

Original articles

Summary

Generic substitution of salbutamol lags behind that of other drugs in Scotland and a negative perception by both patients and doctors may explain this. The aim of this study was to assess whether, in clinical practice, there was any difference in efficacy between branded salbutamol (Ventolin) and a generic preparation. Asthmatic patients using a Ventolin metered-dose inhaler at least twice a day for symptom relief were entered into a double-blind cross-over study, comparing Ventolin, blinded Ventolin and a generic salbutamol in random order for two weeks each. Daily peak flows, inhaler use and bronchodilator response were recorded. At the end of each treatment period patients rated their inhaler against their usual Ventolin on a 5-point scale. Forty patients were entered into the study; 90% received 1000 µg or more of inhaled steroids per day. Eleven patients dropped out during the run-in phase. In the remaining 29 patients, no significant difference between treatments could be found in any of the objective parameters measured. Fifty-five per cent of patients said they could detect a difference between the inhalers, and 45% noted a difference between their usual Ventolin and the open or blinded Ventolin. This study showed clinical equivalence between a generic and branded salbutamol. Patients' own assessment of their relief inhaler seems to be influenced by factors other than efficacy. The study highlights that careful encouragement is required when changing to a generic product and has particular implications for the forthcoming conversion to CFC-free products.

Keywords: salbutamol, generic prescribing

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Generic inhaled salbutamol versus branded salbutamol. A randomised double-blind study

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In the face of cost constraints and an escalating drug bill, general practitioners are encouraged to prescribe generically whenever possible. The overall rate of generic prescribing in Scotland is 45% but the use of generic inhaled salbutamol accounts for only 27% of prescriptions for salbutamol metered-dose inhalers. Anecdotally, we have found that there is a belief among some general practitioners and patients that generic inhaled salbutamol is inferior to the branded product (Ventolin). There is no evidence to support this and, indeed, a quality control study of all generic devices currently available has shown that generic metered dose inhalers deliver similar quantities of salbutamol to the branded version.¹ This study aimed to assess whether a commonly prescribed generic salbutamol is as effective as Ventolin in a clinical setting and whether patients' assessment of their relief inhaler is related to objective measures of outcome.

Patients and methods

Patients with physician-diagnosed asthma attending a hospital asthma clinic were considered for the study. Eligible patients had to be using a Ventolin metered-dose inhaler as their usual relief medication at least twice daily with a technique assessed as adequate by the Asthma Nurse. Patients who had received a course of oral steroids within the previous month were ineligible. The patients used a Wright's mini peak flow meter to record their peak flow rate before and 20 minutes after using their relief therapy on rising and once prior to therapy in the evening. After their morning dose they were asked to use their relief inhaler only when required and the number of puffs used daily was recorded.

After a two week run-in period on their usual Ventolin inhaler, patients used Ventolin, 'blinded' Ventolin and salbutamol (Norton Health Care) inhalers for two weeks each in random order; the latter two inhalers were delivered via similar blanked cartridges and white actuators. At the end of each two-week treatment period, patients underwent spirometry before and 20 minutes after using their relief inhaler, and were asked to compare their current relief inhaler with their usual Ventolin inhaler using a 5-point scale (much worse, worse, as good as, better, much better). At the end of the study period they were asked if there were any of the three inhalers they would not like their doctor to prescribe and whether they preferred any one inhaler to the other two.

Measure of reversibility were calculated as follows:

$$\frac{\text{PFR/FEV}_1 \text{ post-MDI} - \text{PFR/FEV}_1 \text{ pre-MDI}}{\text{PFR/FEV}_1 \text{ post-MDI}} \times 100$$

where PFR=peak flow rate, FEV₁=forced expiratory volume in one second, MDI=metered dose inhaler.

Data were analysed using two-way analysis of variance and paired *t*-test to estimate the 95% confidence limits for the differences between means.

Results

Forty asthmatic patients were recruited and all were taking prophylactic therapy and using their Ventolin inhaler at least twice a day. Patient details are given in table 1. Ninety per cent were on level 3 or above of the British Thoracic Society treatment guidelines for chronic asthma². Eleven patients dropped out during the run-in phase, usually for domestic or work-related reasons; one patient suffered an acute exacerbation during the run-in period and one was lost to follow-up. This group did not differ in terms of age, sex or treatment level from

Table 1 Patient details, treatment levels taken from British Thoracic Society guidelines for the management of chronic asthma

No patients:	40
Mean age (years) (SD):	37 (range 17–57)
Sex:	21 females, 19 males
Mean FEV ₁ /FVC% (SD):	73 (11)
Treatment level:	Step 2: 4 (10%) Step 3: 16 (40%) Step 4: 17 (42.5%) Step 5: 3 (7.5%)

Table 2 Objective measurements of efficacy for 29 patients completing study. There was no significant difference between any of the measurements. All figures are means (95% CI)

Treatment period	Run-in	Ventolin	Blinded Ventolin	Generic salbutamol
Morning PFR	359 (323–395)	353 (317–389)	361 (325–397)	363 (327–399)
Evening PFR	372 (335–409)	379 (342–416)	378 (342–414)	375 (337–413)
Reversibility PFR (%)	10 (7–13)	17 (11–23)	13 (9–17)	12 (9–15)
Reversibility FEV ₁ (%)	11 (7–15)	10 (6–14)	10 (7–13)	9 (5–13)
MDI usage puffs/24 h	6.0 (4.8–7.3)	5.9 (4.5–7.2)	6.2 (4.7–6.8)	5.9 (4.4–7.3)

Abbreviations: PFR: peak flow rate, FEV₁: forced expiratory volume, MDI: metered dose inhaler

Table 3 Mean differences and the 95% confidence intervals for differences between the means

	Open vs generic Ventolin	Blinded vs generic Ventolin
PFR reversibility (%)	5 (–1, 12) (p=0.1)	1 (–1, 4) (p=0.3)
FEV ₁ reversibility (%)	0 (–6, 6) (p=1.0)	0 (–6, 6) (p=1.0)
MDI usage (puffs/24 h)	0 (–0.6, 0.6) (p=1.0)	0 (–0.3, 1.0) (p=0.3)

Abbreviations: PFR: peak flow rate, FEV₁: forced expiratory volume, MDI: metered dose inhaler

Table 4 Patient response to the question 'compared with my usual Ventolin inhaler this inhaler was - - -' made at the end of each treatment period

	Much worse/worse	As good	Better/much better
Study Ventolin	2	24	3
Blind Ventolin	5	21	3
Generic	6	16	7

the remaining patients. Mean results in 29 patients of daily peak flow measurements, reversibility using peak flow and FEV₁ together with the 95% confidence intervals for the differences between the means, are given in tables 2 and 3. No significant differences were found between any of the measurements.

The patients' assessment at the end of each treatment period, comparing their current inhaler with their usual Ventolin inhaler, is shown in table 4. Only 13 patients (45%) were unable to detect any difference between the inhalers. When asked at the end of study period if there were any of the inhalers they would not like to have prescribed by their doctor, five said blinded Ventolin and six said generic. When asked which, if any, inhaler they preferred, three preferred Ventolin, two blinded Ventolin and six the generic.

Discussion

The study failed to find any objective evidence that generic salbutamol is in any way less effective than its branded counterpart in a clinical setting. Subjects prior to the study were all symptomatic, using relief medication at least twice daily, and 90% were at level 3 or above of the British Thoracic Society treatment guidelines, ie, requiring 1000 µg or more of inhaled steroid. The majority of patients were stable as reflected in the low mean diurnal variations, mean FEV₁ ratio and levels of reversibility. To have studied a more severe, unstable, group would have required a very prolonged or alternatively a very short period of follow-up on each inhaler and would have raised difficult logistic and interpretive problems. Although stable, our subjects required symptomatic relief several times a day and a two-week treatment period on each inhaler was considered an adequate period in which to make a comparative assessment of efficacy. It was certainly long enough for patients to have a view as to whether or not they thought their inhalers were as effective as their usual Ventolin. It is possible that a more sensitive dose-response type study might have shown

Learning points

- this study, in a group of moderate to severe asthmatics, demonstrates clinical equivalence between a generic salbutamol and Ventolin
- patients' own assessment of their relief inhaler is very subjective and should be viewed critically
- when changing inhaler brand, careful explanation and encouragement will be required to avoid patient dissatisfaction

differences in response at lower doses, but it is unlikely that this would have any clinical relevance given the standard dosage of relief medication in current use.

A beta-2 stimulant would not usually affect overall asthma control as measured by morning and evening peak flow readings but one might have expected to see a difference in the number of puffs of inhaler used in 24 hours if one inhaler was clinically less effective than another, since patients are asked to titrate their treatment against symptoms. Similarly, we might have expected a difference in the degree of reversibility measured on a daily basis or at the end of each treatment period, although again a dose-response study may have been able to detect differences at lower drug doses.

While only 29 patients completed the study, each acted as their own control, increasing the statistical power of the study. No significant differences between the means of any of the measurements were found and the 95% confidence limits for the differences between the means were narrow. We believe that it is unlikely that we missed a clinically significantly difference in drug efficacy in our patient group.

Despite the lack of objective evidence, 55% of patients said that they were able to detect a difference between the three inhalers. Positive and adverse scoring was spread fairly evenly between the three inhalers. Of particular interest were the five patients who thought that the open Ventolin provided in this study was superior or inferior to their usual Ventolin (used during the run-in period), while eight patients felt that blinded Ventolin was superior or inferior to their usual Ventolin, demonstrating perhaps a small 'placebo' effect of the brand name. Thus, 13 patients (45%) thought that there was a detectable difference between three identical preparations of branded salbutamol. It would seem reasonable to conclude that patients' reported response to a change in a metered-dose inhaler might be unreliable.

Given that generic inhalers deliver the same active compound in equivalent amounts to the branded product, the absence of any difference in efficacy is not surprising. Nevertheless, use of generic salbutamol lags behind the use of other generic products (28% generic salbutamol compared with 98% generic allopurinol in Scotland). Some doctors are reluctant to concede, in the absence of clinical data, that generic salbutamol is indeed as effective as the branded product.³ Part of this perception may be the negative feedback that doctors have received from patients which, as we have shown, can be highly suspect. Thus, in this study 38% of patients said they would not have liked at least one of the inhalers used in the study to be prescribed by their doctor.

This study provides clinical data to show that generic salbutamol is equivalent in efficacy to the branded product in the day-to-day control of a group of asthmatic patients who all require daily prophylactic therapy and relief medication for their asthma. Based on current usage and prices, if all patients currently using a Ventolin metered-dose inhaler were converted to the generic product, the savings in Scotland alone would be in excess of £1.5 million per annum. These savings would go some way to off-set the increasing costs of medication, generally encouraged as reflecting good quality asthma care.

For the future, our data on patients' own assessment of their relief inhaler suggests that a great deal of care will be required when converting patients from their usual inhaler to a CFC-free product. Fortunately data is now available showing that at least one CFC-free formulation is pharmacologically equivalent to the current branded product⁴ and this should help convince doctors at least, that the new product can be prescribed with confidence. Convincing the patient may prove more difficult.

1 Lee MG, Ireland DS, Dwyer PJ, Weir PJ. Comparison of salbutamol inhalers available in the United Kingdom. *Int J Pharm Pract* 1993; 2: 172-5.

2 Anon. Guidelines on the management of asthma. *Thorax* 1993; (suppl): 1-24.

3 Pearson M, Lewis R, Watson J *et al*. Generic inhalers for asthma. *BMJ* 1994; 309: 1440.

4 Taggart SCO, Custovic A, Richards DH, Woodcock A. GRI06642 X: a new non-ozone depleting propellant for inhalers *BMJ* 1995; 310: 1639-40.