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PHARMAC responds on salbutamol

We disagree with Dr John Gillies and colleagues' views (published in the 12 August 2005 issue of the *Journal*; http://www.nzma.org.nz/journal/118-1220/1616/) on the introduction of a new brand of salbutamol (Salamol) onto the New Zealand Pharmaceutical Schedule. Salamol is efficacious, and blockages can occur with any CFC-free inhalers (including Ventolin).

Patient perceptions are important—but some data suggest that nearly half of patients will report subjective differences between their own and study-supplied Ventolin inhalers.[1] However, we acknowledge that this issue did highlight the need to consider better education campaigns around sole supply arrangements for asthma products. Patient education needs to include regularly washing CFC-free inhalers—including Ventolin CFC-free inhalers.

Efficacy, published research and use internationally

Salamol was approved by Medsafe (the New Zealand Medicines and Medical Devices Safety Authority, a business unit of the Ministry of Health) in 2004, following a standard approval process, meaning that it meets the standards of safety and efficacy required of medicines in New Zealand. The approval process includes a rigorous review of the literature and proof of bioequivalence with the innovator (in this case, Ventolin). The submission made to Medsafe for approval of Salamol included clinical trial data. The approval of a medicine by Medsafe is independent of PHARMAC.

International randomised double-blind studies have demonstrated that respiratory function did not differ between generic and branded salbutamol and that there was clinical equivalence between the generic and the branded salbutamol[1,2] (PubMed search using the keywords "generic salbutamol").

Salamol is, like Ventolin, a brand of salbutamol and is bioequivalent. Salamol is also widely used internationally, having been approved in the United States and the United Kingdom. In the United Kingdom (where it is manufactured), Salamol has been registered and prescribed for over four years and has a significant share of the salbutamol market there, with over 600,000 units being dispensed each month. There is nothing to compare this product's introduction with fenoterol's safety concerns.

In response to the complaints PHARMAC had received from patients and clinicians, Medsafe asked both Environmental Science Research (ESR) and the Australian Therapeutic Goods Administration (TGA) to test Salamol and investigate. PHARMAC and Medsafe are awaiting the final results and will advise clinicians of Medsafe's findings once these are available.

Patient perception and palatability

We do note that users of Salamol who have previously used the Ventolin inhaler have reported that inhaler feels different when used. Indeed the "force" and coldness of the spray feel different between the two inhalers. This does not, however, affect the actual

delivery of the chemical. It is possible that this difference in delivery has led some patients to conclude that the Salamol inhaler is less effective.

The Williamson study above,[1] which compared open-label Ventolin, blinded Ventolin and a generic salbutamol, indicates that generic substitution of salbutamol is often affected by subjective negative perception by both patients and doctors, which are not based on any clinical differences. These may well resolve with time as people become accustomed to using the new inhaler and realise that it is as effective as their old one.

In the same study, fifty-five per cent of patients said they could detect a difference between the inhalers, when there were no significant differences between treatments in any of the objective parameters measured. Of particular interest however, 45% noted a difference between their usual Ventolin and the open or blinded Ventolin. The authors concluded *inter alia* that patients' own assessment of their relief inhaler seems to be influenced by factors other than efficacy.[1]

Clinicians should also recognise that patients equate the "coldness" and the impact of the propellant on the post pharyngeal wall with efficacy. This does suggest that there should be more education around proper inhaler technique to ensure that devices are being used properly.

Device issues including blockages

The manufacturers of Salamol acknowledge that the device can clog and advise that it should be washed regularly. All CFC-free salbutamol inhalers can clog if not cared for by careful washing.[3–5] Washing each week with warm running water for at least 30 seconds prevents possible clogging. The makers of Ventolin give the same advice on their packaging.

The PTAC submission included a study comparing the blockage rates of Aeromir, Salamol and Ventolin. The study showed no significant difference in blockage rates when the devices are cleaned in accordance with manufacturers recommendations.

These factors highlight the importance nowadays, with the advent of CFC-free inhalers, for clinicians to advise patients that, regardless of the product, CFC-free inhalers can clog, and teach how and when to clean the devices. Washing instructions are included in the patient information sheets provided with each inhaler. Washing is important, as even if the device does not completely obstruct, the doses delivered may still be reduced. This equally applies to Ventolin.

The Salamol device's size and shape is appears to be identical to that of Serevent long-acting beta-agonist (LABA) metered dose inhalers.

Alcohol content

Alcohol is a common solvent in many pharmaceuticals especially liquid preparations. The amount of alcohol contained in each puff of Salamol is in the thousandths of a millilitre—less than the amount of naturally occurring alcohol found in a glass of freshly squeezed orange juice.[6]

The amount of alcohol used in MDIs is insufficient to have a pharmacological effect[7] or affect driving.[8] Claims that inhaling micrograms of alcohol will affect an adult's driving ability have been refuted by the NZ Police and in the United Kingdom (see

footnote #1). Salamol is approved for use in a number of predominantly Islamic countries, including the United Arab Emirates and Kazakhstan.

Consultation with expert and patient groups

In addition to our standard consultation processes,[9–11] the issues around generic salbutamol were discussed in detail by the Pharmacology and Therapeutics Advisory Committee (PTAC[12]) and its Respiratory subcommittee (both independent clinical advisory committees to PHARMAC) and the Tender Medical subcommittee (which consists of clinicians and pharmacists). The consultation document identifying which drugs are being considered for tender was widely distributed to suppliers, professional bodies and interested clinicians and other groups on 16 October 2002. This included the Asthma and Respiratory Foundation of New Zealand (ARFNZ), the Thoracic Society of Australia and New Zealand (TSANZ), the Paediatric Society of New Zealand, New Zealand Medical Association, the Royal Australasian College of Physicians, and the Royal New Zealand College of General Practitioners.

As outlined in the October 2002 letter, the Tender Medical subcommittee considers all products proposed for tender before the final list is approved by PHARMAC's Board. It also considers all the products where bids were received to give it the opportunity to review the products that are to be proposed for sole subsidised supply. In the case of Salamol the subcommittee considered there was no clinical reason not to award a tender, but did request that the Respiratory subcommittee review the device before any decision was made to accept the tender.

The Respiratory subcommittee in turn was satisfied with the device, highlighting only that it may present an issue for Islamic patients who may object to alcohol on religious grounds. This has since been discounted by comment from Islamic spokespeople, and as the subcommittee noted, if a patient did strongly object to taking a medicine containing alcohol they could use terbutaline. The relevant part of the minutes of the subcommittee's September 2003 meeting is in footnote #2.

In May 2005 PTAC considered that Salamol should remain on the Pharmaceutical Schedule and, subject to satisfactory TGAL results, saw no clinical reason why PHARMAC should not proceed with a sole supply arrangement for the product. However, it recommended that any continuation of subsidised access to Salamol should be associated with an awareness campaign in which PHARMAC emphasised the need to regularly wash all CFC free inhalers. The relevant part of the minutes of PTAC's May 2005 meeting is in footnote #3, which further details various issues around Salamol.

Lesson learnt

We acknowledge that there were a number of complaints about Salamol with a great deal of media interest. Most complaints reported to CARM were from pharmacists rather than doctors, with relatively few pharmacists at that. Once we realised that public confidence in the product had been unreasonably shaken, we reached agreement with Airflow to continue the listing of both products. PHARMAC had no concerns over Salamol's efficacy. Ventolin now has the same access to subsidy as Salamol, and it remains up to the supplier (GSK) as to whether it maintains a surcharge on Ventolin.

We understand from Medsafe that the UK experience showed that any concerns were resolved simply by patient education. Medsafe also states that in the UK that the Asthma Society and patient groups were all onside in a background of CFC to non-CFC substitution.

This issue did highlight the need to consider education campaigns around sole supply arrangements for asthma products. Both patients and clinicians can be very "brand loyal" and any change to an "iconic" product needs to be handled carefully. The Williamson study concluded that careful encouragement is required when changing to a generic product, and that this has particular implications for converting to CFC-free products.[1] Further, with hindsight we should have asked the supplier to give more information to clinicians about the different taste and feel of Salamol.

Comment

Advice to patients must now include regularly washing all CFC free inhalers—as has been needed since CFC-free Flixotide was introduced in January 1998 and CFC-free Ventolin was introduced in June 2001.

PHARMAC considers sole supply arrangements in general to be appropriate for the asthma market.

The authors' arguments about role of the Asthma and Respiratory Foundation (ARFNZ) might have been stronger had someone ensured that any of the authors' own conflicts of interest were declared. The Journal's policy on conflicts is clear,[13] and such statements have occurred in other Special Series articles.[14,15] ARFNZ is but one of a number of organisations with an advisory role that fund themselves in part through the supply of pharmaceutical products.

There are larger issues for children with asthma, for instance the lower rates of use of inhaled corticosteroids (ICSs) by some ethnic groups when compared with their higher use of reliever inhalers and rates of hospitalisation—as can be seen below in Figure 1 and Table 1[16] (details can be supplied on request). These are issues we all need to look at together.

Figure 1

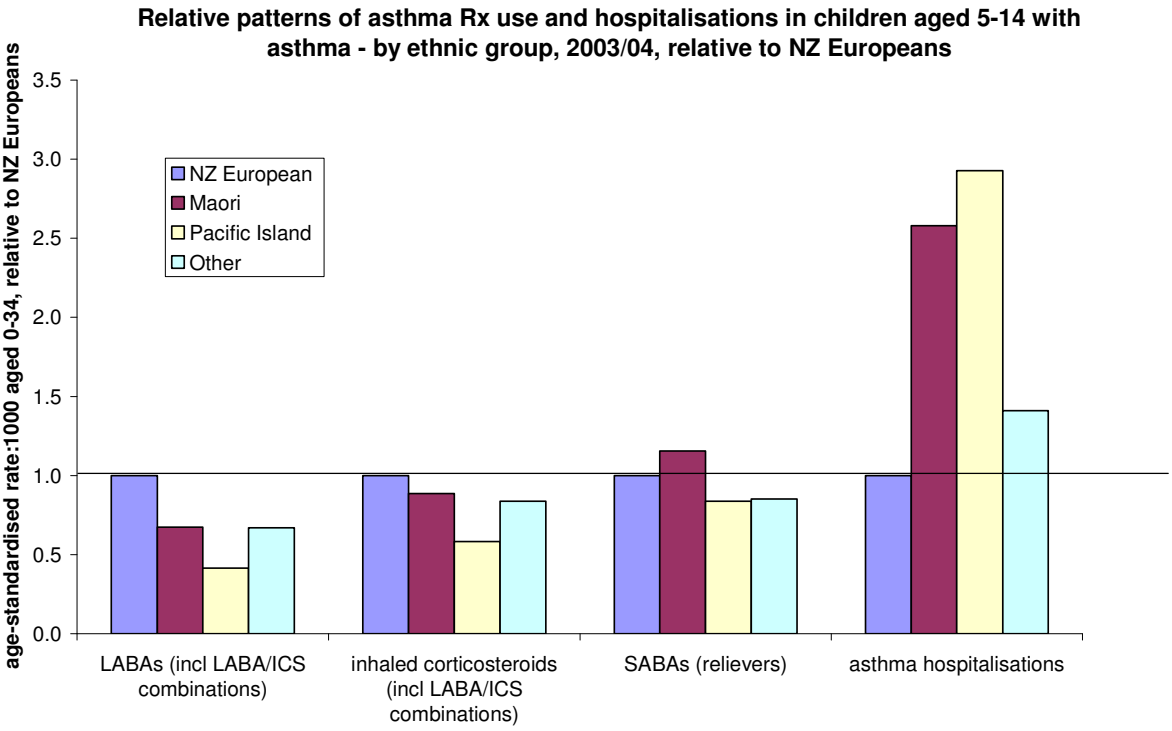

Table 1

Possible rates of Rx use in patients with asthma*
rates:1000 - accounting for missing ethnicity data

ICS (incl LABA/ICS combinations)

agegroup	NZ European	Maori	Pacific Island	Other	Total
0-4	57.8	81.6	56.9	70.1	63.6
5-14	75.2	66.6	43.8	63.0	70.0
15-24	66.9	57.0	32.5	17.3	57.6
25-34	61.2	65.9	38.8	21.7	57.3
(crude total)	60.9	60.5	38.4	33.6	62.2
age-standardised	66.3	66.6	42.0	42.9	62.4

SABA

agegroup	NZ European	Maori	Pacific Island	Other	Total
0-4	104.4	223.1	192.7	161.5	142.7
5-14	99.6	114.9	83.3	84.8	100.2
15-24	111.0	109.2	60.1	24.8	98.0
25-34	99.0	129.1	70.4	29.2	96.1
(crude total)	94.5	123.1	86.1	53.1	104.6
age-standardised	103.3	137.2	95.0	71.1	106.7

LABAinh incl comb ICS

agegroup	NZ European	Maori	Pacific Island	Other	Total
0-4	2.0	2.5	2.8	2.3	2.2
5-14	6.4	4.3	2.7	4.3	5.5
15-24	9.5	6.9	3.3	1.8	7.8
25-34	10.9	10.6	5.2	3.3	9.9
(crude total)	7.3	5.6	3.1	2.7	6.9
age-standardised	8.3	6.8	3.8	3.4	7.3

*probable underestimate of pt nos., through overestimating dispensings/pt
(because earlier data less likely to have NHIs ascribed, hence too few pts)

Rates of hospitalisations for asthma, 2003/04
hospitalisations for asthma
rates:1000 - accounting for missing ethnicity data

agegroup	NZ European	Maori	Pacific	Other	Total
0-4	7.8	20.5	24.6	11.7	12.5
5-14	1.9	4.3	5.3	3.4	2.8
15-24	1.3	3.0	2.7	0.7	1.6
25-34	0.9	3.0	2.7	0.9	1.3
(crude total)	2.2	6.5	7.6	2.7	3.4
age-standardised	2.6	6.8	7.7	3.7	4.0

Conflict of interest: Scott Metcalfe is externally contracted to work with PHARMAC for public health advice. Peter Moodie, Andrew Davies, Wayne McNee, and Sean Dougherty declare no conflicts.

Footnotes:

#1. Extract from Airflow media statement 6 May 2005.

UK analysis by Lion Laboratories, manufacturers of evidential breath machines, shows that if a subject with no alcohol in his body used a similar inhaler to Salamol, sealed his mouth closed and immediately blew into an intoximeter it would produce a breath reading of 32 microgram per 100ml (three points below the UK upper limit for driving). One minute later, not having used the inhaler again, the reading was 1 microgram. Six minutes after using the inhaler there was no trace of alcohol in a breath test. Provided a period of at least six minutes elapses between the use of an inhaler and a breath test there is no effect on the alcohol reading.

Lion Laboratories also calculated that to raise the breath or blood, alcohol level from zero to the UK legal limit for driving, a 70kg man would need to take over 5500 actuations of the inhaler product in less than 30 minutes. This equates to around 27 containers.

#2. Relevant record from PTAC's Respiratory subcommittee meeting 11 September 2003

Salbutamol metered dose inhaler

The subcommittee noted that in response to the 2002/03 Invitation to Tender PHARMAC had received bids from [deleted] suppliers for the salbutamol 100 mcg per dose aerosol inhaler, Airflow Products' being the best provisional bid. The subcommittee noted that this product was not yet approved by Medsafe.

The subcommittee noted that this product came from the UK based manufacturer Norton. The subcommittee noted that the CFC-free inhaler contained small amounts of ethanol, which may be an issue with some patients, such as Muslims. However, the subcommittee noted that these patients could switch to terbutaline which was fully funded on the Pharmaceutical Schedule.

The subcommittee considered that there was no clinical reason not to award the tender for salbutamol metered dose inhaler to Airflow, subject to Medsafe approval.

#3. Relevant record from the Pharmacology and Therapeutics Advisory Committee meeting 19 May 2005

Salamol (salbutamol)

The Committee noted that, following consideration by the Tender Medical and Respiratory Sub-committees of PTAC in 2003, the distributor of Salamol had been awarded a contract for sole supply status, which was due to take effect on 1 July 2005. It noted that both sub-committees had indicated that there was no clinical reason not to award sole supply status to Salamol.

The Committee noted that Salamol had been approved by Medsafe for distribution in New Zealand in December 2004 and that it had been available in the UK for almost 4 years and in the United States for about 1 year.

The Committee noted that, following listing on the Pharmaceutical Schedule in New Zealand, PHARMAC had received 268 complaints about Salamol. The main areas of complaint were categorised as follows:

- Less perceived effect
- Reduced number of doses
- Taste
- Alcohol content
- Clogging
- Does not fit into all spacer types

The Committee noted that similar problems with blocking had been reported in the UK. It noted that the manufacturer (IVAX) had supplied studies, which showed that the majority of complaints received in the UK related to clogging and dose delivery failure. These problems were resolved when the inhalers were cleaned. The Committee noted that the rate of complaints in the UK after 10 months of sales in the UK was 110 per million inhalers sold, and this rate decreased over time while sales increased.

The Committee noted that Medsafe, using the technical expertise of ESR and the TGA laboratories (TGAL) in Australia, had tested samples from two batches of Salamol as well as six "faulty" inhalers. It noted that, while the results of the TGAL testing were not yet available, Salamol had passed the tests conducted by ESR which meant that the product met its quality specifications. The Committee considered that the results of these tests to date showed no quality issues associated with Salamol in regard to effectiveness and the number of doses.

The Committee considered some of the possible reasons for the other types of complaint. It noted that Salamol does not have as strong an emission force compared to Ventolin and that this may have contributed to perceptions of reduced effect. It also noted that the product tastes different to Ventolin but did not regard the taste to be less pleasant.

The Committee noted that other inhalers also contain alcohol. It noted that, given the negligible levels of alcohol contained in Salamol, the supplier had established that patients would need to take 5,500 inhalations of Salamol in order to raise alcohol levels significantly. The Committee also noted that a Muslim community spokesperson had no objections to small amounts of alcohol in prescribed medications when used under medical guidance. The Committee noted that it is sold in the Middle East and registered in UAE. The Committee also noted that an Alcoholic's Anonymous (AA) worker had indicated no concern with the alcohol content.

The Committee noted that, while Salamol may not fit all spacers, it fits a range including both subsidised brands and the Volumatic spacer.

The Committee concluded that the main complaint of significance was the issue of clogging. It noted that this is a problem common to all CFC-free inhalers and that proper cleaning is important. It noted that the datasheet for Salamol recommends storage at < 25°C compared with < 30°C for Ventolin but did not consider there to be any evidence that this difference might impact on the rate of clogging.

The Committee noted that clogging of the inhaler may result in patients becoming anxious. It acknowledged that fear can have an adverse effect on a clinical situation, but considered that this can generally be overcome by education.

The Committee considered that Salamol should remain on the Pharmaceutical Schedule and, subject to satisfactory TGAL results, saw no clinical reason why PHARMAC should not proceed with a sole supply arrangement for the product. However, it recommended that any continuation of subsidised access to Salamol should be associated with an awareness campaign in which PHARMAC emphasised the need to regularly wash all CFC free inhalers.

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