Determination of the minimum dose of lactose drug carrier that can be sensed during inhalation

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Lactose is commonly used as a carrier for inhaled drugs. Twenty healthy volunteers without respiratory symptoms inhaled seven different doses of lactose and a placebo (empty) dose through the four place Diskhaler® device, in order to determine the lowest dose that could be reliably sensed. The minimum dose for which all subjects reported taste or feel sensations was 10 mg. This has implications regarding the amount of carrier used in future drug delivery systems.

Keywords lactose inhalation sensation

Introduction

The inhaled route has well established benefits for drug delivery in the treatment of airway diseases, and a number of different inhaled drug delivery systems have been developed [1]. Dry powder inhalers have certain advantages over metered dose inhalers since they do not involve aerosol constituents, which can have direct adverse effects on health [2] and indirect effects due to their impact on the environment [3]. Being breath operated they obviate the need for hand-breath coordination and are considered easier to use [4]. Dry powder devices commonly use sealed individual doses of medication ('caps' or 'blisters'), allowing patients and physicians to monitor usage and thus potentially improving compliance. Each dose usually comprises active drug and lactose carrier, the dose of lactose varying considerably in different devices.

It has been proposed that one advantage of using lactose as a carrier is that it may allow patients to register that they have taken a dose, due to its irritant effect on the back of the throat [5]. We have observed that patients often complain that they cannot detect actuation of one of the dry powder devices which delivers pure drug without any lactose carrier. However, we have found no published reports of controlled studies of individuals' ability to recognise that a dose of medication has been inhaled. The present study was undertaken in order to determine the minimum dose of lactose which can be reliably sensed when inhaled. This may have implications for future development of inhaled drug formulations.

Methods

Twenty healthy volunteers without recent respiratory symptoms, documented lactose intolerance, taste disturbance or nasal blockage were studied. Five were female. Mean age was 31.0 [range 24.2–44.5] years. Eight subjects were current cigarette smokers, five were ex-smokers and seven were lifelong non-smokers. All were naive to inhaler use. Subjects were asked to refrain from smoking or eating for 2 h prior to attending the laboratory, so as not to affect taste perception. Written informed consent was obtained from each subject, and the study was approved by the Royal Postgraduate Medical School and Hammersmith Hospital Research Ethics Committee.

Each subject inhaled lactose 1, 3, 5, 7, 10, 12.5 and 25 mg via the four place Diskhaler® device (Allen & Hanburys Ltd, UK) in random order and double-blind. An empty Diskhaler blister was used as a placebo control. Doses were separated by 10 min intervals. Inhaler use was initially demonstrated to subjects, and each inhalation was monitored and judged to be satisfactory. Subjects rinsed their mouths with water prior to each dose. Immediately after inhalation they were asked the standard questions 'Could you taste the dose?' and 'Could you feel the dose as you inhaled?'

Results

There was no clear threshold dose for a positive sensation when the answers to each question were plot-

ted separately (Figure 1a, 1b). However, frequency distribution of a positive response to either question (Figure 1c) suggests a threshold dose of 10 mg for a

Figure 1 Frequency distributions of positive responses to the questions 'Could you taste the dose?', 'Could you feel the dose as you inhaled?' and to the questions combined.

distinct sensation. In two subjects who, by chance, received lactose doses in ascending order an apparent dose-response was demonstrated.

There did not appear to be any obvious difference in response according to gender or smoking status, although the number of subjects studied was relatively small.

Discussion

We found that the minimum dose of lactose which could be sensed by all subjects during inhalation was 10 mg. Different subjects appeared to interpret the sensations of taste and feel of an inhaled powder differently. The experimental design deliberately chose not to allow subjects to define sensation beforehand. Only positive or negative responses were allowed and amendment of the first reply was not permitted.

In Europe the current packing dose of lactose with various drugs delivered by Diskhaler is 25 mg, while 12.5 mg is being investigated for salmeterol in the USA. Our data suggest that the packing dose in Europe could be reduced by half, while still enabling patients to confirm to themselves that they have taken a dose of drug correctly. Various questions remain. Does perception in patients, such as older smokers with chronic obstructive lung disease or younger children with asthma, differ from that in normal volunteers? Could tachyphylaxis to the taste or feel sensations develop? It is not clear how far these results with one specific device can be extrapolated to others, but studies of this kind have implications for future development of dry powder devices. Reduction of the present lactose carrier dose may be possible while still retaining the sensation of delivery to the oral cavity.

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