. Isawa T, Teshima T, Hirano I, et al. Does a B₂-stimulator really facilitate mucociliary transport in the human lungs in vivo? A study with procaterol. *Am Rev Resp Dis* 1990;141:715-20.
8. Jenkins SC, Heaton RW, Fulton T, et al. Comparison of domiciliary nebulized salbutamol from a metered-dose inhaler in stable chronic airflow limitation. *Chest* 1991;6:804-7.
9. Banner AS, Sunderrajan EV, Argarwal MK, et al. Arrhythmogenic effects of orally administered bronchodilators. *Arch Intern Med* 1979;139:434-7.
10. Higgins RM, Cookson WOCM, Lane DJ, et al. Cardiac arrhythmias caused by nebulized beta-agonist therapy. *Lancet* 1987;ii:863-4.
11. Crane J, Burgess C, Beasley R. Cardiovascular and hypokalemic effects of inhaled salbutamol, fenoterol, and isoprenaline. *Thorax* 1989;44:136-40.
12. Breeden C, Safirstein B. Albuterol and spacer-induced atrial fibrillation. *Chest* 1990;98:762-3.
13. Wahi R, McMurtrey MJ, DeCaro LF, et al. Determinants of perioperative morbidity and mortality after pneumonectomy. *Ann Thorac Surg* 1989;48:33-7.
14. von Knorring J, Lepantalo M, Lindgren L, et al. Cardiac arrhythmias and myocardial ischemia after thoracotomy for lung cancer. *Ann Thorac Surg* 1992;53:642-7.
15. Krowka MJ, Pairolero PC, Trastek VF, et al. Cardiac dysrhythmia following pneumonectomy. *Chest* 1991;4:491-5.
16. Gayman J, Tapley D. Drug-usage evaluation and the patient-care pharmacist: A synergistic combination. *Top Hosp Pharm Manag* 1991;11:31-43.