



Ventolin to Salamol—a crossover study in New Zealand

Shane Reti

Abstract

Aims To assess asthma stability in adults converted from Ventolin® to Salamol®.

Methods Thirty-six general practice adults with documented asthma and using Ventolin at least weekly in the previous 12 months, changed their Ventolin for Salamol for a period of 4 weeks. The validated Asthma Control Questionnaire was applied at the beginning and end of the study period.

Results Of the 36 adults, 6/36 (17%; 95%CI 4–29%) prematurely withdrew mainly due to Salamol ineffectiveness. A further 15/36 (42%; 95%CI 25–58%) could not maintain Salamol alone and returned to Ventolin at some time during the study period with 10/15 (67%; 95% CI 42–91%) citing Salamol ineffectiveness. Of the remaining 15/36 who maintained the study design, nearly all had worse asthma stability 14/15 (93%; 95%CI 80–100%).

Conclusions Asthma stability was significantly worse with Salamol compared to Ventolin. Psychological features related to changing inhalers, different physical aspects of Salamol inhalers, and pharmacological ineffectiveness are possible explanations.

In July 1 2005, PHARMAC (the New Zealand body responsible for government-funded pharmaceutical subsidies) removed the subsidy on the Ventolin® metered dose inhaler (MDI) (salbutamol – GlaxoSmithKline) in favour of a chlorofluorocarbon (CFC)-free equivalent, Salamol® MDI (salbutamol – Baker Norton).

From February 2005, the government agency responsible for monitoring adverse drug reactions—Centre for Adverse Reactions Monitoring (CARM)—noted increasing reports relating to patients crossing over from Ventolin to Salamol, even “exceeding the normal capacity of CARM’s processing systems, and exceeding the usual reporting rate for brand switching complaints”.¹ The three main complaints were decreased therapeutic effect, blockage, and taste. Paediatricians also reported particular concerns for children converting to Salamol, and questioned the overall cost effectiveness of the crossover.²

A formal investigation was undertaken by Medsafe, the government agency responsible for registering pharmaceuticals, which primarily examining the functionality of both new (16 inhalers) and returned faulty inhalers (33 inhalers) against such measures as dose deposition, content uniformity, and average dose per actuation.

Medsafe’s report was published in December 2005 with the main finding pointing to device blockage as the likely main cause for decreased therapeutic effect.¹ Increased patient education and adherence to the manufacturer’s weekly cleaning recommendations was the suggested solution. Under these conditions, the testing of

Salamol appeared to pass appropriate laboratory tests of functionality, however it is a completely different issue to then discuss the clinical implications for asthmatics and the overall effects on their asthma stability”.

Several studies have demonstrated clinical equivalence between various salbutamol-containing MDIs with and without CFCs.³⁻⁸ One question is whether these findings can be generalised to all CFC-free salbutamol-containing MDIs, or whether company specific formulations and MDI design have differences that matter for asthma stability. Lumry et al drew attention to CFC-free salbutamol MDIs variably containing “excipients such as oleic acid, lecithin, or alcohol”.⁹

Lee has suggested that patient familiarity with the physical aspects of salbutamol inhalers is important for asthmatics.¹⁰ To this effect, there are few studies that specifically compare brand name Salamol with Ventolin as is being introduced in New Zealand. A 1996 randomised crossover study of 10 patients found both to be equally effective,¹¹ as did a 1994 crossover study of 11 patients.¹²

Comparing Salamol and Ventolin in the current New Zealand setting is significant in that New Zealand has the one of the highest asthma rates in the world (15% of adults, 20% of children¹³), the range of available asthma inhalers is less than in larger countries, and medication choice is mostly driven by government subsidies.

Ventolin has been the main stay of beta-agonist treatment for many years. In this context, this study examines the effects of converting asthma patients from Ventolin to Salamol.

Method

Subjects were computer selected from the general practice of the author with the following criteria:

- Registered patients aged 17 years and over at 1 April 2005.
- An existing diagnosis of asthma.
- Prescribed Ventolin in the previous 12 months.
- Using Ventolin at least weekly.

Subjects then met with the author (SR) who explained that the study was exploring the conversion from Ventolin to Salamol, that the author had faith in both, and safety measures associated with the study. Signed patient consent to participate was then obtained.

The author then applied the validated New Zealand version of the Asthma Control Questionnaire which is a combination of validated questions on asthma symptoms, limitations, inhaler usage, and a peak flow measurement.¹⁴ Demographic questions on age, gender and ethnicity were also asked.

Subjects were then given a prescription for Salamol, and instructed to completely replace Ventolin with Salamol for a period of 4 weeks. All existing medications, asthma and non-asthma related, were to remain unchanged.

Four weeks later, the patients were recalled for follow-up and the Asthma Control Questionnaire reapplied. During the study, any subjects who were unable to complete the study, or who had to return to Ventolin, were returned for consultation, and appropriate questioning made with responses recorded.

As per the questionnaire validation, a change in asthma stability was accepted as being a change of > 0.5 points on the questionnaire scale. The statistical means were calculated for all categories, with the standard error of the mean reported as 95% confidence intervals.

Results

Thirty-six subjects were initially enrolled in the study, 21 women and 15 men with an age range of between 17–76, and an average age of 48.83 years. None had hospital

admissions for asthma in the previous year; 18/36 (50%) were using a preventer daily, and the average percentage predicted peak expiratory flow rate was 70.11%.

Of the 36, 6/36 (17%; 95%CI 4–29%) withdrew during the month-long study period; 5 of the 6 (83%, 95% CI 53 – 100%) withdrew due to Salamol ineffectiveness, and the remaining subject withdrew citing the unpleasant taste of Salamol.

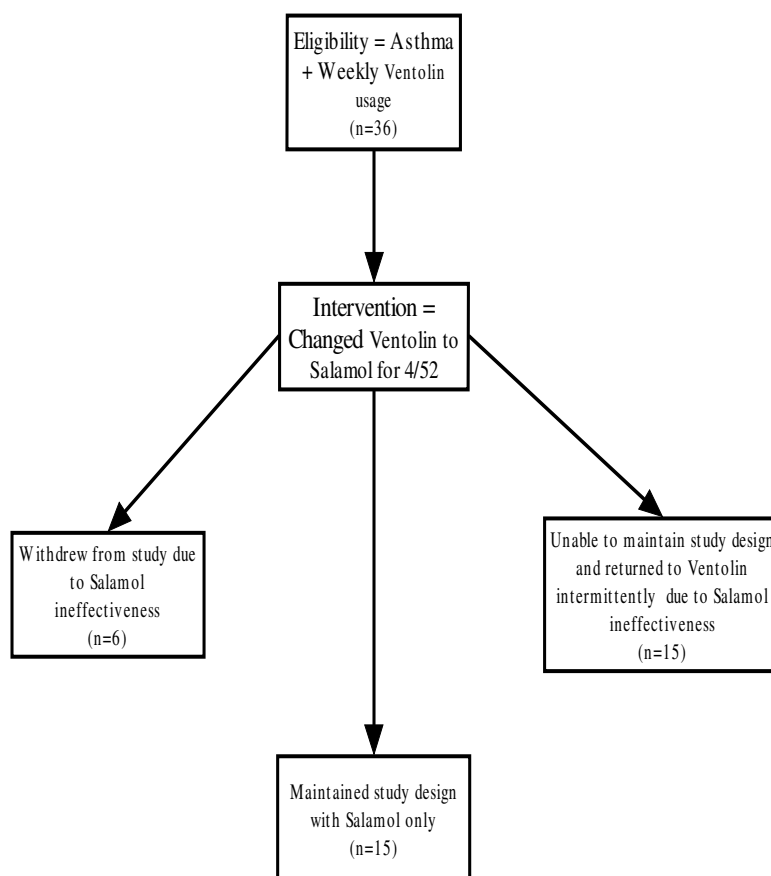
A further 15/36 of the original subjects (42%; 95%CI 25–58%) could not maintain Salamol alone, and had to return to Ventolin at some point during the month.

Of the 15 who returned to Ventolin, 10/15 (67%, 95%CI 42–91%) cited Salamol ineffectiveness, 1/15 device blockage, 3/15 the convenience of having Ventolin handy, and 1/15 gave no reason.

This left 15/36 (42%; 95%CI 25–58%) of the original subjects successfully maintaining ‘Salamol only’ as per the study design. Figure 1 shows a flow diagram of participant outcomes.

Assessment of asthma stability with the asthma control questionnaire showed 14/15 (93%; 95%CI 80–100%) had worse asthma stability, and the remaining subject had unchanged asthma stability; 2 of the 15 (13%; 95%CI 0–31%), who maintained Salamol only, gave possible influences on their asthma over the study period—both citing chest infections.

Figure 1. Flow diagram of participant outcomes



Discussion

Only 15 subjects out of 36 in this study were able to maintain the study design using Salamol; and in this group of 15, 93% has worse asthma stability.

For all study participants, Salamol ineffectiveness was a significant factor. However these findings need to be considered in the context of several potential limitations. Firstly, study numbers are small (this particularly limits demographic analysis), although consistent in size with several other asthma inhaler crossover studies.^{11,12,15}

Secondly, there are external variables such as the weather, pollen counts, winter chest infections, change in home or work environment or lifestyle, change in preventer use, and negative media that could have had an influence over the month-long study period. Most of these variables are discussed under the heading “Peripheral Related Factors”, and to summarise here, are not considered to be significant influences in this study.

Self directed changes in steroid usage could influence the findings, however none of the subjects completing the study reported changed their steroid inhaler usage. Furthermore, Bleecker et al demonstrated the non-significance of inhaled steroid use in a similar crossover study comparing Airomir® CFC-free (another CFC-free formulation of salbutamol) and Ventolin.¹⁶

There are several explanations for the findings of apparent ineffectiveness and deteriorated asthma stability on the crossover to Salamol. These can be considered under the headings patient-related, peripheral-related, or product-related factors.

Patient-related factors—Patient related factors primarily relate to how change alone, and not Salamol ineffectiveness, may contribute to the findings.

Indeed, anxiety, apprehension, and caution are likely to be the norm in a crossover study of this type, possibly precipitating an early return to a previous trusted inhaler. This uncertainty under change was demonstrated in a crossover study of 29 patients using either branded salbutamol, generic salbutamol, or their usual salbutamol (blinded).

Juniper concluded “patients’ own assessment of their relief inhaler seems to be influenced by factors other than efficacy”.¹⁵ If change is accepted as an operative factor, then with these two products the effect was further magnified by Salamol being significantly smaller in size than Ventolin, having a less forceful particle actuation, and having a different taste.

Lee has suggested that patient familiarity with the physical aspects of salbutamol inhalers is important for asthmatics.¹⁰ While change-related patient factors may well have contributed to subjects returning to Ventolin and reporting ineffectiveness, these factors cannot fully account for the 93% who maintained Salamol only, and who by ACQ testing had worse asthma stability.

Peripheral-related factors—These factors are outside the control of the study design and are known to have an influence in asthma, and could possibly have contributed to Salamol ineffectiveness. These factors include weather, pollen, chest infections, change in home or work environment or lifestyle, and negative media.

To assess the effect of these external factors, subjects were asked if they were aware of anything that might have altered their asthma over the study period. This form of subjective self-analysis is more blunt than definitive, however it did contribute some useful information suggesting a small influence particularly from chest infections.

External effects were also minimised by choosing a month that was not a recognised change of season month, nor overtly mid-winter.

Salamol had also received mostly negative reporting in the media up to 5 months prior to the study onset. The effect of this on this study is difficult to assess, however it was mitigated as far as possible through patient education in the consent process, and the unbiased support for Salamol from the author as their family doctor. Overall, the influence of these peripheral factors is considered to be minimal.

Product-related factors—The apparent ineffectiveness of Salamol in this crossover study is in contrast to the few previously mentioned crossover studies from Ventolin to Salamol.

In this study, subjects complained about the taste, device blockage, and the uncertainty of whether they were getting anything in their mouth after using Salamol.

Other studies with similar products e.g. Ventolin and Aeromir (another CFC-free formulation of salbutamol) demonstrate a slower particle speed for the CFC-free formulation that may account for the delivery uncertainty.¹⁷

Bamber reported blockage difficulties with CFC-free inhalers and Chew confirmed blockage-induced reductions in fine particle mass requiring weekly mouthpiece washing.^{18,19} These device-related factors may certainly account for the observed poor asthma stability, and to this must be added the final possibility that the absolute effectiveness of CFC-free salbutamol in Salamol is simply not as effective as that in Ventolin.

It is possible that inter-company preferences for non-active ingredients such as excipients eg alcohol, alters the effectiveness of Salbutamol itself.

Conclusions

While promoted as being pharmaceutically similar, Salamol was less effective than Ventolin in this study. This could be due to several factors, including true differences in active ingredient efficacy, physical differences in inhaler devices, and subject-related change anxiety. Further work needs to be done to identify these individual factors with greater recognition especially, of the “change-related” contributions to asthma.

If the physical delivery features of a device are different, and patients are not adequately reassured, educated, and safely trialled, then it is highly likely any new asthma inhaler introduction will face difficulties no matter how bioequivalent it may pharmaceutically turn out to be.

Disclosures: The author of this article is an independent researcher and has not been the recipient of any funding from GlaxoSmithKline (the manufacturer of Ventolin), or funding from any other source.

Author information: Shane Reti, Medical Practitioner and Researcher, Whangarei (and Senior Lecturer, School of Population Health, Auckland University, Auckland)

Acknowledgments: I thank Allen Liang for peer review and Mike Mullany for statistical support.

Correspondence: Dr Shane Reti, 15 Rust Ave, Whangarei. Fax (09) 438 2011; email: salamol@selectpost.com

References:

1. Medsafe [website]. Salamol. URL: <http://www.medsafe.govt.nz/hot/papersreports/salamol.htm>
2. Gillies J, Brown J, Byrnes C, et al. PHARMAC and Ventolin in New Zealand. *N Z Med J*. 2005;118(1220). URL: <http://www.nzma.org.nz/journal/118-1220/1616>
3. Dockhorn D, Vanden Burgt JA, Ekholm BP, et al. Clinical equivalence of a novel non-chlorofluorocarbon-containing salbutamol sulfate metered-dose inhaler and a conventional chlorofluorocarbon inhaler in patients with asthma. *J Allergy Clin Immunol*. 1995;96:50–6.
4. Bleecker ER, Tinkelman DG, Ramsdell J, et al. Proventil HFA provides bronchodilation comparable to Ventolin over 12 weeks of regular use in asthmatics. *Chest*. 1998;113:283–9.
5. Ramsdell JW, Colice GL, Ekholm BP, et al. Cumulative dose response study comparing HFA 134a albuterol sulfate and conventional CFC albuterol in patients with asthma. *Ann Allergy Asthma Immunol*. 1998;81:593–9.
6. Baumgarten CR, Dorow P, Weber HH, et al. Equivalence of as-required salbutamol propelled by propellants 11 and 12 or HFA 134a in mild to moderate asthmatics. *Respir Med*. 2000;94:S17–21.
7. Brocklebank D, Ram F, Wright J, et al. Comparison of the effectiveness of inhaler devices in asthma and chronic obstructive airways disease: a systematic review of the literature. *Health Technol Assess*. 2001;5:1–149.
8. Langley SJ, Sykes AP, Batty EP, et al. A comparison of the efficacy and tolerability of single doses of HFA 134a albuterol and CFC albuterol in mild-to-moderate asthmatic patients. *Ann Allergy Asthma Immunol*. 2002;88:488–93.
9. Lumry W, Noveck R, Weinstein S, et al. Switching from Ventolin CFC to Ventolin HFA is well tolerated and effective in patients with asthma. *Ann Allergy Asthma Immunol*. 2001;86:297–303.
10. Lee MG, Ireland DS, Dwyer PJ, et al. Comparison of Salbutamol inhalers available in the United Kingdom. *Int J Pharm Prac*. 1993;2:172–5.
11. Clark DJ, Gordon-Smith J, McPhate G et al. Lung bioavailability of generic and innovator salbutamol metered dose inhalers. *Thorax*. 1996;51:325–6.
12. Chege JK, Chrystyn H. Volumatic usage: some generic salbutamol metered dose inhalers can be used. *Thorax* 1994;49:1162–3.
13. Asthma New Zealand [website]. URL: http://www.asthmanz.co.nz/in_new_zealand.php
14. Juniper EF. Asthma Control Questionnaire; 2003. URL: <http://www.qoltech.co.uk>
15. Williamson IJ, Reid A, Monie RDH, et al. Generic inhaled salbutamol versus branded salbutamol. A randomised double-blind study. *Postgrad Med J*. 1997;73:156–8.
16. Bleecker ER, Klinger NM, Ekholm BP, et al. Twelve week efficacy and safety comparisons of salbutamol formulated with HFA134a and standard CFC metered dose inhaler devices. *Am J Resp Crit Care Med*. 1995;151:A58.
17. Barry PW, O'Callaghan C. In vitro comparison of the amount of salbutamol available for inhalation from different formulations used with different spacer devices. *Eur Respir J*. 1997;10:1345–8.
18. Bamber MG. Difficulties with CFC-free salbutamol inhaler. *Lancet*. 1996;348:1737.

19. Chew N, Reddel HK, Bosnic-Anticevich SZ, et al. Effect of mouthpiece washing on aerosol performance of CFC-free ventolin. *Asthma*. 2004;41:721–7.