Drug Metabolism and Pharmacokinetics 30 (2015) 253–256

Contents lists available at ScienceDirect

Drug Metabolism and Pharmacokinetics

journal homepage: http://www.journals.elsevier.com/drug-metabolism-and-pharmacokinetics

Note

Effect of high fat intake on the pharmacokinetic profile of ivermectin in rabbits

Atsushi Miyajima [1], Yosuke Yamamoto, Takashi Hirota*

Department of Biopharmaceutics, Faculty of Pharmaceutical Sciences, Tokyo University of Science, 2641 Yamazaki, Noda-shi, Chiba 278-8510, Japan

ARTICLE INFO

Article history:
Received 17 December 2014
Received in revised form
3 February 2015
Accepted 16 February 2015
Available online 24 February 2015

Keywords:
Ivermectin concentration
High-fat meal
Total cholesterol
Lipoprotein
Rabbits

ABSTRACT

Ivermectin (IVM) is used as an oral drug for treatment of scabies. It was reported that the area under the plasma concentration-time curve (AUC) of IVM was higher in healthy volunteers after a high-fat meal than in those who were fasting, but the mechanism has not been clarified yet. In fasted rabbits, the AUC after oral administration of IVM as a solution was higher than that of a suspension, indicating that the absorption of IVM depends on how much is dissolved in the gastrointestinal tract. On the other hand, the AUC was higher in rabbits pre-treated with a high-fat solution (HF; fat and cholesterol) than in those that had fasted, when IVM was administered orally not only in suspension but also in solution, and even when it was administered intravenously. In addition, the increase in total cholesterol level in the HF condition was correlated with the increase in IVM level. These results suggest that enhancement of solubility may not be the only reason for the increase of AUC in rabbits. It is also suggested that the increase of cholesterol concentration might change the distribution profile of IVM in plasma, and accordingly its concentration could be increased.

1. Introduction

Ivermectin (IVM) is an extremely hydrophobic derivative of the avermectin family of macrocyclic lactones, and is used widely in humans in many countries for treatment of scabies, a mite infection of the skin caused by Sarcoptes scabiei. For such treatment, IVM is given orally once or twice in the fasting state. It was reported that systemic availability of IVM was higher when it was given in hydroalcoholic solution than when it was given in solid formulation to humans [1], suggesting that the absorption was limited by its dissolution. It was also reported that the area under the plasma concentration-time curve (AUC) of IVM was approximately 2.6 times higher in healthy volunteers who had eaten a high-fat meal than in those who were fasting [2]. Considering these findings, it was thought that the increased AUC was caused by promotion of bile secretion by the intake of the high-fat meal, followed by higher dissolution of IVM in the intestine.

On the other hand, bioavailability of IVM was higher in sheep fed 400 g of food/day than in those fed 800 g food/day [3]. The authors suggested that this food effect was due to the differences of gastrointestinal motility. Bassissi et al. reported that the avermectins including IVM were distributed *in vitro* to lipoproteins in plasma of several animal species and including humans [4]. From these findings, they pointed out that the pharmacokinetic profile of IVM might be influenced by the plasma lipoprotein levels. Thus, another mechanism in addition to promotion of dissolution might contribute to the change of IVM pharmacokinetics by food intake including high-fat. In the present study, we evaluated the pharmacokinetics of IVM in rabbits to clarify the mechanism by which high-fat intake increases the AUC of IVM.

2. Materials and methods

2.1. Animals

Male Japanese white rabbits were obtained from Japan SLC Inc. (Shizuoka, Japan) and used after 5 or more days of acclimatization. Rabbits were appropriate animals for the present study because their plasma cholesterol levels well responded to HF diets [5]. All animals were housed in temperature-controlled rooms with 12-h light/dark cycle. Water and food were available ad libitum throughout the study except as described below. The protocols were approved by the institutional review committee in the Tokyo University of Science as animal experiment protocols No. Y11015 and Y12020. All animals were handled in accordance with the

* Corresponding author.
E-mail address: hirotas5@rs.noda.tus.ac.jp (T. Hirota).
[1] Present affiliation: Department of Biopharmaceutics, Meiji Pharmaceutical University, 2-522-1 Noshio, Kiyose-shi, Tokyo 204-8588 Japan.

http://dx.doi.org/10.1016/j.dmpk.2015.02.002

institutional and national guidelines for the care and use of laboratory animals.

2.2. Preparation of dosing formulations and high-fat solution

Ivermectin (IVM, Wako Pure Chemical Industries, Ltd., Osaka, Japan) was suspended in 0.5% (w/v) aqueous carboxymethyl cellulose-Na for oral administration in suspension or Ivomec® Injection (commercially available injectable formulation, Merial Japan Co., Ltd., Tokyo, Japan) was diluted in the same manner as described by Pérez et al. [6] for oral administration in solution and intravenous administration.

In these experiments, the animals were pretreated with a high-fat solution (HF) rather than high-fat food to minimize the effects of food on gastrointestinal motility. The HF solution for pretreatment was prepared by dissolving cholesterol in peanut oil (10 mg/mL).

2.3. Animal study and determination of plasma concentration of IVM and total cholesterol

Animal studies using 4 of rabbits were performed according to a crossover design with 2 weeks washout period between treatments. Each rabbit (2.5–3.5 kg) fasted for about 15 h and then received the following four regimens: A, oral administration of IVM suspension in the fasted state (the non-HF condition); B, oral administration of IVM suspension 30 min after the treatment with 2 mL/kg of HF by oral gavage (the HF condition); C, oral administration of IVM solution in the non-HF condition; D, oral administration of IVM solution in the HF condition. The dosage of IVM was 1.0 mg/kg. Rabbits were prohibited food intake until 4 h postdose. Blood samples were collected with heparinized syringes from the ear vein at predetermined sampling times. It was confirmed that the washout period was long enough that the IVM concentration decreased to the undetectable level.

After an additional 2-week washout period, 4 of rabbits were equally divided into two groups and an intravenous administration study was performed according to a crossover design with 2 weeks washout period between administrations. Each rabbit was administered IVM intravenously at a dose of 0.2 mg/kg (solution) under HF and non-HF condition, and blood was also collected in the same manner as mentioned above.

Plasma was separated from the blood by centrifugation and stored at −80 °C until the measurement of IVM and total cholesterol concentration. IVM concentration was determined by LC-MS/MS systems as described in our previous report [7]. The total cholesterol concentration was determined at 0.5, 2, 6, 12 and 24 h after intravenous administration of IVM using Cholesterol E-test Wako Kit (Wako pure chemical industries. Ltd.) according to its instruction.

2.4. Data analyses

Pharmacokinetic data were analyzed by a moment analysis method with the computer program 'MOMENT (EXCEL)' [8]. The AUC from time zero to the last sampling time ($AUC_{0\text{-last}}$) was calculated by a trapezoidal method. The elimination rate constant (k_e) was determined by linear regression of the last 3 points on the terminal phase of the logarithmic plasma concentration-time curve. The AUC from time zero to infinity ($AUC_{0\text{-}\infty}$) was calculated by the following equation; $AUC_{0\text{-last}} + C_{last}/k_e$; C_{last} means the IVM concentration of the last measurable sampling point. The half-life ($t_{1/2}$) was calculated by the following equation; $t_{1/2} = Ln(2)/k_e$. Bioavailability (BA) was calculated by following equation; $BA = (AUC_{0\text{-}\infty,\ p.o.}/Dose_{p.o.})/(AUC_{0\text{-}\infty,i.v.}/Dose_{i.v.})$; p.o. and i.v. means the oral and intravenous administration of IVM.

Statistical analyses of pharmacokinetic parameters, plasma IVM concentrations between groups were performed using paired *t*-tests. AUC ratios among the three administration conditions (oral administration of suspension and solution, and intravenous administration of solution) were analyzed by one-way analysis of variance. The coefficient of correlation between IVM and cholesterol concentrations in plasma was determined using linear regression analysis as reported by Humberstone et al. [9] All of the differences were considered statistically significant when $p < 0.05$.

3. Results and discussion

The plasma concentrations of IVM were determined after oral or intravenous administration to rabbits under HF and non-HF conditions. In the non-HF condition, the maximum concentration (C_{max}) and $AUC_{0\text{-last}}$ after administration of IVM solution were 5.3 and 2.5 times higher than those after administration of the suspension, respectively ($p < 0.05$, Fig. 1A, B and Table 1). In addition, the time to C_{max} (T_{max}) after administration of IVM solution was significantly shorter than that after the suspension ($p < 0.05$). These results indicate that the absorption of IVM is increased by its dissolution, which is consistent with the clinical report that the AUC after taking IVM hydroalcoholic solution was markedly higher than that after taking IVM tablets or capsules [1]. In addition, this result is consistent with the clinical research reported by Guzzo et al. [2], on the basis of which they suggested that a high-fat meal increased the absorption by promoting dissolution of IVM.

After oral administration of the suspension, the $AUC_{0\text{-last}}$ in the HF condition was 1.5 times higher than that in the non-HF condition ($p < 0.05$, Fig. 1A). Unexpectedly, after oral administration of IVM solution, the $AUC_{0\text{-last}}$ in the HF condition was 1.3 times higher than that in the non-HF condition ($p < 0.05$, Fig. 1B). These results demonstrate that the increase of plasma IVM exposure by intake of a HF solution is not due to promoted dissolution of IVM in the gastrointestinal tract at least in rabbits. After administration of either formulation, the T_{max} in the HF condition was longer compared with that in the non-HF condition ($p < 0.05$, Table 1). That would be caused by a decrease of gastrointestinal motility due to intake of HF solution. Meanwhile at 9–24 h after intravenous administration of IVM, plasma IVM concentration was significantly higher in the HF condition compared to that in the non-HF condition ($p < 0.05$, Fig. 1C). It is suggested that there is another mechanism for the increase of plasma IVM concentration, which is not related to its absorption. In addition, the increase of $AUC_{0\text{-last}}$ by HF solution intake was 1.4-fold, almost the same as after oral administration of either formulation (Table 1), which could explain the effect of HF solution intake on $AUC_{0\text{-last}}$ after oral administration of IVM. The oral bioavailabilities of IVM under non-HF and HF conditions were comparable regardless of the formulation (Table 1). These findings suggest that the change of the absorption was not the main reason. Also the decrease of gastrointestinal motility by HF intake would not be the main reason for the change of $AUC_{0\text{-last}}$ at least in rabbits.

It has been already reported that IVM was distributed to the lipoproteins in plasma in an *in vitro* study, and the possibility that lipoprotein levels affected the IVM pharmacokinetic profile was pointed out [6]. For exploratory investigation of the association of lipoprotein with the elevation of IVM concentration by HF solution intake, total cholesterol concentration as an indicator of plasma lipoprotein level was determined using all the available samples obtained until 24 h after intravenous administration of IVM. The correlation between the increase of total cholesterol and IVM concentration was analyzed at these time points (Fig. 1D). As the results, there was a significant correlation between the increases of total cholesterol and IVM concentrations in plasma by HF solution