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Comparison of the IV pharmacokinetics in sheep of miconazole–cyclodextrin solutions and a micellar solution.

G. Piel *, B. Evrard, T. Van Hees, L. Delattre

Laboratoire de Technologie Pharmaceutique, Institut de Pharmacie, Université de Liège, Tour 4, Bat. B36, Avenue de l'Hôpital 1, 4000 Liege 1, Belgium

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Abstract

The pharmacokinetics of miconazole were studied after intravenous administration to six sheep (4 mg/kg) of three aqueous solutions: a marketed micellar solution containing polyoxyl-35 castor oil (Daktarin IV®) was compared with two solutions both containing 50 mM lactic acid and a cyclodextrin derivative (100 mM HP-βCD or 50 mM SBE_7-βCD). The aim of this work was to demonstrate that these cyclodextrin derivatives (CDs) have no effect on the pharmacokinetics of miconazole by comparison with the micellar solution. The plasma concentration time curves have shown that there is no significant difference between the three solutions.

Keywords: Miconazole; Cyclodextrin derivatives; Intravenous pharmacokinetics; Sheep

1. Introduction

Miconazole is a drug substance well known for its antimycotic activity. More particularly, miconazole is an antimycotic drug with a wide activity spectrum; it is endowed with a powerful activity against dermatophytes and Candida albicans, as well as against some gram-positive germs. It acts by combination of two mechanisms: ergosterol biosynthesis inhibition, which causes lysis of the fungal cell membrane integrity and fluidity, and direct membrane damage of the fungal cell (Kauffman and Carver, 1997).

Unfortunately, miconazole is practically insoluble in water (< 1.03 μg/ml) and is consequently formulated with a non-ionic surfactant, polyoxyl-35 castor oil (Cremophor EL®), for parenteral administration. Polyoxyl-35 castor oil is associated with several side effects most notably an allergic reaction comparable with anaphylactic shock (Howrie et al., 1984; Hopkins, 1988; Brew-

* Corresponding author. Tel.: + 32-4-3664-307; fax: + 32-4-3664-302.

E-mail address: geraldine.piel@ulg.ac.be (G. Piel)

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ster et al., 1989; Reynolds and Aronson, 1992). The use of this solution is limited because of the toxic effects related to the presence of this surfactant.

It has been shown that cyclodextrins (αCD, βCD, hydroxypropyl-βCD (HP-βCD) and sulfobutylether$_7$-βCD (SBE_7-βCD)) are able to form an inclusion complex with miconazole and that they are able to increase its aqueous solubility (Van Doorne et al., 1988a,b; Mura et al., 1992; Pedersen et al., 1993a,b; Perdersen, 1994; Bononi, 1995 Piel et al., 1998).

It was also demonstrated that CDs and acids have a synergistic effect on the aqueous solubility of miconazole. HP-βCD and SBE_7-βCD were chosen to develop a new non-surfactant parenteral solution in order to avoid the anaphylactic reactions ascribed to polyoxyl-35 castor oil. These CD derivatives were chosen because of their high solubilizing power and their low systemic toxicity (Yoshida, 1988; Brewster et al., 1990; Rajewski et al., 1995; Stella, 1996). A combination of HP-βCD (100 mM) and lactic acid (50 mM) or of SBE_7-βCD (50 mM) and lactic acid (50 mM) allows to solubilize more than 10 mg of miconazole/ml, which is the concentration of the marketed solution. These solutions have an acceptable pH value, do not precipitate when diluted and are stable at 4, 25 and 45°C for at least 9 months (Piel et al., 1997, 1998).

The objective of this work is the comparison of the pharmacokinetics of miconazole after intravenous (IV) administration to sheep of three solutions: a marketed micellar solution (Daktarin® IV), a solution containing HP-βCD and a solution containing SBE_7-βCD.

2. Materials and methods

2.1. Materials

Miconazole was obtained from Janssen Pharmaceutica (Beerse, Belgium). β-CD and γ-CD were obtained from CNI (Neuilly-sur-Seine, France) and Wacker Chemie GmbH (Munchen, Germany). HP-βCD and SBE_7-βCD were kindly supplied by Janssen Biotech (Olen, Belgium) and Cydex (Kansas, USA), respectively. All other products were of analytical grade.

Six sheep (male and female) weighing between 48.5 and 75 kg were used.

2.2. Dosage form preparation

As recommended, the Daktarin® IV solution was diluted five times with NaCl 0.9% before administration.

The miconazole–HP-βCD solution was prepared by dissolving miconazole (10 mg/ml) in a solution of HP-βCD (100 mM), lactic acid (50 mM) and NaCl (4.48 mg/ml) to obtain an isoosmotic solution. This solution was filtered on a 0.22 μm filter and diluted five times with NaCl 0.9% to have the same concentration as the Daktarin® IV solution.

The miconazole–SBE_7-βCD solution was prepared in the same way: miconazole (10 mg/ml) was dissolved in a solution of SBE_7-βCD (50 mM) and lactic acid (50 mM). This solution is isoosmotic. This solution was filtered on 0.22 μm and diluted five times with NaCl 0.9% for the same reasons as the HP-βCD solution.

2.3. Animal experimental protocol and drug administration

All six sheep received 4 mg/kg of miconazole. The solution was administered through the left jugular vein within 5 min. Blood samples were taken from the right jugular vein before administration and 5, 10, 15, 30, 60, 90 min, 2, 3 and 4 h after starting the administration of the drug.

The blood samples were centrifuged and the plasma were stored at −20°C until assayed.

The study was realized in crossover following the scheme of Table 1, with a wash out period of 3 weeks between the three treatments.

2.4. Sample extraction and analysis

The method described by Hosobuto (Hosobuto, 1988) was slightly modified: 250 μl of acetonitrile were added to 250 μl of plasma or plasma standard to precipitate the protein. The tube was vortexed for 30 s, kept standing for 5 min at room

temperature and then centrifuged at 3000 rpm for 5 min. Fifty μl of the supernatant were injected in the high performance liquid chromatography (HPLC) system.

A calibration curve was constructed in the concentration range of 0.1, 1.0, 5.0 and 20.0 μg of miconazole/ml of drug-free plasma.

HPLC was performed using a system consisting of a LaChrom Merck Hitachi system L-7100 pump, a L-7400 UV detector operating at 230 nm, a L-7200 autosampler and a D-2500 chromato integrator.

Elution of each 50 μl sample was accomplished on a Lichrocart column (125 × 4 mm i.d.) prepared with an octylsilane (C8) phase Lichrospher 60 RP-select B 5 μm (Merck) maintained at 25°C, using a mobile phase consisting of a mixture of 0.05 M Na acetate pH 7.2: acetonitrile (30:70).

The method was validated and showed good linearity, reproducibility and accuracy.

2.5. Pharmacokinetic analysis

The pharmacokinetics of miconazole from the surfactant mixture and the CDs solutions were considered as a two-compartment model, fitting to Eq. (1):

$$C = A\ e^{-\alpha t} + B\ e^{-\beta t} \quad (1)$$

where C is the plasma concentration of miconazole in μg/ml and t is the time in minutes. A, B, α and β were calculated: α and β are respectively the distribution and the elimination rate constants and A and B are the intercepts or the extrapolated concentrations at the origin.

Table 1
Animal experimental protocol[a]

Sheep	1st period	2nd period	3rd period
A	HP	SBE	DAK
B	HP	DAK	SBE
C	DAK	SBE	HP
D	DAK	HP	SBE
E	SBE	DAK	HP
F	SBE	HP	DAK

[a] HP, miconazole–HP-βCD solution; SBE, miconazole–SBE_7-βCD solution; DAK, Daktarin® IV solution.

2.6. Statistical analysis

Results were expressed as means ± S.D.

The comparison of pharmacokinetic parameters for the three solutions have been performed with an analysis of variance (ANOVA).

With regard to plasma concentrations, a log transform was used to normalize the distribution. A generalized linear mixed model (GLMM) for repeated measures was applied. The effects of solution, time, interaction time–solution and period were studied. Multiple comparisons were performed.

All results were considered to be significant at the 5% critical level ($p < 0.05$). Statistical calculations were carried out using the SAS package (SAS, Cary, NC, 1996) and the NANOSTAT package (AlphaBridge, 1992).

3. Results and discussion

The mean miconazole plasma concentration versus time curves for the miconazole surfactant solution and both HP-βCD and SBE_7-βCD solutions after IV administration (4 mg/kg) to sheep are shown in Fig. 1(a) and (b). The marketed solution was used as a control in these pharmacokinetic studies. Fig. 1(b) (logarithm of the plasma concentration vs time) shows that the pharmacokinetics of miconazole can be considered as a two-compartment model.

Miconazole plasma concentration versus time profiles from the micellar, HP-βCD and SBE_7-βCD solution can be defined by Eqs. (2)–(4), respectively:

$$C = 83.94\ e^{-0.148t} + 2.56\ e^{-0.012t} \quad (2)$$

$$C = 104.47\ e^{-0.508t} + 2.66\ e^{-0.011t} \quad (3)$$

$$C = 91.2\ e^{-0.497t} + 2.79\ e^{-0.013t} \quad (4)$$

No significant difference between the three different solutions was observed at each time.

Some pharmacokinetic parameters are listed in Table 2. It can be seen that the different pharmacokinetic parameters obtained are very close. The distribution half-life ($t_{1/2\alpha}$) is very short (< 2.2 min) showing that miconazole is very rapidly

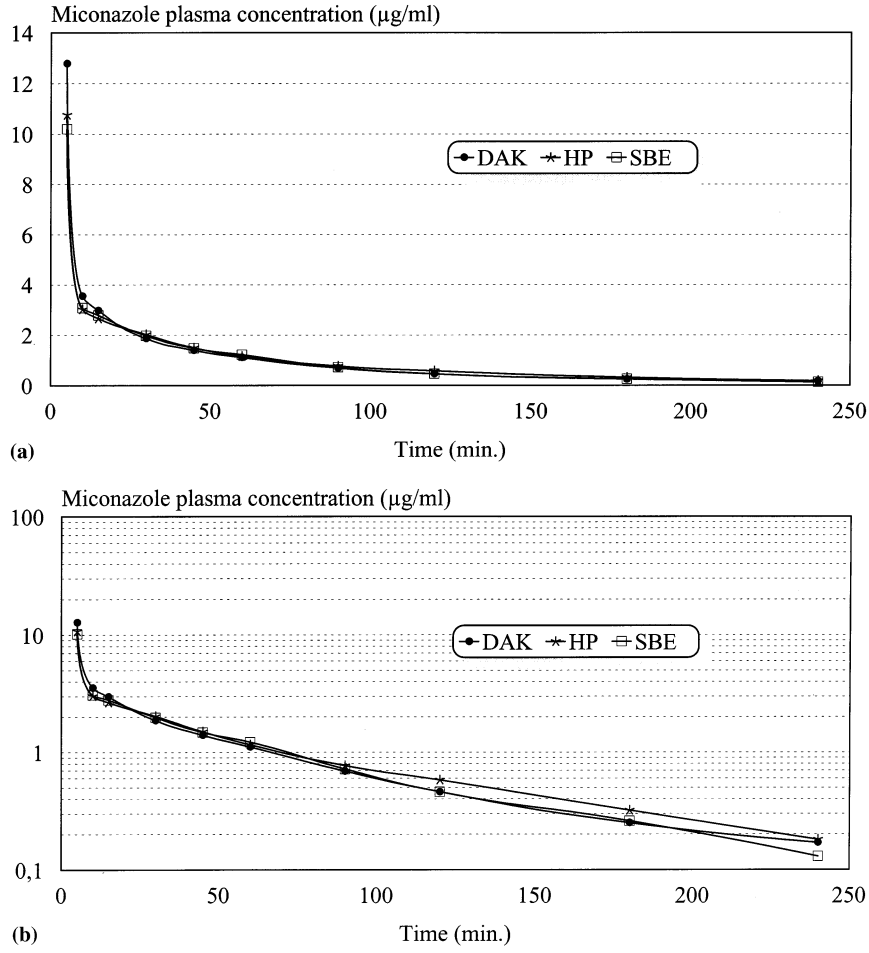

Fig. 1. (a) Mean miconazole plasma concentration vs time curve for the miconazole surfactant solution (DAK), the HP-βCD solution (HP) and the SBE_7-βCD solution (SBE) after IV administration (4 mg/kg) to sheep ($n = 6$). (b) Logarithm of the mean miconazole plasma concentration vs time curve for the miconazole surfactant solution (DAK), the HP-βCD solution (HP) and the SBE_7-βCD solution (SBE) after IV administration (4 mg/kg) to sheep ($n = 6$).

distributed in the organism. The mean values for the half-life of miconazole from the three solutions are not significantly different. The $AUC_{0-240min}$ values were calculated by linear trapezoidal rule. The AUC values were not significantly different. The clearance values and the elimination half-life ($t_{1/2\beta}$) were also calculated and no significant difference was found

Table 2
Average miconazole pharmacokinetic parameters (± S.D.) for the three different dosage forms after IV administration (4 mg/kg) to sheep ($n = 6$)[a]

Dosage form	$t_{1/2\alpha}$ (min)	$t_{1/2\beta}$ (min)	$AUC_{0-240min}$ (µg/ml per min)	Cl (ml/min per kg)
DAK	2.33 ± 0.69	55.60 ± 12.12	247.03 ± 85.89	16.54 ± 7.09
HP	1.42 ± 0.42	57.72 ± 22.48	240.33 ± 82.08	11.11 ± 4.26
SBE	1.42 ± 0.48	51.80 ± 11.25	239.47 ± 64.75	12.78 ± 4.54

[a] HP, miconazole–HP-βCD solution; SBE, miconazole–SBE_7-βCD solution; DAK, Daktarin® IV solution.

between the three solutions for both parameters.

As shown in Table 2, the pharmacokinetic parameters were not significantly different from those of the marketed solution. This suggests that HP-βCD and SBE_7-βCD do not interfere with the release of miconazole compared to the polyoxyl-35 castor oil. The release of miconazole from the complex is rapid and complete. This can be explained by the relatively low stability constant of these complexes. The apparent stability constant of the miconazole HP-βCD or the SBE_7-βCD complex in a 50 mM lactic acid solution are 112.2 and 172.5 M^{-1}, respectively. The relatively low stability constant explains the complete and rapid release of miconazole when the complex is diluted in the blood circulation.

In conclusion, it can be said that both HP-βCD and SBE_7-βCD do not interfere with the release of miconazole compared to the polyoxyl-35 castor oil. HP-βCD and SBE_7-βCD can be proposed as safe solubilizing agents alternatively to the use of surfactants for the parenteral delivery of miconazole.

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