Pharmaceutical Research, Vol. 7, No. 10, 1990

Report

A Method for Determination of the Absolute Pulmonary Bioavailability of Inhaled Drugs: Terbutaline

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Received January 22, 1990; accepted April 12, 1990

Terbutaline sulfate (4 × 0.250 mg) was given to 11 healthy volunteers by inhalation from a metered dose inhaler (MDI), with and without oral administration of a charcoal slurry. Before the inhalations, the adsorbing capacity of the charcoal slurry was tested. Deuterated terbutaline, 0.125 mg, was given intravenously at the same time as the test doses. The charcoal slurry adsorbed 97% of an oral dose. The oral contribution to the overall systemic bioavailability after inhalation, when charcoal was coadministered, could thus be neglected. After inhalation of terbutaline, 9.1% of the dose was deposited in the lungs and an additional 6.7% was systemically available via the oral route. The method presented measures the absolute pulmonary bioavailability after inhalation from a MDI. Since a deuterated analogue is given intravenously together with the inhalations, fewer subjects are needed to obtain reliable data.

KEY WORDS: terbutaline sulfate; lung deposition; bioavailability; metered dose inhaler; stable isotope.

INTRODUCTION

Most drugs are administered by the oral or parenteral route even when local effects, e.g., in the lung, are desired. In such cases the drug exerts its effects only after being distributed in the whole body, and the bioavailability at the target site is low. Thus, there are high drug levels in all parts of the body and the patient may experience unwanted side effects.

Local administration may reduce unwanted side effects since lower total doses can often be given. For many drugs used in the treatment of pulmonary diseases, e.g., the β_2-agonist terbutaline, inhalation is the preferred route of administration. For terbutaline it has been shown that good clinical effects can be achieved even if the systemic plasma concentrations are negligible (1). However, only a small portion of the inhaled drug is deposited in the lungs after inhalation, while the greater portion of a given dose is deposited in the oropharynx and eventually swallowed (2). The swallowed drug is absorbed and metabolized in the same way as an oral formulation. The degree of deposition in the lungs is thus of interest when evaluating new drugs and inhalation devices.

Different experimental designs have been used to estimate the amount deposited in the lungs. Radioactively labeled particles, assumed to behave like the drug aerosol, were given by inhalation, and the degree of deposition in the lungs was measured with a gamma camera (2). In other studies, differences in metabolism after pulmonary and oral absorption were used to calculate the pulmonary availability (3). In some studies, a charcoal slurry was given at the same time as the inhalation to prevent the gastrointestinal (GI) absorption of the swallowed drug (1,4). It is generally agreed that an average of 10% of an inhaled dose reaches the lungs when given by a metered dose inhaler (MDI) (2). For powder inhalers somewhat higher figures for pulmonary deposition have been reported (5,6). There is, however, a large variation in the presented figures because of different experimental designs. The number of subjects in most studies has been low and no absolute reference formulation has been included.

Traditionally, a bioavailability study consists of two separate experiments, involving the test formulation and the reference formulation. When the absolute bioavailibility is determined, an intravenous infusion, or its equivalent, is used as the reference formulation. However, if a deuterium-labeled tracer is used as reference formulation, both test and reference formulation can be given at the same time. Thereby the number of subjects needed to detect an assigned difference could be reduced by a factor of five (7). The rationale for using deuterated terbutaline as a pharmacokinetic internal standard has been discussed recently (8).

The present study aimed at determining the absolute pulmonary bioavailability of inhaled terbutaline by intravenous coadministration of a deuterated analogue.

MATERIALS AND METHODS

Eleven healthy volunteers (six men and five women; Table 1) participated, some of them in both parts of the study.

Their age was between 21 and 37 years (mean, 29 years),

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0724-8741/90/1000-1068$06.00/0

Table I. Demographic Data of the Volunteers and Bioavailability of Terbutaline When Given as a Solution or by MDI[a]

Subject No.	Sex	Age (years)	Weight (kg)	Solution + coal	MDI + coal	MDI	MDI,gut
1	F	26	57	≤0.10	5.47	15.03	9.56
2	M	21	82	≤0.10	9.00	12.34	3.34
3	F	20	65	0.58	11.46	19.52	8.06
4	M	26	61	0.42	10.76	16.09	5.33
5	M	31	78	0.31	12.41	19.57	7.16
6	M	36	100	—	5.89	—	—
7	F	31	57	—	8.62	—	—
8	M	37	85	—	13.04	—	—
9	F	30	52	—	8.17	—	—
10	M	33	83	—	3.91	—	—
11	F	26	55	—	11.85	—	—
$\bar{X}$				0.30	9.14	16.51	6.69
SD				0.21	3.06	3.10	2.42
Range		21–40	52–100				

[a] The values are given as the percentage of a simultaneously administered intravenous dose of deuterated terbutaline. MDI,gut is calculated as MDI − (MDI + coal).

and they weighed from 52 to 100 kg (mean, 70 kg). Before inclusion into the study they were judged to be healthy by a physician after physical examination and laboratory tests.

The study was approved by the local Ethics Committee and registered by the Swedish National Board of Health and Welfare. The study was performed in accordance with the Declaration of Helsinki. Written informed consent was obtained from the subjects prior to inclusion in the study.

The study was divided into two parts. In the first part, the bioavailability of terbutaline from an oral terbutaline solution, taken together with activated charcoal, was evaluated. This part was performed to determine to what degree the GI absorption of terbutaline was prevented by concomitant charcoal intake. In the second part, the pulmonary and the combined pulmonary and oral bioavailabilities of terbutaline given by a MDI were investigated. Within this part of the study the experimental days were randomized and a crossover design was used. There was a washout period of at least a week between 2 experimental days.

Terbutaline sulfate (Bricanyl), MDI, 0.250 mg/dose, [$^2H_6$]terbutaline hydrochloride, solution for infusion, 0.025 mg/ml, and terbutaline sulfate, solution for oral intake, 0.3 mg/ml, were used. All three terbutaline formulations were from AB Draco, Sweden. Carbomix, charcoal, 50.0 g (to be suspended in 200 ml water), was from Medica Pharmaceutical, Sweden.

The same MDI was used for all the inhalations. The nominal dose of the MDI was 0.250 mg/actuation. The actual dose (dose to patient) was 0.202 mg/actuation as determined by a cascade impactor (9). The actual dose was used in all calculations.

The actual amount given, as an infusion, of deuterated terbutaline was, in each case, obtained by weighing the syringe before and after infusion. In the following, the term terbutaline refers to the respective salts given.

Treatment

All administrations were given in the morning, within an hour after breakfast. A light lunch was served approximately 4 hr after drug intake.

Part 1: Bioavailability of Terbutaline from an Oral Solution

Five subjects (1–5) participated. The subjects were given an intravenous infusion of 0.125 mg of deuterated terbutaline during 5 min. Three minutes later, 5 g of charcoal was administered, and then within 2 min, 5 mg of terbutaline as an oral solution. Another 5 g of charcoal was given within 2 min after the oral terbutaline solution. The subjects were told to swirl the charcoal solution around in the mouth before swallowing it. At 1, 2, 3, and 4 hr after drug intake the subjects were given another 10 g of charcoal. Not until 1 hr after drug intake were the subjects allowed to rinse their mouths with water.

Urine was collected in four 12-hr pools: 0–12, 12–24, 24–36, and 36–48 hr after the start of the intravenous infusion. Three 10-ml samples from each pool were saved. The urine was kept at −18°C until analyzed by GC-MS for its content of terbutaline and [$^2H_6$]terbutaline as previously described but with [$^2H_9$]terbutaline as internal standard (10). The analyses were performed at AB Draco.

Part 2: Bioavailability of Terbutaline from the MDI

Before entering part two of the study the volunteers were instructed how to use the MDI.

In this part of the study the volunteers inhaled a nominal dose of 4 × 0.250 mg of terbutaline from a MDI. All subjects inhaled terbutaline *with* charcoal administration, and in addition, the five subjects who participated in Part 1 of the study also inhaled terbutaline *without* charcoal administration. All inhalations were controlled by measurement of peak inspiratory flow, as well as time for actuation of the MDI. After each inhalation the volunteers held their breath for 10 sec. A pulmonary function analyzer, Monaghan M403 (Littleton, CO), was connected to the MDI via specially de-

signed interfaces and used in the measurements. The four dosings were given within 2 min.

Also, in this part of the study the subjects were given an infusion of 0.125 mg deuterated terbutaline intravenously.

Urine was sampled, handled, and analyzed as in the first part of the study.

The subjects were not allowed to take other medications the day before and during the experimental days.

Calculations

The systemic bioavailability of terbutaline was calculated by comparing the amounts excreted in the urine of terbutaline and [$^2H_6$]terbutaline during the 48-hr period with due corrections for the doses given. Since no metabolism of terbutaline takes place in the lungs (11) and since no drug was found to be absorbed over the gut wall (cf. below), when charcoal is given before and after the inhalation, the pulmonary bioavailability is the same as the calculated systemic bioavailability.

RESULTS

The subjects complied well with the study protocol. All inhalations (flow rate vs time) were followed on an oscilloscope and were judged to be performed adequately. In the second part of the study, for subjects 6 to 11, the peak inspiratory flow (PIF) was registered: the mean PIF was 86 (range, 57–118) liters/min.

The bioavailable amount of terbutaline after intake of an oral solution of terbutaline together with charcoal was in no case higher than 0.6% (Table I).

The mean pulmonary bioavailability of terbutaline from the MDI was 9.14% (Table I). For the first five subjects the value was 9.83%, and when the oral component was added to the bioavailability for these subjects (administration without charcoal), the value rose to 16.51%, i.e., an increase of 6.68%.

DISCUSSION

The oral bioavailability of terbutaline, when administered together with food, is approximately 10% (12). The oral bioavailability of terbutaline after concomitant intake of terbutaline solution and activated charcoal in the present study was, on average, 0.3%. Thus, 97% of the given oral solution of terbutaline was adsorbed on the charcoal and not available for absorption through the gut wall. Thus, the experimental design, with inhalation of terbutaline and coadministration of charcoal, makes it possible to measure the pulmonary bioavailability of terbutaline with little influence from the swallowed drug. When terbutaline was given by the MDI, together with charcoal, 9.14% was absorbed from the lungs. This value is in accordance with earlier studies on MDIs where other methods have been used (2).

After inhalation without concomitant charcoal administration, for subjects 1 to 5, the oral component of the added pulmonary and oral bioavailability was 6.68%. The bioavailability of the swallowed part of the dose was thus approximately 7%, i.e., nearly half of the systemically available dose. As the bioavailability of the swallowed part of the dose was calculated as the difference between values obtained on 2 different experimental days, the dispersion is larger than in the values for pulmonary bioavailability, which were calculated from values from 1 experimental day. The value, 7%, should be considered a rough estimate of the oral component of the bioavailability of inhaled drug.

It seems likely that the amount deposited in the lungs is correlated with the clinical effect. However, a study where the effects *and* the pulmonary bioavailability are measured concurrently should be performed to confirm this.

In summary, a method to measure pulmonary deposition of inhaled substances has been presented, with terbutaline as the example. The method is simple and uses drug measurements to determine pulmonary deposition, rather than radioactively labeled particles or microspheres.

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