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Pharmacokinetics and relative bioavailability of salbutamol metered-dose inhaler in healthy volunteers

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KEY WORDS salbutamol; lung; pharmacokinetics; biological availability; high pressure liquid chromatography

ABSTRACT

AIM: To study the pharmacokinetics and relative bioavailability of salbutamol metered-dose inhaler (MDI) in healthy volunteers. **METHODS**: An HPLC method for the determination of salbutamol in human plasma was improved. Ten healthy male Chinese volunteers were enrolled in a randomized crossover study. After the subjects inhaled or orally administered 1.2 mg salbutamol, fourteen blood samples were collected at predetermined time points. The concentrations of salbutamol in plasma were assessed with non-compartment model to obtain the pharmacokinetic parameters. The relative bioavailability of MDI versus water solution was calculated. **RESULTS**: The HPLC assay was sensitive, specific, accurate, and precise. The pharmacokinetics of salbutamol MDI was described well with two-compartment model. The parameters for salbutamol inhaled and orally administered were as following: T_{max} (0.22 ± 0.07) and (1.8 ± 0.6) h, C_{max} (3.4 ± 1.1) and (3.9 ± 1.4) $\mu g \cdot L^{-1}$, $T_{1/2}$ (4.5 ± 1.5) and (4.6 ± 1.1) h, $AUC_{0-20\ min}$ (0.9 ± 0.3) and (0.16 ± 0.10) $\mu g \cdot h \cdot L^{-1}$, respectively. There were significant differences in T_{max} and $AUC_{0-20\ min}$ between the two dosage forms. The $AUC_{0-20\ min}$ (*inhal*) was 8 times as high as the $AUC_{0-20\ min}$ (*po*). The relative bioavailability of salbutamol MDI was 57 % ± 24 % compared with oral solution. **CONCLUSION**: The absorption process of salbutamol MDI in human was significantly different from that of oral solution.

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INTRODUCTION

Salbutamol metered-dose inhaler (MDI) is an effective formulation for relieving the acute symptoms of asthma. But limited literatures on its pharmacokinetics in human are available due to its low dosage and low plasma concentration. Early studies, which adopted isotope label method, concluded that salbutamol MDI had the same pharmacokinetic characteristics with its oral dosage form[1,2]. However, some researchers recently investigated the disposition of the drug in plasma within 20 min after inhalation[3,4]. But the complete drug concentration-time profile has not been investigated.

This study investigated the pharmacokinetics of salbutamol MDI and its oral solution in healthy volunteers and calculated the relative bioavailability of MDI versus oral solution.

MATERIALS AND METHODS

Drugs and reagents Salbutamol MDI (Ventolin Inhaler, lot № 980902A, Chongqing Glaxo Wellcome Pharmaceuticals Ltd) was purchased. Salbutamol water solution was obtained by actuating Ventolin Inhaler 1.2 mg into 100 mL deionized water. Salbutamol reference standard (purity 99.1 %) was offered by Chongqing Glaxo Wellcome Pharmaceuticals Ltd. The internal standard bamethan was ordered from Sigma Company. Other reagents of HPLC grade were purchased from Tianjin Siyou Chemical Reagent Company.

Chromatographic condition The HPLC system consisted of Waters M510 pump, Shimadzu RF530 fluorescence detector and Shimadzu data processing unit C-R2Ax Chromatopac. The analytical column was Zorbax ODS column, 4.6 mm × 25 cm, 5 μm. The mobile phase was composed of phosphate buffer (pH 2.5)-methanol-acetonitrile (900:160:20, v:v:v). The flow rate was 0.8 mL/min. The excitation wavelength and emission wavelength were 275 nm and 309 nm,

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respectively.

Assay of salbutamol[5,6] Supelco LC-18 SPE columns (1 mL) were used to extract salbutamol in plasma. The column was washed once at a slow rate with 1 mL of methanol and once with water. Then 50 μL of the internal standard solution (0.2 mg/L) and 1 mL of the sample (standard or unknown) were transferred into the column. After about 2 min, mild suction was applied so that the sample passed through the column at a slow rate of less than 1 mL/min. The suction was increased after the sample passed through the column, to expel all the trapped liquid. The column was washed slowly thrice with 1 mL of water and once with 1 mL of acetonitrile. Then 2 mL of methanol was used to elute salbutamol and the internal standard from the sorbent. The eluted liquid was evaporated to dryness under nitrogen flow. The residue was reconstituted in 50 μL of the mobile phase, with 40 μL injected into the HPLC system.

Assay validation Blank human plasma was spiked with salbutamol standard solution to achieve the standard samples at 0.2, 0.5, 1.0, 5.0, 10.0 , and 20.0 μg/L, respectively. The within-run and between-run precisions were determined by analyzing salbutamol control samples at three different concentrations for ten times in one day or six times in six consecutive days respectively. The limit of detection was defined as three times background noise.

Subjects Ten healthy male volunteers aged (26 ± 4) a participated in the study that was approved by the Ethics Committee of Peking Union Medical College Hospital, with the written informed consent of each subject. All subjects had normal cardiac, respiratory, hepatic, and renal function. They did not take any medication in the two weeks prior to or during the study.

Protocol The study adopted an open randomized crossover design, with a washout period of 1 week. The subjects were carefully instructed about the inhalation technique according to the manufacturer's direction. Single dose of 1.2 mg salbutamol *via* Ventolin MDI (12 × 100 μg) or the self-made salbutamol oral solution were given. Mouth rinsing was performed after every inhalation to obviate gastrointestinal absorption. The blood samples were collected before administration and at 5, 10, 15, 20, and 30 min and 1, 1.5, 2, 3, 4, 6, 8, and 12 h after administration.

Pharmacokinetics and statistical analysis The concentrations of salbutamol were assessed with PCNONLIN software (version 4.0, SCI, USA). Non-compartment model was used to obtain the pharmacokinetic parameters for calculating the relative bioavailability of MDI versus water solution. For all pharmacokinetic parameters, comparison was made by paired two-tailed t-test. A probability value of $P < 0.05$ was considered as significant.

RESULTS

Quality control of HPLC assay The linearity was obtained over the range of 0.2 – 20.0 μg/L. The within-run and between-run RSD were 7.01 % and 2.10 % at 0.4 μg/L, 2.18 % and 5.25 % at 4.0 μg/L, and 4.61 % and 4.85 % at 15.0 μg/L, respectively. The limit of detection was 0.1 μg/L.

Concentration-time profile The average concentration-time profiles of salbutamol MDI and oral solution were both described well with two-compartment model (Fig 1). The concentration-time profile of the volunteer (not within the ten subjects) who swallowed the mouth rinsing water was also shown in Fig 2 for discussion.

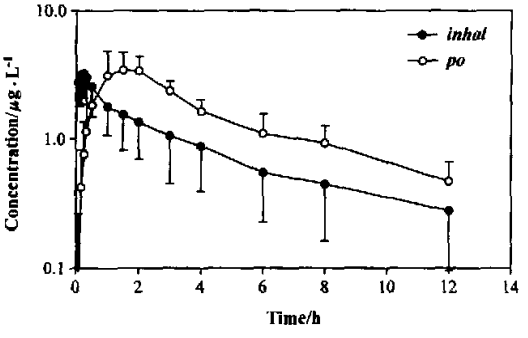

Fig 1. Profiles of mean concentrations versus time after inhalation and oral administration of 1.2 mg salbutamol in healthy volunteers. $n = 10$. $\bar{x} \pm s$.

Pharmacokinetics The pharmacokinetic parameters were listed in Tab 1. Significant differences were found between the MDI and oral solution for T_{max} (0.22 *vs* 1.80 h), $AUC_{0-20\,min}$ (0.91 *vs* 0.16 μg·h·L^{-1}), and $AUC_{0-\infty}$ (12 *vs* 21 μg·h·L^{-1}), $P < 0.01$. The relative bioavailability of salbutamol MDI was 57 % ± 24 %.

DISCUSSION

There are a few studies on the pharmacokinetics of

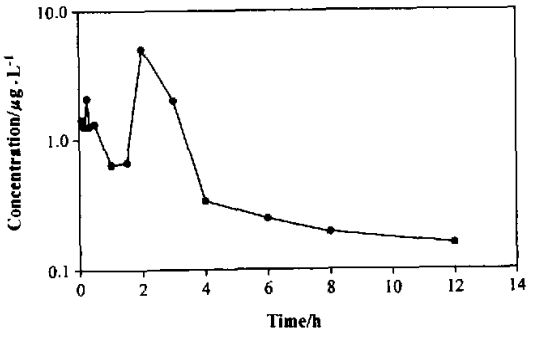

Fig 2. Plasma concentration-time profile of the subject who swallowed mouth-rinsing water after inhalation.

Tab 1. Pharmacokinetic parameters after administration of salbutamol MDI and oral solution in healthy volunteers. $n = 10$. $\bar{x} \pm s$. $^cP < 0.01$ *vs inhal*.

Parameter	*inhal*	*po*
T_{max}/h	0.22 ± 0.07	1.8 ± 0.6[c]
C_{max}/μg·L^{-1}	3.4 ± 1.1	3.9 ± 1.4
β/h^{-1}	0.17 ± 0.06	0.15 ± 0.05
$T_{1/2}$/h	4.5 ± 1.5	4.6 ± 1.1
MRT/h	5.9 ± 2.0	6.9 ± 2.0
$AUC_{0-20\ min}$/μg·h·L^{-1}	0.9 ± 0.3	0.16 ± 0.10[c]
$AUC_{0-12\ h}$/μg·h·L^{-1}	10 ± 5	17 ± 5[c]
$AUC_{0-\infty}$/μg·h·L^{-1}	12 ± 6	21 ± 6[c]
$AUC_{12-\infty}$/μg·h·L^{-1}	2.2 ± 1.4	4.0 ± 2.2[c]
[1] *F*/%	57 ± 24	
[2] I/O	8 ± 5	

[1] $AUC_{0-\infty}$ (*inhal*)/$AUC_{0-\infty}$ (*po*) × 100 %
[2] $AUC_{0-20\ min}$ (*inhal*)/$AUC_{0-20\ min}$ (*po*)

salbutamol MDI in human so far. The available literatures generally took the point of view that per actuation dose could be divided into three parts: a little remains in the device, most of the dose (60 % – 80 %) deposits in mouth and enters the gastrointestinal tracts after being swallowed, only 10 % – 20 % of the dose reaches the lungs[7-9]. The swallowed fraction undergoes extensive (48 %) first-pass conjugation in intestinal wall and liver. The parent drug was found in urine up to 32 % of the dose[10]. The metabolism of salbutamol in lung is little. The drug absorbed *via* lung remains unchanged.

Our study was designed to investigate the "fates" of the two parts (ie, the drug reaching lungs and that reaching gastrointestinal tracts) of per actuation dose emitted by salbutamol MDI. Therefore, oral solution was used to imitate sheer gastrointestinal absorption and inhalation followed by mouth rinsing to imitate lung absorption.

The early literatures utilized isotope label method to determine the plasma drug concentrations in a limited number of subjects. It was concluded that the T_{max} of inhaled salbutamol was 3 – 5 h[1,2]. Although both drug concentration-time profiles obtained in our study complied with two-compartment pharmacokinetic model with similar C_{max}, the T_{max} after inhalation was far shorter than that after oral administration (0.22 h *vs* 1.8 h, $P < 0.01$). It was assumed that the different major absorption positions of the two administration paths caused such substantial difference between the T_{max}. The drug was rapidly absorbed *via* numerous lung blood vessels after inhalation. While it was orally administered, the drug had to pass through more barriers before it approached circulation.

There may be two reasons, which led to the results of early studies. First, the sampling points within the first 20 min after inhalation were not adequate thus the real plasma concentration peak produced by lung absorption was missed. Meanwhile, the authors did not take the effect of mouth rinsing into consideration. Thus the high plasma concentration resulted from mouth deposition covered up the lung contribution. It was clearly confirmed in our study that mouth rinsing could remove the majority of those deposited in oropharynx.

There was significant difference between the two drug concentration-time profiles during the first 20 min (Fig 1). The plasma concentration rose rapidly up to 2.77 μg/L at 5 min after inhalation. In contrast, it took nearly 20 min for the oral concentration to surpass 1 μg/L. $AUC_{0-20\ min}$ (*inhal*) was 8 times as high as $AUC_{0-20\ min}$ (*po*). These data demonstrated that the amount of drug reaching the lungs was far greater after inhalation than that after orally administration. That was why inhaled salbutamol could relieve the asthmatic symptoms within a few minutes.

One volunteer (not within the ten subjects) non-intentionally swallowed the mouth rinsing water. This action resulted in double peaks on the drug concentration-time profile (Fig 2). The first one emerged at 15 min and the second at 2 h. Comparing Fig 2 with Fig 1, it was easy to recognize that the two peaks resulted from lung and gastrointestinal absorption separately. Combining this phenomenon with the high ratio of $AUC_{0-20\ min}$ (*inhal*) versus $AUC_{0-20\ min}$ (*po*) obtained here, we assumed that $AUC_{0-20\ min}$ reflected the lung

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availability of salbutamol MDI.

In the two salbutamol MDI studies carried out in healthy male volunteers which used the same dosage with our study, the C_{max} within 20 min were 2.93 μg/L and 3.29 μg/L respectively, similar with our result (3.42 μg/L)[3, 4]. It seemed that there was no race difference in salbutamol bioavailability in human.

The difference was significant in the absorption process between salbutamol MDI and oral solution.

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沙丁胺醇气雾剂在健康受试者体内的药物动力学和相对生物利用度

R96 A

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关键词 沙丁胺醇; 肺; 药物动力学; 生物利用度; 高压液相色谱法

目的: 研究沙丁胺醇气雾剂在健康受试者的药物动力学和生物利用度. **方法**: 十名健康男性志愿者单剂量吸入 1.2 mg 沙丁胺醇气雾剂或口服沙丁胺醇水溶液. 用HPLC法测定人血浆中沙丁胺醇浓度. 以非房室模型计算药物动力学参数, 计算气雾剂相对水溶液的生物利用度. **结果**: 气雾剂和口服溶液的药物动力学参数如下: T_{max} (0.22 ± 0.07) 和 (1.8 ± 0.6) h, C_{max} (3.4 ± 1.1) 和 (3.9 ± 1.4) μg·L^{-1}, $T_{1/2}$ (4.5 ± 1.5) 和 (4.6 ± 1.1) h, $AUC_{0-20\ min}$ (0.9 ± 0.3) 和 (0.16 ± 0.10) μg·h·L^{-1}. 两种给药途径的 T_{max} 和 $AUC_{0-20\ min}$ 之间差异显著 ($P < 0.01$). $AUC_{0-20\ min}$ (*inhal*) 为 $AUC_{0-20\ min}$ (*po*) 的 8 倍. 沙丁胺醇气雾剂相对口服溶液的生物利用度为 57 % ± 24 %. **结论**: 沙丁胺醇气雾剂在人体的吸收过程与口服溶液差异有显著性.

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