Does dexamethasone enhance control of acute cisplatin induced emesis by ondansetron?

J F Smyth, R E Coleman, M Nicolson, W M Gallmeier, R C F Leonard, M A Cornbleet, S G Allan, B K Upadhyaya, U Bruntsch

Abstract

Objective—To determine the contribution of dexamethasone to the efficacy of the 5-hydroxytryptamine antagonist ondansetron in control of cisplatin induced nausea and vomiting.

Design—Randomised double blind crossover study.

Setting—Two cancer centres in teaching hospitals, one in the United Kingdom and the other in Germany.

Subjects—100 patients (53 men and 47 women) new to cisplatin chemotherapy, 84 of whom completed two consecutive courses of chemotherapy.

Interventions—Patients were given intravenous dexamethasone (20 mg) or physiological saline with intravenous ondansetron 8 mg before cisplatin, then ondansetron 1 mg/h for 24 hours. Oral ondansetron 8 mg was taken three times daily on days 2-6.

Main outcome measures—Incidence of complete or major control of emesis (0-2 episodes in the 24 hours after chemotherapy).

Results—Complete or major control was obtained in 49 out of 71 (69%) of patients after receiving ondansetron plus dexamethasone compared with 40 out of 71 (56%) when they were given ondansetron alone ($p=0.012$). This effect was most pronounced in the first 12 hours after chemotherapy. Patients receiving the combination also had significantly less nausea. Of the 53 patients who expressed a preference, 38 (72%) preferred the combination treatment ($p=0.002$) to ondansetron alone. The effect of ondansetron on delayed emesis was less pronounced.

Conclusions—Dexamethasone makes a significant contribution to the efficacy of ondansetron in the control of acute platinum induced emesis.

Imperial Cancer Research Fund Medical Oncology Unit, Western General Hospital, Edinburgh EH4 2XU
J F Smyth, MD, *professor*
R E Coleman, MD, *senior registrar*
M Nicolson, MSC, *unit pharmacist*
R C F Leonard, MD, *senior lecturer*
M A Cornbleet, MD, *consultant physician*
S G Allan, MD, *senior registrar*

Klinikum Nord, Nürnberg, Germany
W M Gallmeier, MD, *medical oncologist*
U Bruntsch, MD, *consultant medical oncologist*

Glaxo Group Research Limited, Greenford, England
B K Upadhyaya, PHD, *senior clinical research scientist*

Correspondence and requests for reprints to: Professor Smyth.

BMJ 1991;303:1423-6

Introduction

Cisplatin is one of the most emetogenic chemotherapeutic agents and treatment with high doses produces acute nausea and vomiting in all patients within 24 hours unless antiemetic drugs are used.[1] Partial control of emesis can be obtained, but none of the widely used antiemetic drugs is fully effective. Furthermore, high doses of antiemetic drugs such as metoclopramide, which act by antagonism at central dopamine receptors, may produce extrapyramidal effects in up to 10% of patients.[2]

Ondansetron is a selective 5-hydroxytryptamine receptor antagonist which is devoid of any effects on dopamine receptors.[3] It can usually prevent emesis and nausea produced by chemotherapy[4] or radiotherapy.[5] In controlled studies ondansetron has been shown to be superior to high dose metoclopramide in preventing cisplatin induced emesis and nausea.[6] However, emesis and nausea in about 30% of patients remains inadequately controlled by ondansetron. Dexamethasone is known to have antiemetic properties, especially when used in high dosage.[7] Its mechanism of action is unknown, but we have shown that dexamethasone can enhance the efficacy of metoclopramide in treating cisplatin induced emesis.[8]

In a recent study in ferrets treated with cyclophosphamide considerable enhancement of the antiemetic effect of a suboptimal dose of ondansetron was shown when it was combined with dexamethasone.[9] Recent pilot studies have shown an increased clinical effectiveness of ondansetron when given with dexamethasone for preventing emesis in patients who were refractory to ondansetron treatment.[10,11]

We compared the clinical efficacy and safety of ondansetron alone and in combination with dexamethasone in the prophylaxis of nausea and vomiting in the first 24 hours after cancer chemotherapy with cisplatin. We also studied the efficacy and safety of ondansetron alone in the prophylaxis of delayed nausea and vomiting (on days 2-6) induced by cisplatin.

Patients and methods

The study comprised 100 patients (53 men and 47 women) with various malignancies and a median age of 51 years (range 18-74 years) who were receiving their first course of cancer chemotherapy with cisplatin 100 mg/m^2 over one hour and scheduled to receive at least two courses. It was conducted at one centre in the United Kingdom and one in Germany and was approved by their respective local ethics committees. Consent was obtained from each patient before participation in the study. Patients were considered ineligible if they were clinically jaundiced, had active peptic ulceration, had vomited in the 24 hours before chemotherapy or had received antiemetics during this period, or were receiving concurrent benzodiazepines (except for night sedation).

The study had a randomised, double blind, crossover design. Randomisation was computer generated by using a patient allocation for clinical trials program. All patients were inpatients for at least 24 hours. According to the randomisation code, patients first received either intravenous dexamethasone (20 mg) or physiological saline 30 minutes before receiving cisplatin. The injections were blinded by the hospital pharmacist. This was followed by a slow intravenous injection of 8 mg of ondansetron and an infusion of ondansetron at 1 mg/hour for 24 hours, starting 15 minutes before the cisplatin infusion. At the end of the 24 hour infusion of ondansetron patients started taking oral ondansetron (8 mg), which was continued three times a day for five days (days 2-6), on an outpatient basis.

Patients were monitored for the first 24 hours, and the time and number of vomits and retches recorded. If

any patient totally failed to respond—that is, experienced more than five episodes of vomits or retches, or both, in the 24 hours after starting to receive cisplatin—then he or she could be given an antiemetic as a rescue medication. At the end of the first 24 hours an overall assessment of nausea and appetite was made by the patient according to the scale shown in the box. Any adverse events during this period were recorded.

A blood sample was taken for routine haematological testing; measurement of urea, creatinine, and electrolyte concentrations; and liver function tests (bilirubin, concentration and aspartate aminotransferase, alanine aminotransferase, and γ-glutamyltransferase activities) before treatment and at 24 hours and seven days later. On days 2-6 the patients were asked to complete a diary card daily for each preceding 24 hour period of the outpatient oral treatment. The number of vomits or retches, graded values for nausea and appetite, the number of ondansetron tablets taken, and any other symptoms of note were recorded. Patients receiving modified doses of cisplatin (because of renal toxicity) in the second or subsequent courses were allowed to continue. After completion of the second course patients were asked to indicate which antiemetic treatment they preferred. The study code was not broken and patients continued to receive four further courses of randomised, double blind, crossover treatments.

A total of 100 patients were estimated to give the study a power of 0·8 at the 5% significance level to discriminate between overall success rates (0-2 emetic episodes) of 65% with ondansetron plus dexamethasone and 45% with ondansetron alone. Sixty patients were recruited from the British centre and 40 from the German centre. The analyses included tests for interaction between treatment and centre. The primary response to antiemetic treatment was based on the percentage of patients who experienced complete or major (0-2 emetic episodes) control of emesis over the first 24 hours. An emetic episode was defined as any vomit productive of liquid or 1-5 retches within a five minute period. The time to first emetic episode during the first 24 hours was calculated from the records of vomits and retches. If the number of emetic episodes was 0, the time to first emetic episode was censored at 24 hours and an arbitrary value of 25 hours used in the analysis of ranked times. Data were analysed on the basis of intention to treat for all patients completing the first two courses and for patients considered fully evaluable by adequate protocol compliance over those courses.

The number of emetic episodes was compared between treatments by using non-parametric methods for a crossover design based on Wilcoxon rank sum tests.[12] The response to treatment was graded a success if the patient experienced 0-2 emetic episodes and a failure otherwise. These binary response data were analysed according to methods appropriate to the crossover design.[13,14] The patient preference data were analysed by Prescott's method.[13] Emetic response data from the first course only were also analysed by Mantel-Haenszel χ^2 test.

Grading of nausea, emesis, and appetite after cisplatin chemotherapy

Vomits/retches:
- 0=Complete control
- 1-2=Major control
- 3-5=Minor control
- >5=Failure

Appetite:
- 1=Better than usual
- 2=As usual
- 3=Could take some solids
- 4=Could take only liquids

Nausea:
- None
- Mild —did not interfere with normal daily life
- Moderate—interfered with normal daily life
- Severe —bedridden due to nausea

Results

Of the 100 patients entered into the study, 84 completed two consecutive courses; 65, three courses; 46, four courses; 28, five courses; and 21, six courses. Demographic characteristics at entry including tumour site(s) were similar for the 53 patients starting treatment with ondansetron and the 47 starting with ondansetron plus dexamethasone. Seventy one of the 84 patients completing two courses of chemotherapy showed adequate compliance with the protocol over both courses. Table I gives the reasons for 16 patients not progressing to the second chemotherapy course and 13 patients not being considered fully evaluable.

The results below refer to efficacy based on intention to treat analysis. The results for the fully evaluable patients were similar and are referenced as appropriate.

EMETIC RESPONSE

Table II shows the control of emesis during the 24 hours after treatment with cisplatin and table III the primary response rates in the 84 patients completing both courses. There was no evidence of treatment by period interaction. The fully evaluable patients also showed a significantly greater response with the combination of ondansetron plus dexamethasone (49/71, 69%) than with ondansetron alone (40/71, 56%) (p=0·035). Analysis of course 1 data (as parallel group) showed complete plus major response in 32 out of 53 (60%) patients randomised to ondansetron and 35/47 (74%) to the combination. Although the combination provided a clinically superior response, the power was insufficient to show a significant difference (p=0·137).

The time to the first emetic episode was delayed with dexamethasone (p<0·001); 33 (39%) of patients given

TABLE I—*Reasons for withdrawal of patients after course 1 and protocol violations during courses 1 or 2*

Reason	Treatment sequence: Ondansetron alone then ondansetron plus dexamethasone	Treatment sequence: Ondansetron plus dexamethasone then ondansetron alone
Not progressing beyond course 1		
Death	3	2
Cisplatin toxicity	2	2
Poor emesis control	1	2
Physician's decision	3	
Severe constipation		1
Protocol violation during course 1 or 2		
Concurrent benzodiazepines	3	1
Pretreatment vomiting	2	1
Incorrect cisplatin infusion	1	2
Prior cisplatin chemotherapy	1	
Ondansetron infusion <24 h		1
Concurrent antiemetics	1	

TABLE II—*Control of emesis and nausea during 24 hours after treatment with cisplatin. Figures are numbers (percentages) of patients*

Response	Ondansetron alone	Ondansetron plus dexamethasone
Emesis control* (vomits and retches):		
Complete (0 episodes)	35 (42)	49 (58)
Major (1-2 episodes)	12 (14)	9 (11)
Minor (3-5 episodes)	10 (12)	7 (8)
Failure (>5 episodes)	27 (32)	19 (23)
Nausea grade†:		
None	27 (33)	43 (52)
Mild	26 (32)	20 (24)
Moderate	25 (30)	17 (21)
Severe	4 (5)	2 (3)

*Complete plus major; p=0·012 (Prescott's test based on binary response).
†p<0·001 (Prescott's test for treatment with better grade).

TABLE III—*Number of patients with complete or major control of acute emesis after courses 1 and 2*

Treatment sequence	Response (course 1, course 2)*				
	Failure, failure	Failure, success	Success, failure	Success, success	Total
Ondansetron alone then ondansetron plus dexamethasone	12	5	6	21	44
Ondansetron plus dexamethasone then ondansetron alone	8	0	12	20	40
Total	20	5	18	41	84

*Success=0-2 emetic episodes, failure=>2 emetic episodes.
Success rates: 47/84 (56%) with ondansetron, 58/84 (69%) with ondansetron plus dexamethasone. Difference=11/84 (13%); approximate 95% confidence interval 2 to 24; $\chi^2=6{\cdot}37$, df=1, p=0·012.

TABLE IV—*Patients' preference for treatment by treatment sequence*

Treatment sequence	Preferred treatment		
	Ondansetron alone	Ondansetron plus dexamethasone	No preference
Ondansetron alone then ondansetron plus dexamethasone	7	19	16
Ondansetron plus dexamethasone then ondansetron alone	8	19*	12

*p=0·002.

ondansetron alone experienced an emetic episode within the first 12 hours compared with 10 (12%) given the combination. The median times to the first emetic episode for the respective treatments were 18·9 hours and >24 hours. These differences were also evident in the fully evaluable patients.

NAUSEA GRADE

Eighty three (99%) patients had not had any pretreatment for nausea. The grades of nausea for each treatment 24 hours after treatment with cisplatin are shown in table II. Of the 45 patients with different grades when receiving the two treatments, 35 showed a better grade with ondansetron plus dexamethasone than with ondansetron alone (p<0·001). For the 38 fully evaluable patients who had different grades when receiving the two treatments, 28 favoured the combination (p=0·003).

TREATMENT PREFERENCE

Table IV gives the distribution of patient preference. Preference for the combination was significant (38/53 (68%); p=0·017) in the fully evaluable group.

DELAYED EMESIS AND NAUSEA

For both treatment groups continuing to take oral ondansetron the control of emesis and nausea over days 2-6 was similar. Despite effective acute control delayed nausea and vomiting was still a major problem. On day 2 only 23/84 (27%) of patients experienced no vomiting and 11 (13%) reported no nausea; 37 (46%) of patients had >2 vomits, and 47 (56%) had moderate or severe nausea. During days 3-6, the severity of emesis subsided, but on day 6, 24 (29%) of patients were still vomiting and 35 (42%) experiencing nausea.

SAFETY

Adverse events reported during treatment for up to six courses were headache in 17/98 (17%) patients receiving ondansetron alone and 13/91 (14%) patients receiving ondansetron plus dexamethasone; constipation in 15/98 (15%) and 21/91 (23%) patients; diarrhoea in 16/98 (16%) and 5/91 (5%) patients; and transient increases in the results of liver function tests in 15/98 (15%) and 18/91 (19%) patients respectively. Two major adverse events were thought probably to be related to antiemetic treatment. One patient had severe constipation after the first course and required readmission to the hospital and withdrawal from the study. The other patient had a rise in aspartate aminotransferase activity from 13 to 111 U/l at 24 hours after starting treatment with intravenous ondansetron and did not proceed with oral treatment; the activity returned to baseline level spontaneously and the patient continued in the study for a further two courses.

Discussion

There were significant improvements in the antiemetic efficacy of ondansetron when it was given in combination with dexamethasone. Corticosteroids possess limited intrinsic antiemetic activity but when given in combination substantially enhance the efficacy of several antiemetic drugs.[8 15 16] The exact mechanism of the antiemetic action of corticosteroids when given singly or in combination is not clearly understood.

In this study of patients receiving chemotherapy comprising 100 mg/m^2 of cisplatin, ondansetron completely prevented acute emesis (during the first 24 hours after treatment) in 42% of patients compared with 58% of those receiving dexamethasone. The combination of ondansetron and dexamethasone also provided significantly greater complete plus major control (0-2 episodes) of acute emesis than ondansetron alone (69% *v* 56%). The differences in antiemetic efficacy were significant for analysis both by intention to treat (p=0·012) and of the fully evaluable (p=0·035) patient population. Although there was no significant evidence of any treatment and centre interactions, examination of the data on efficacy of treatment and treatment preference showed that the advantage of dexamethasone was more apparent in the British centre.

Our observations support, although do not match, the data of Roila *et al.*[17] In their study complete control of cisplatin induced emesis was achieved in 91% of patients treated with a combination of ondansetron and dexamethasone compared with 64% given ondansetron alone. Also, in agreement with this study, acute nausea induced by cisplatin was controlled more effectively by ondansetron when it was given with dexamethasone. In all, 80% of patients receiving the combination treatment graded their nausea within 24 hours as none or mild compared with 68% of patients treated with ondansetron alone.

Double blind crossover studies can be useful in providing information such as a patient's preference for treatment. In this study patient preference was assessed after the completion of both treatment courses. Of the 53 patients indicating a preference, 38 (72%) preferred the combination treatment compared with 15 (28%) who preferred treatment with ondansetron alone (p=0·002).

The superior control of emesis with ondansetron and dexamethasone in the first 24 hours did not seem to influence the pattern of delayed nausea and vomiting, which still affected most of the patients, being particularly troublesome on day two. The persistence of delayed nausea and vomiting despite treatment with ondansetron suggests that a different mechanism(s), and presumably neurotransmitter(s), are involved. A short course of oral dexamethasone has been shown to enhance the efficacy of metoclopramide in treating delayed nausea and vomiting.[18] The role of prolonged administration of the study drugs should be investigated in a randomised controlled study.

Ondansetron given intravenously with or without dexamethasone followed by oral treatment as a single agent was safe and tolerated well for up to six courses of chemotherapy. Mild or moderate headache, constipation, and diarrhoea were the most commonly reported transient adverse events with both treatments. Any observed increases in serum activities of

aspartate aminotransferase, alanine aminotransferase, or γ-glutamyltransferase were transient and asymptomatic.

We conclude that dexamethasone clearly improves the antiemetic efficacy of ondansetron for the control of acute nausea and vomiting after high dose chemotherapy with cisplatin. It remains to identify the optimum antiemetic chedule to minimise delayed emesis as the next step in improving the acceptability of treatment to patients.

1 Lazlo J, Lucas VS Jr. Emesis as a critical problem in chemotherapy. *N Engl J Med* 1981;305:948-9.
2 Allan SG, Cornbleet MA, Lockhart SP, Warrington PS, Leonard RCF, Smyth JF. Emesis due to cancer chemotherapy: results of a prospective, randomised, double-blind trial of varying doses of metoclopramide in the management of cisplatin-induced vomiting. *European Journal of Cancer and Clinical Oncology* 1984;20:1481-4.
3 Tyers MB, Bunce KT, Humphrey PPA. Pharmacological and anti-emetic properties of ondansetron. *European Journal of Cancer and Clinical Oncology* 1989;25(suppl 1):S15-9.
4 Marty M. Ondansetron in the prophylaxis of acute cisplatin-induced nausea and vomiting. *European Journal of Cancer and Clinical Oncology* 1989;25 (suppl 1):S41-5.
5 Priestman TJ. Clinical studies with ondansetron in the control of radiation-induced emesis. *European Journal of Cancer and Clinical Oncology* 1989;25 (suppl 1):S29-33.
6 Marty M, Pouillart P, Scholl S, Droz JP, Azab M, Brion N, *et al*. Comparison of the 5-hydroxytryptamine$_3$ (serotonin) antagonist ondansetron (GR38032F) with high dose metoclopramide in the control of cisplatin-induced emesis. *N Engl J Med* 1990;322:816-21.
7 Aapro MS, Alberts DS. High dose dexamethasone for prevention of cisplatin-induced vomiting. *Cancer Chemotherapy and Pharmacology* 1981;7:11-4.
8 Allan SG, Cornbleet MA, Warrington PS, Golland IM, Leonard RCF, Smyth JF. Dexamethasone and high dose metoclopramide: efficacy in controlling cisplatin-induced nausea and vomiting. *BMJ* 1984;289:878-9.
9 Hawthorn J, Cunningham D. Dexamethasone can potentiate the anti-emetic action of a 5HT$_3$ receptor antagonist on cyclophosphamide-induced vomiting in the ferret. *Br J Cancer* 1990;61:56-60.
10 Cunningham D, Turner A, Hawthorn J, Rosin RD. Ondansetron with and without dexamethasone to treat chemotherapy-induced emesis. *Lancet* 1989;i:1323.
11 Smith DB, Newlands ES, Spruyt OW, Begent RHJ, Rustin GJS, Mellor B, *et al*. Ondansetron (GR38032F) plus dexamethasone: effective anti-emetic prophylaxis for patients receiving cytotoxic chemotherapy. *Br J Cancer* 1990;61:323-4.
12 Koch GG. The use of non-parametric methods in the statistical analysis of the two-period change-over design. *Biometrics* 1972;28:577-84.
13 Prescott RJ. The comparison of success rates in crossover trials in the presence of an order effect. *Applied Statistics* 1981;30:9-15.
14 Hills M, Armitage P. The two-period crossover clinical trial. *Br J Clin Pharmacol* 1979;8:7-20.
15 Allan SG, Farquhar DF, Harrison DJ, Leonard RCF. Anti-emetic efficacy of dexamethasone in combination for outpatients receiving combination chemotherapy. *Cancer Chemotherapy and Pharmacology* 1986;18:86-7.
16 Benrubi GI, Norvell M, Nuss RC, Robinson H. The use of methylprednisolone and metoclopramide in control of emesis in patients receiving cisplatin. *Gynecol Oncol* 1985;21:306-13.
17 Roila F, Tonato M, Cognetti F, Cortesi E, Favalli G, Marangolo K, *et al*. A double-blind multi-centre randomised crossover study comparing the anti-emetic efficacy and tolerability of ondansetron vs ondansetron plus dexamethasone in cisplatin-treated cancer patients. *Proceedings of the American Society of Clinical Oncology* 1990;9:A1312.
18 Kris MG, Gralla RJ, Tyson LB, Clark RA, Cirrincione C, Groshen S. Controlling delayed vomiting: double-blind, randomised trial comparing placebo, dexamethasone alone, and metoclopramide plus dexamethasone in patients receiving cisplatin. *J Clin Oncol* 1989;7:108-14.

(Accepted 25 September 1991)

Bronchodilator treatment in moderate asthma or chronic bronchitis: continuous or on demand? A randomised controlled study

Constant P van Schayck, Edward Dompeling, Cees L A van Herwaarden, Hans Folgering, Andre L M Verbeek, Henk J M van der Hoogen, Chris van Weel

Abstract

***Objective*—To examine the effect of bronchodilator treatment given continuously versus on demand on the progression of asthma and chronic bronchitis and to compare the long term effects of a β_2 adrenergic drug (salbutamol) and an anticholinergic drug (ipratropium bromide).**

***Design*—Two year randomised controlled prospective crossover study in which patients were assigned to one of two parallel treatment groups receiving continuous treatment or treatment on demand.**

***Setting*—29 general practices in the catchment area of the University of Nijmegen.**

***Patients*—223 patients aged ≥30 with moderate airway obstruction due to asthma or chronic bronchitis, selected by their general practitioners.**

***Interventions*—1600 μg salbutamol or 160 μg ipratropium bromide daily (113 patients) or salbutamol or ipratropium bromide only during exacerbations or periods of dyspnoea (110). No other pulmonary treatment was permitted.**

***Main outcome measures*—Decline in ventilatory function and change in bronchial responsiveness, respiratory symptoms, number of exacerbations, and quality of life.**

***Results*—Among 144 patients completing the study, after correction for possible confounding factors the decline in forced expiratory volume in one second was −0·072 l/year in continuously treated patients and −0·020 l/year in those treated on demand ($p<0·05$), irrespective of the drug. The difference in the decline in patients with asthma was comparable with that in patients with chronic bronchitis (asthma: 0·092 *v* −0·025 l/year; chronic bronchitis: −0·082 *v* −0·031 l/year). Bronchial responsiveness increased slightly (0·4 doubling dose) with continuous treatment in chronic bronchitis, but exacerbations, symptoms, and quality of life were unchanged. Salbutamol and ipratropium bromide had comparable effects on all variables investigated.**

***Conclusions*—Continuous bronchodilator treatment without anti-inflammatory treatment accelerates decline in ventilatory function. Bronchodilators should be used only on demand, with additional corticosteroid treatment, if necessary.**

Nijmegen University, PO Box 9101, Nijmegen 6500 HB, The Netherlands
Constant P van Schayck, PHD, *research lecturer, department of general practice*
Edward Dompeling, MD, *research fellow, department of general practice*
Cees L A van Herwaarden, MD, *professor of pulmonology*
Hans Folgering, MD, *head, pulmonary function laboratory*
Andre L M Verbeek, MD, *senior lecturer, department of epidemiology*
Henk J M van der Hoogen, *statistician, department of general practice*
Chris van Weel, MD, *professor of general practice*

Correspondence to:
Dr C P van Schayck.

BMJ 1991;303:1426-31

Introduction

Asthma and chronic bronchitis are considered to be progressive diseases.[1,2] The hypothesis has been put forward that early continuous bronchodilator treatment of reversible airflow obstruction will improve their prognosis,[3] and this led to the recommendation to use continuous inhaled β_2 adrenergic drugs as a first step in treating chronic airflow obstruction.[4,5] However, recent reports indicate adverse effects caused by continuous use of β_2 adrenergic inhalants,[6-8] resulting in advice to reserve these drugs for treatment on demand.[8,9] Neither of these contradictory recommendations are based on evidence from intervention studies lasting long enough to establish an effect on decline in ventilatory function, which is generally believed to be the most important measure of progression of asthma or chronic bronchitis. Another question is which type of bronchodilator inhalant is more efficacious in long term treatment of asthma or chronic bronchitis: an anticholinergic drug or a β_2 adrenergic drug? Until now only the immediate bronchodilating effects of these drugs have been compared. Adverse effects of the continuous use of bronchodilators have