

## Comparison of elderly people's technique in using two dry powder inhalers to deliver zanamivir: randomised controlled trial

Paul Diggory, Christophe Fernandez, Amanda Humphrey, Valerie Jones, Maeve Murphy

### Abstract

**Objective** To determine whether elderly people can learn to use the inhaler used to deliver zanamivir (Relenza Diskhaler) as effectively as the Turbohaler and to identify which aspects of inhaler technique are most problematic.

**Design** Randomised, controlled, intervention study.

**Setting** Wards for acute elderly care in a large district general hospital.

**Participants** 73 patients who were unfamiliar with the use of an inhaler, aged 71 to 99 (mean 83) years.

**Main outcome measures** Initial scores and changes in scores 24 hours later using a 10 point scoring system of five aspects of inhaler technique.

**Results** 38 patients were allocated the Relenza Diskhaler and 35 the Turbohaler. The mean total score was significantly greater in the Turbohaler than Diskhaler groups both initially (8.74 *v* 7.05) and after 24 hours (8.28 *v* 5.43). The major difference between inhalers was in loading and priming. After tuition 50% (19 of 38) of patients allocated the Diskhaler were unable to load and prime the device and 65% (24 of 37) were unable to do so 24 hours later. Of those allocated the Turbohaler, two patients were unable to load and prime the device after initial review and one after 24 hours.

**Conclusion** Most elderly people cannot use the inhaler device used to deliver the anti-influenza drug zanamivir. Treatment with this drug is unlikely to be effective in elderly people unless the delivery system is improved.

### Introduction

Influenza causes an acute respiratory illness, mainly during a two month period in the winter. It affects people of all ages, but 80% of deaths occur in elderly people—that is, those aged over 65—who are more likely to develop complications than younger people. Vaccination is effective in preventing or ameliorating influenza in elderly people but each year less than half the elderly population are vaccinated, leaving many at risk.<sup>1 2</sup>

Zanamivir (Relenza, GlaxoWellcome) is an inhibitor of influenza A and B virus neuraminidase. It is delivered to the lungs by a dry powder inhaler, the Diskhaler, which is also available as a delivery system for

salbutamol and beclomethasone. A five day course of inhaled zanamivir twice daily has been shown to reduce the duration and severity of influenza symptoms.<sup>3 4</sup> No trial designed specifically to test zanamivir's effectiveness in elderly people with influenza has been published, and the evidence of effectiveness in elderly people comes from subgroup analysis of trials recruiting both young and old patients.

If a significant amount of an inhaled drug is to reach a patient's lungs then the patient must be able to use an inhaler. Elderly people often have difficulty in using inhaler devices.<sup>5-7</sup> A study of elderly people unfamiliar with the use of an inhaler has shown that the dry powder device Turbohaler (Astra) is easily learnt<sup>8 9</sup> and proved superior to the metered dose inhalers plus Volumatic spacer combination.

Turbohaler is small and does not require inspiration to be coordinated with triggering. Priming consists of two stages: removal of the top and turning the base clockwise and back. An audible click indicates the device is ready to use. The click still occurs even if the device is empty, but a flag in a window shows when no drug remains.

The Diskhaler is pocket sized and does not require inspiration to be coordinated with triggering. The drug is contained in one of four blisters in a disc, inserted on a tray. One blister should be used for each inhalation. The recommended dose of zanamivir is two inhalations (2 × 5 mg) twice daily for five days, providing a total daily inhaled dose of 20 mg. Priming consists of several stages: taking the top off; sliding the tray backwards and forwards to rotate the disc to an intact blister; and raising a perforator to 90 degrees, which is then lowered to its original position. This perforates the blister and delivers the drug to the inhaler chamber. If no blisters are intact a new disc must be loaded by unlatching and removing the tray, changing the disc, and replacing the tray.

We aimed to determine if elderly people unfamiliar with the use of an inhaler could learn to use the Diskhaler as effectively as the Turbohaler and to identify which aspects of the devices were most problematic.

### Participants and methods

After approval from our local research ethics committee, we recruited patients aged over 65 years from seven wards providing acute elderly care at Mayday Hospital.

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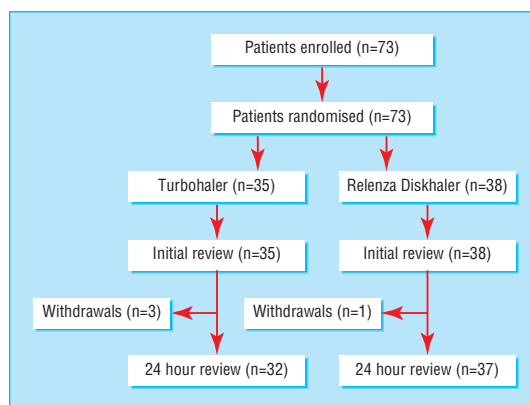
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Trial profile

Patients were enrolled provided their medical condition was stable, they were either ready or shortly to be discharged from hospital, and they had given written informed consent. Patients had to be able to read a sentence; the font of which corresponded in size to the window in the Turbohaler that signals when the inhaler is empty. Exclusion criteria were previous use of an inhaler, cognitive impairment (defined as a score of less than seven out of 10 on the Hodgkinson mental test<sup>10</sup>), illness affecting ability to use inhalers, such as stroke or arthritis, and due to leave hospital in less than 24 hours.

Patients were randomly allocated Diskhaler or Turbohaler and, after 15 minutes' tuition, were assessed for their inhaler technique. We considered five aspects: loading and priming, exhaling to residual volume, hand and breath coordination, breath holding for 10 seconds, and awareness that the inhaler was empty. Each aspect was scored for technique: 0 for poor; 1 for moderate; and 2 for perfect.<sup>8 11</sup> Assessments of seven aspects of ability to load and prime the Diskhaler were also recorded. After initial assessment, up to five further minutes' tuition was given if necessary. Assessment was repeated 24 hours later to see if the inhaler could still be used. Initial tuition and assessment and the assessment at 24 hours were conducted by different, single investigators unaware of the previous score.

The primary outcome measure was the differences in mean total scores after initial tuition and at 24 hours. Secondary outcome measures were differences in mean scores for each of the five aspects of inhaler technique.

Mean (SD) initial and review scores for patients learning to use the Diskhaler or Turbohaler devices

	Diskhaler n=38	Turbohaler n=35	Mean difference (95% CI)	P value
<b>Initial scores</b>				
Load and prime	0.87 (0.93)	1.83 (0.53)	0.96 (0.68 to 1.31)	<0.001
Exhale to residual volume	1.60 (0.72)	1.61 (0.77)	0.005 (-0.35 to 0.34)	0.976
Hand and breath coordination	1.77 (0.54)	1.94 (0.24)	0.18 (-0.18 to 0.37)	0.068
Breath holding	1.74 (0.50)	1.80 (0.47)	0.06 (-0.16 to 0.29)	0.583
Aware of empty device	1.08 (0.97)	1.57 (0.78)	0.49 (0.2 to 0.9)	0.019
<b>Total</b>	<b>7.05 (2.46)</b>	<b>8.74 (1.98)</b>	<b>1.69 (0.65 to 2.73)</b>	<b>0.002</b>
<b>Review scores</b>				
Load and prime	0.54 (0.80)	1.81 (0.47)	1.27 (0.95 to 1.58)	<0.001
Exhale to residual volume	1.24 (0.86)	1.63 (0.71)	0.38 (-0.45 to 0.76)	0.48
Hand and breath coordination	1.43 (0.73)	1.78 (0.49)	0.35 (4.5 to 0.64)	0.021
Breath holding	1.30 (0.74)	1.53 (0.76)	0.23 (-0.13 to 0.60)	0.202
Aware of empty device	0.92 (1.01)	1.53 (0.76)	0.61 (0.19 to 1.04)	0.006
<b>Total</b>	<b>5.43 (2.82)</b>	<b>8.28 (1.90)</b>	<b>2.85 (1.70 to 3.99)</b>	<b>&lt;0.001</b>

## Statistical analysis

We estimated that at least 35 patients needed to be recruited into each group to have a 90% chance of detecting a difference of 1.5 in mean total score at the 5% significance level. The independent *t* test compared the mean differences in scores of the five aspects of inhaler technique and the mean differences of the summated total scores of these five aspects between the two groups.

## Results

We enrolled 73 patients into the study (figure). The mean age (84 *v* 83 years), number of females (25 *v* 28), and mean mental test scores (9.28 *v* 9.58) were similar between the two groups; the number of patients with mental test scores of 10 was higher in the Diskhaler group (20 *v* 26).

After enrolment 20 (57%) of the patients in the Turbohaler group and 10 (26%) in the Diskhaler group achieved perfect scores. These were sustained at 24 hours by 15 of 32 (47%) patients allocated Turbohaler and 5 of 37 (13%) allocated Diskhaler. Mean total scores were significantly higher in the Turbohaler than the Diskhaler group; the difference between groups was greater at the 24 hour review (table). The biggest difference in aspects of inhaler technique was in the patients' ability to load and prime the devices. Mean loading and priming scores for the Diskhaler were significantly lower both after the initial review and at 24 hours. More patients in the Diskhaler than Turbohaler group had poor (zero) scores, consistent with the inability to load and prime the device. Nineteen of 38 patients (50%) in the Diskhaler group had a poor score for loading and priming on initial review and 24 of 37 (66%) after 24 hours, whereas only 2 of 35 patients in the Turbohaler group had a poor score on initial review and 1 of 32 after 24 hours.

## Discussion

Most of the elderly people in our study were unable to use the Diskhaler device used to deliver zanamivir satisfactorily, but those allocated the Turbohaler were more successful. Patients scored significantly better in the Turbohaler than Diskhaler group both initially and at 24 hours. Patients in the Turbohaler group also had a higher proportion of perfect scores than those in the Diskhaler group at 24 hours.

Although our patients were in hospital, they were in the recovery stage of their illness when recruited. Elderly patients with influenza may be confused and very ill making them more likely to have difficulties using the Diskhaler than those patients in our study. In addition we excluded patients with poor cognitive function and gave up to 15 minutes of personal tuition in inhaler usage before and up to five minutes after initial assessment. Such levels of selection and tuition are impractical for elderly patients presenting with influenza to their doctor in the community. It is likely that elderly patients with influenza will have more difficulties using the Diskhaler than our patients who were about to return to the community.

Elderly people are at particular risk of serious illness if they contract influenza. It is possible that inhaled zanamivir is effective in ameliorating the

### What is already known on this topic

Inhaled zanamivir is effective in reducing the symptoms and duration of influenza

Elderly people have difficulty in using inhalers

### What this study adds

Elderly patients are unlikely to be able to use the dry powder inhaler that is used to deliver zanamivir

Improvements should be made to the inhaler

Particular attention should be paid to the loading and priming of the device

symptoms, shortening the course of the disease, and reducing complications. More studies of the effectiveness of zanamivir treatment of influenza are needed, but without an improved delivery system they will be difficult to interpret. Our study shows that zanamivir treatment for elderly people with influenza is unlikely to be effective. Better delivery systems for inhalers should be used or developed.

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Contributors: PD developed the scoring system and with VJ conceived the original idea for the study. PD, VJ, AH, and MM designed the study and the scoring of aspects of loading the Diskhaler and collected the data. CF contributed to the design of the study as well as the power calculations and performed the analysis. PD will act as guarantor for the paper.

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## Comparison of effects of amphotericin B deoxycholate infused over 4 or 24 hours: randomised controlled trial

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### Abstract

**Objective** To test the hypothesis that amphotericin B deoxycholate is less toxic when given by continuous infusion than by conventional rapid infusion.

**Design** Randomised, controlled, non-blinded, single centre study.

**Setting** University hospital providing tertiary clinical care.

**Patients** 80 mostly neutropenic patients with refractory fever and suspected or proved invasive fungal infections.

**Intervention** Patients were randomised to receive 0.97 mg/kg amphotericin B by continuous infusion over 24 hours or 0.95 mg/kg by rapid infusion over four hours.

**Main outcome measures** Patients were evaluated for side effects related to infusion, nephrotoxicity, and mortality up to three months after treatment. Analysis was on an intention to treat basis.

**Results** Patients in the continuous infusion group had fewer side effects and significantly reduced nephrotoxicity compared with those in the rapid infusion group. Overall mortality was higher during treatment and after three months' follow up in the rapid infusion than in the continuous infusion group.

**Conclusion** Continuous infusions of amphotericin B reduce nephrotoxicity and side effects related to infusion without increasing mortality.

### Introduction

Amphotericin B deoxycholate has remained the mainstay of treatment for life threatening fungal infections in immunocompromised patients because of its broad fungicidal activity and cheapness. Treatment with amphotericin B, however, is associated with acute reactions related to infusion and dose dependent nephrotoxicity. It is recommended that amphotericin B is infused slowly over two to six hours, based on the assumption that the severity and frequency of toxic reactions increase during more rapid infusions.<sup>1-4</sup>

Incorporation of amphotericin B into liposomal formulations reduces its toxicity, but the reasons for this are unclear.<sup>5-11</sup> As liposomes do not specifically target fungal cells it would seem that the reduction in toxicity, at least in part, depends on a slower delivery of amphotericin B to tissues. The question as to whether a slower delivery of amphotericin B from lipid formulations might be reproduced by a slow infusion rate therefore arises. The hypothesis that a continuous infusion of amphotericin B results in reduced toxicity

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