Practitioner C D Williams, Dr Medical Centre, Heathcot Practice, York St Peter’s G Kruchek, BMJ 25 SEPTEMBER 1993 771 with lactulose. senna-fibre the of these lactulose tion was constipation lactulose.’ metered dose aerosol inhalers require mortality excess are and were well tolerated. Both treatments were well tolerated. The superior efficacy of the senna-fibre combination, without increase in side effects, resulted in considerable cost benefit compared with lactulose.

Study participants were Dr A Mehrzad, Mr J Milligan, and

**Problems in assessing contents of metered dose inhalers**

**D J Williams, A C Williams, D G Kruchek**

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D J Williams, general practitioner A C Williams, psychologist St Peter’s Hospital, Chertsey, KT6 9PZ

D G Kruchek, anaesthetics registrar

Correspondence to: Dr Williams. BMJ 1993;307:771-2

Treatment of asthma with β agonists delivered via metered dose aerosol inhalers has been associated with excess mortality from asthma. The canister of these inhalers is opaque, and patients cannot see how much medication remains in a canister. This means that such patients may tend to run out of medication, which could be related to the excess mortality from asthma. We investigated whether asthmatic patients were able to reliably assess the amount of medication remaining in a metered dose inhaler and whether they ever ran out of medication.

Subjects, methods, and results

From details of repeat prescriptions we identified all asthmatic patients attending a general practice who were aged 13-22 and used a metered dose inhaler. We notified the patients to come to the surgery with the inhalers they were currently using and any held in reserve. We asked the patients about their use of inhalers and assessed the inhalers by weight. When an inhaler’s canister floats (at its floating weight) it has delivered its licensed number of doses. Although expellant may be obtained from an inhaler beyond its licensed number of doses (36 extra puffs on average for a Ventolin inhaler), there are no published data on the drug content of each puff. As 48 hours is generally required to get a repeat prescription from a general practice, a canister’s red weight is when it contains enough expellant for 48 hours’ use. β Agonists in metered dose inhalers are usually prescribed at two puffs four times daily. The red weight is thus the empty weight (when no further expellant can be obtained) plus the weight of eight doses. We emptied four canisters of each of the metered dose inhalers available (allowing 30 seconds between each expelled dose), measured the appropriate weights, and calculated average weights.

The table shows the answers given by the 51 patients who were interviewed. Only three patients assessed their inhalers by flotation, and when given a nearly empty inhaler none of the patients asked to float the canister before saying that they would continue to use it. Altogether 37 patients sought a replacement when their last inhaler was almost or completely empty, and 36 subjects occasionally or frequently ran out of inhalant (33 of whom had consequently become wheezy or very wheezy). Of the 81 inhalers in current use that were assessed, 21 were at their floating weight and 12 were at their red weight. For five patients both their inhaler for prophylaxis and their inhaler for symptomatic relief were at their floating weights, and for three patients both inhalers were at their red weights. Nineteen patients had no inhaler in reserve.

The table shows the answers given by the 51 patients who were interviewed. Only three patients assessed their inhalers by flotation, and when given a nearly empty inhaler none of the patients asked to float the canister before saying that they would continue to use it. Altogether 37 patients sought a replacement when their last inhaler was almost or completely empty, and 36 subjects occasionally or frequently ran out of inhalant (33 of whom had consequently become wheezy or very wheezy). Of the 81 inhalers in current use that were assessed, 21 were at their floating weight and 12 were at their red weight. For five patients both their inhaler for prophylaxis and their inhaler for symptomatic relief were at their floating weights, and for three patients both inhalers were at their red weights. Nineteen patients had no inhaler in reserve.

We thank the medical, nursing, and pharmacy staff in the participating units for their assistance with this study and Galen Limited and Madaus AG for their contributions towards the study.


(Accepted 23 July 1993)
Answers given by 51 asthmatic patients to questions about their use of metered dose inhalers

<table>
<thead>
<tr>
<th>Question</th>
<th>Answer</th>
<th>No of subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>When do you stop using your inhaler?</td>
<td>When nothing comes out of inhaler</td>
<td>48</td>
</tr>
<tr>
<td></td>
<td>When inhaler floats</td>
<td>3</td>
</tr>
<tr>
<td>When do you ask for a repeat prescription of your inhaler?</td>
<td>When inhaler completely empty</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>When inhaler nearly empty</td>
<td>28</td>
</tr>
<tr>
<td></td>
<td>When reserve inhaler started</td>
<td>14</td>
</tr>
<tr>
<td>Have you ever found yourself without an inhaler?</td>
<td>Never without inhaler</td>
<td>15</td>
</tr>
<tr>
<td>If so, what were the consequences?</td>
<td>No consequences when without inhaler</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Became wheezy when without inhaler</td>
<td>25</td>
</tr>
<tr>
<td></td>
<td>Became very wheezy when without inhaler</td>
<td>8</td>
</tr>
<tr>
<td>Do you always have inhalers in reserve?</td>
<td>Never</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>Usually</td>
<td>28</td>
</tr>
<tr>
<td></td>
<td>Often no</td>
<td>15</td>
</tr>
<tr>
<td>Would you carry on using this inhaler?</td>
<td>Yes</td>
<td>51</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>0</td>
</tr>
</tbody>
</table>

*Patient handed a salbutamol inhaler that was nearly empty.

Comment

Nearly all the patients in the study continued to use their inhalers after the canisters had delivered their licensed number of doses. More than half of the patients had run out of medication at some time and had consequently become wheezy. Regular inhalation of β agonists desensitises the β receptors of the airways, and withdrawn of the medication (or running out of it) may provoke rebound bronchospasm after 16 hours. The use of one canister of a salbutamol metered dose inhaler (Ventolin) a month is associated with a mortality odds ratio of 2·4, and greater use of the inhaler substantially increases the odds ratio. This may be because greater use of such an inhaler increases airway desensitisation and increases the chance of running out of medication, increasing the probability of rebound bronchospasm.

Manufacturers of metered dose inhalers are aware of this flaw, and Glaxo stated in a patent for a counter mechanism for inhalers: "the patient cannot determine the amount of medicament in the aerosol container. This could mean that the patient, possibly suffering from severe bronchospasm and needing a dose of medicament, will find that the aerosol container will not dispense a dose because its contents have already been exhausted."

We conclude that aerosol metered dose inhalers give insufficient information about the drug remaining in the inhaler and are therefore unsafe. A counter mechanism would rectify the problem.

(Accepted 24 June 1993)

Smoking and periductal mastitis

N J Bundred, M S Dover, Nedra Aluwihare, E B Faragher, J M Morrison

Periductal mastitis and duct ectasia are well recognised,1,2 presenting either with acute inflammation of the breast or with chronic breast symptoms such as nipple discharge. The acute inflammatory changes seen in younger women are probably due to periductal inflammation (periductal mastitis) without duct dilatation whereas the chronic symptoms seen in older women are probably due to duct dilatation (duct ectasia) with minimal inflammation. As recurrent breast abscesses are common in smokers, we investigated the association between smoking and either periductal mastitis or duct ectasia in patients with a histological diagnosis.

Patients, methods, and results

Between 1981 and 1990, 71 women were identified with a histological diagnosis of periductal mastitis or duct ectasia (cases). Their clinical presentation, use of oral contraceptives, and smoking habits were recorded. They were designated as non-smokers, light smokers (1-10 cigarettes/day), or heavy smokers (11-40 cigarettes/day).

Two age matched controls were selected for each case from women who underwent surgery for a benign non-breast condition during the same year as the cases (varicose vein removal or cholecystectomy (49), gynaecological procedure (27), otorhinolaryngological procedure (23), skin biopsy (33), and dental procedure (10)). Smoking habits were available for all women but details of oral contraceptive use were unobtainable in 32 controls.

The histopathological specimens from all cases were reviewed, and the degree of periductal inflammation and duct dilatation was graded using a previously described method.3 Analysis was based on χ² and Student’s t tests, with analysis of variance and conditional logistic regression.

The mean age of both cases and controls was 43-3 years (range 19-80). The 48 cases with acute symptoms were significantly younger (mean age 40 (SD 13)) than the 23 with chronic disease (47 (14); t=2·06, P=0·043). The cases were significantly more likely to be heavy smokers than the controls (37 (52%) vs 24 (17%) heavy smokers, 11 (15%) vs 22 (16%) light smokers, and 23 (33%) vs 96 (67%) non-smokers, respectively; P<0·001). Of all factors considered, smoking emerged as the only significant risk factor for periductal mastitis or duct ectasia, with a relative risk of 6·2 (95% confidence interval 2·9 to 13·4). Eleven patients had recurrent disease after surgery, of whom 10 were heavy smokers and one a non-smoker.

Smoking and degree of histological inflammation in 71 patients with periductal mastitis or duct ectasia. Values are numbers (percentages) of patients

<table>
<thead>
<tr>
<th>Histological inflammation</th>
<th>Acute</th>
<th>Moderate</th>
<th>Chronic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smokers (n=48)</td>
<td>11 (23)</td>
<td>18 (37)</td>
<td>19 (40)</td>
</tr>
<tr>
<td>Non-smokers (n=23)</td>
<td>3 (11)</td>
<td>3 (11)</td>
<td>17 (74)</td>
</tr>
</tbody>
</table>

χ²=7·5, df=2, P=0·023.

Smoking correlated significantly with the degree of periductal inflammation (χ²=7·5, P=0·023) (table). Duct ectasia was not associated with smoking but was inversely related to the degree of periductal inflammation (p<0·05) and increased with age (mean age of patients with no dilatation 37 (9), with some dilatation 38 (12), and much dilatation 47 (14); F(2, 67)=5·022, P=0·009).

Comment

Histologists have always considered periductal mastitis and duct ectasia to be a single disease.1