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Bioavailability assessment of salbutamol sulfate suppositories in human volunteers

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Abstract

The purpose of this investigation was to evaluate the bioavailability of three salbutamol sulfate suppository formulations. The formulations were; 2 mg salbutamol sulfate in Suppocire® NA base containing 6% Eudispert gel (F1), 2 mg salbutamol sulfate in Witepsol® H15 base containing 3% methyl cellulose gel (F2), and 2 mg salbutamol sulfate in Witepsol® W25 base containing 3% methyl cellulose gel (F3). The formulations were administered via rectal route in six healthy male adult volunteers. The bioavailability of the three suppository formulations was compared with the oral bioavailability of salbutamol sulfate 2 mg tablets (F4). Six volunteers participated in a four-way crossover study, where each study was separated from the other by an interval of 1 weak. Venous blood samples of 5 ml were taken immediately before dosing and after predetermined time intervals of 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6 and 8 h. The result showed that $C_{max} \pm$ S.D. observed were 12.96 ± 2.11, 14.87 ± 2.33, 10.02 ± 1.42 and 11.51 ± 1.22 ng ml^{-1} for F1, F2, F3 and F4, respectively. The $T_{max} \pm$ S.D. were found to be 1.91 ± 0.20, 1.83 ± 0.26, 2.50 ± 0.00 and 2.67 ± 0.24 h for F1, F2, F3 and F4, respectively. AUC ± S.D. values were 40.25 ± 1.88, 42.16 ± 1.55, 28.62 ± 1.98 and 37.63 ± 1.44 ng h per ml for F1, F2, F3 and F4, respectively. The relative bioavailabilities of the investigated formulations were 112.04, 106.96 and 76.06 for formula F2, F1 and F3, respectively, when compared with the oral preparation (F4). The finding indicates that the bioavalaibility of salbutamol sulfate can be enhanced by delivering it rectally with Suppocire® NA base containing 6% Eudispert® gel or with Witepsol W25 base containing 3% methyl cellulose to match that of oral tablets. Salbutamol sulfate can be rectally administered in patients who are less compliant with the oral administration.

Keywords: Suppository bases; Salbutamol sulfate; Gels; First-pass metabolism; Bioavailability; Rectal administration

Oral administration is the route choice in the daily practice of pharmacotherapy. However, oral route becomes impractical in certain cases such as nausea, vomiting or convulsion. In such situations, the rectal route may provide a practical alternative. The human rectum represents a body cavity in which drugs can be easily introduced and retained well documented absorption (Jantzen and Diehl, 1991; Kokki et al., 2003; Lennernas et al., 2002; Berko et al., 2002; Debleay and Tukker, 1988). Rectal route is also good for drugs that irritate gastrointestinal (GI) mucosa and/or get inactivated in the stomach environment (Ansel, 1985;

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Rawlins, 1979). Other reasons for preferring the rectal over the oral route is when the drug is extensively metabolised or deactivated by liver enzymes (Jay et al., 1985). The superior rectal vein, perfusing the upper part of the rectum, drains into the portal vein and subsequently into the liver. On the other hand, the middle and inferior rectal veins drain the lower part of the rectum and venous blood is returned to the inferior vena cava. Therefore, drug absorbed in the latter system will be delivered preferentially to the systemic circulation by passing the first-pass metabolism (De Leede et al., 1983). Another mechanism enabling a drug to circumvent hepatic first-pass elimination is absorption into the lymphatic system (Takada et al., 1986).

When a drug is administered as a suppository, several factors may influence the extent and rate of drug absorption into the general circulation (De Boer et al., 1984; Blaey and Polderman, 1980). Melting or liquefaction of the fatty or hydrophilic suppository precedes release of the active drug; the latter process is dependent on rectal environment, drug substance and suppository base. Rectal administration of some high clearance drugs such as propranolol and salicylamide did not result in higher bioavailability compared with oral administration (De Boer, 1979, 1982). It is possible that in these cases, decreased rectal absorption masks the first-pass effect.

Salbutamol (albuterol) is a β2-selective adrenoreceptor agonist, which has demonstrated considerable bronchodilatary effects. The onset of maximum effect of salbutamol is dependent on the formulation used and the rout by which it is administered (Shenfield, 1982; Tattersfield, 1984). Salbutamol is well absorbed orally. However, its systemic bioavailability is about 50% due to extensive presystemic metabolism in the GIT and liver. The metabolite possesses little or no β-adrenergic activity (Morgan et al., 1986). Salbutamol suppository (2 mg dose) showed higher plasma concentration and more improvement in lung function than 0.2 mg inhaler (Stemmann and Wolff, 1980).

In a previous work (Taha et al., 2003), we performed in vitro investigation on the effect of different concentration of gels (methyl cellulose gel and Eudispert® gel, EPICO, Egypt) on stability and drug release kinetics. The bases used were fatty suppository bases (Suppocire and Witepsol) and water-soluble bases (PEG). We also evaluated the prepared suppositories (with and without gel) for their hardness, melting points and content uniformity. It was found that three salbutamol sulfate suppository formulations each containing 2 mg salbutamol sulfate (F1) Suppocire®NA base (Gattefosse, France) containing 6% Eudispert® gel, (F2) Witepsol® H15 base (Nobel Dynamitte, West Germany) containing 3% methyl cellulose gel and (F3) Witepsol® W25 (Nobel Dynamite, West Germany) base containing 3% methyl cellulose gel had higher in vitro drug release (98.3, 97.1 and 94.3%, respectively) than many others investigated, and demonstrated good self-life stability at room temperature for 1 year (salbutamol sulfate remaining was 91, 93.1 and 94.2%, respectively).

A logical extension of the work would be to evaluate whether or not salbutamol sulfate is bioavailable from the suppositories prepared and characterised. Therefore, the objective of this work was to investigate the bioavailability of salbutamol sulfate from these three formulations and compare it with the bioavailability of a tablet formulation.

Six healthy male adult volunteers, ages 37–51 years and body weights 56–94 kg participated in non-fasting open randomised four-way crossover study. The selected volunteers were considered healthy on the basis of detailed medical history. After obtaining the institutional review board approval, and explaining the research protocol with possible side effects, the volunteers were asked to sign consent forms. Verbal assurance was taken from all of them that they have not taken any drugs during, and for 1 week preceding the study. One week was kept as a wash out period before cross over. On the day of experiment, venous blood samples (5 ml) were withdrawn immediately just before dosing and after 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6 and 8 h of dosing. The samples were collected in heparinised tubes, immediately centrifuged (CT5, Germany), and the separated plasma samples were frozen until analysis.

The HPLC method used was a modification of the method used by Emm et al. (1988). The equipment used was HPLC (Phillips, Holland) equipped with UV detector (Pye unichem) and integrator (Spectra Physics, USA). Each plasma sample was prepared for extraction by spiking 1 ml of plasma with 150 μl of internal standard solution, amoxycillin trihydrate in purified distilled water in concentration 200 $\mu g\,ml^{-1}$. First, the extraction column (Bond Elute C 18) was activated with 1 ml methanol (Sigma Chemical Co.,

St. Louis, MO, USA), followed by 1 ml of purified distilled water. The plasma sample was transferred to the top of the column and vacuum was applied. The column was washed with 1 ml of purified distilled water followed by 2 ml of 10% (v/v) of methanol in water and allowed to dry for 2 min under vacuum. Drug and internal standard were eluted from the column with 1 ml of 75% (v/v) of methanol in 0.25 M ammonium acetate (Sigma Chemical Inc.) buffers. The eluent was evaporated to dryness under nitrogen at 50 °C. The residue was reconstituted with 250 μl of aqueous 10% methanol solution. Fifty microliters of this solution was injected into HPLC column (C-18 separation column), analysed using the HPLC and monitored at 278 nm (Pye-Unichem UV detector). The mobile phase was methanol:ammonium acetate (0.02 M) in a ratio 1:1 and the flow rate was 1 ml min^{-1}.

In the drug formulation studies, it is important that the in vitro work is followed by in vivo bioavailability studies. Several formulations that have shown good in vitro release characteristics failed to perform in vivo (Roshdy et al., 2002; Corrigan et al., 2003; Varshosaz and Dehghan, 2002). Studies have also indicated that bioavailability in animal models was not consistent with human bioavailability results (Thrall and Woodstock, 2003). Therefore, it was decided to perform the bioavailability in human volunteers directly.

For convenience in the present study, it was decided to perform relative bioavailability studies with oral tablets instead of absolute bioavailability. Average plasma concentrations were plotted with time to obtain the figure shown in Fig. 1. From this figure, area under the curve (AUC), maximum plasma concentration (C_{max}), and time for maximum concentration (T_{max}) were obtained. Statistical analysis was performed by one-way ANOVA followed by Tukey's post hoc comparison.

From the data obtained in Table 1 and Fig. 1 it appears that F2 showed the highest rate and extent of drug absorption where $C_{max} \pm$ S.D. was 14.87 ± 2.33 ng ml^{-1}. The investigated formulation can be arranged in descending order according to the mean values of C_{max} as follows: F2 > F1 > F4 > F3. However, the statistical analysis indicated that F1 and F2 suppositories were comparable to the oral tablets (F4) with no statistically significant difference ($P < 0.05$). The third formulations, F3, was found to have significantly less AUC ($P < 0.05$) as compared to the control formulation of oral salbutamol (F4).

The T_{max} values for the investigated formulations showed that F1, F2 had the highest rates of drug absorption ($T_{max} \pm$ S.D. were 1.91 ± 0.2 and 1.83 ± 0.26 h, respectively) while F3 and F4 showed the lowest ones ($T_{max} \pm$ S.D. were 2.50 ± 0.00 and 2.67 ± 0.24 h, respectively). The results also show that there is a correlation between the in vitro dissolution data (Buchwald, 2003) and the in vivo bioavailability study. From the results, it was found that the percentage relative bioavailability of the investigated formulations were 106.96, 112.04 and 76.06 for F1, F2 and F3, respectively.

In conclusion, the formulations containing Suppocire® NA + 6% Eudispert (F1) and Witepsol®H15 + 3% MC (F2) showed comparable AUC with the commercial salbutamol sulfate tablet (F4). The AUC

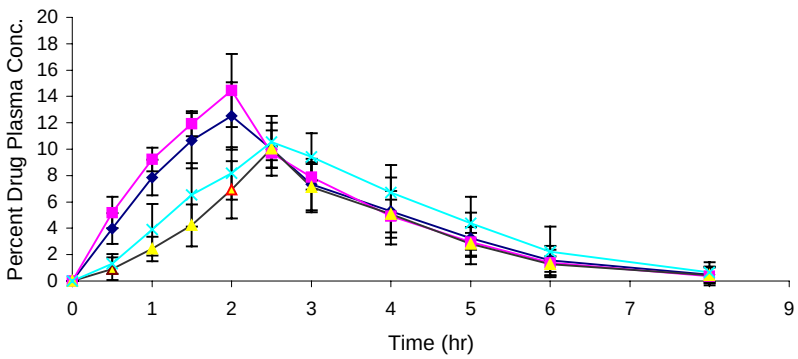

Fig. 1. Plasma profiles of salbutamol sulfate suppository and tablet formulations in human: (◆) formulation 1; (■) formulation 2; (▲) formulation 3 and (×) formulation 4.

Table 1
Pharmacokinetic parameters of salbutamol sulfate suppository formulations

Pharmacokinetic parameters	Formulation number (mean ± S.D.)			
	F1	F2	F3	F4
AUC ($ng\,ml^{-1}\,h$)	40.25 ± 1.88	42.16 ± 1.55	28 ± 1.98	37.63 ± 1.44
C_{max} ($ng\,ml^{-1}$)	12.96 ± 2.11	14.87 ± 2.33	10.02 ± 1.42	11.51 ± 1.22
T_{max} (h)	1.91 ± 0.20	1.83 ± 0.26	2.50 ± 0.00	2.67 ± 0.24
K_{ab} (h^{-1})	0.889 ± 0.02	0.897 ± 0.11	0.71 ± 0.01	0.71 ± 0.12
$T_{1/2ab}$ (h)	0.78 ± 0.10	0.77 ± 0.02	0.98 ± 0.01	0.98 ± 0.13
K_{el} (h^{-1})	0.545 ± 0.07	0.593 ± 0.05	0.570 ± 0.11	0.546 ± 0.05

values were 40.25 ± 1.88, 42.16 ± 1.55, 28.62 ± 1.98 and 37.63 ± 1.44 ng h per ml for F1, F2, F3 and F4, respectively. The F1 and F2 formulations also showed comparable C_{max} values and lower T_{max} values as compared to the controls. The F3 formulations showed less bioavailability than the control. From the results one can conclude that by adequate selection of the vehicle, the rectal bioavailability of salbutamol sulfate could be improved to match that of oral tablets.

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