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The effect of food on the pharmacokinetics of oral ivermectin

Urs Duthaler[1], Rory Leisegang[2], Mats O. Karlsson[2], Stephan Krähenbühl[1] and Felix Hammann[1,3,4]*

[1]*Division of Clinical Pharmacology & Toxicology, Department of Biomedicine, University and University Hospital Basel, Switzerland;* [2]*Department of Pharmaceutical Biosciences, Uppsala University, Uppsala, Sweden;* [3]*Clinical Pharmacology and Toxicology, Department of General Internal Medicine, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland;* [4]*Institute of Pharmacology, University of Bern, Bern, Switzerland*

*Corresponding author. E-mail: felix.hammann@insel.ch

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Background: Ivermectin is an older anthelminthic agent that is being studied more intensely given its potential for mass drug administration against scabies, malaria and other neglected tropical diseases. Its pharmacokinetics (PK) remain poorly characterized. Furthermore, the majority of PK trials are performed under fasted-state dosing conditions, and the effect of food is therefore not well known. To better plan and design field trials with ivermectin, a model that can account for both conditions would be valuable.

Objectives: To develop a PK model and characterize the food effect with single oral doses of ivermectin.

Patients and methods: We performed a population-based PK analysis of data pooled from two previous trials of a single dose of 12 mg ivermectin, one with dosing after a high-fat breakfast (n=12) and one with fasted-state dosing (n=3).

Results: The final model described concentration–time profiles after fed and fasted dosing accurately, and estimated the food effect associated with relative bioavailability to 1.18 (95% CI 1.10–1.67).

Conclusions: In this analysis, the effect of a high-fat breakfast compared with a fasted-state administration of a single oral dose of 12 mg ivermectin was minimal.

Introduction

The antiparasitic agent ivermectin has been in widespread use since the 1980s for the treatment of a variety of conditions such as scabies, river blindness (onchocerciasis) and trichuriasis. The safety profile of ivermectin is considered excellent in humans, and the drug is experiencing renewed interested in the fight against neglected tropical diseases.[1–3] Its high pharmacokinetic (PK) variability is, however, still not fully explained.

Ivermectin is a highly lipophilic and comparatively large compound. Its intestinal solubility and, thereby, absorption could vary with ingestion of food. Previous studies have demonstrated multiple peaks in plasma following oral dosing, which may come from enterohepatic circulation or delays in gastric emptying.[4–6] Its size and lipophilicity could influence its distribution into a deep compartment, for instance fatty tissue. Past trials found no conclusive evidence of the influence of physiological parameters (beyond total body weight) such as age, sex, body fat percentage or organ volumes.[2,5,7,8]

For this analysis, we investigated the influence of fasted versus fed dosing on the oral PK of ivermectin as published data so far have been ambiguous.[4,9] Guzzo *et al.*[10] reported a 2.6-fold increase in AUC with high-fat meals for fixed doses of 30 mg ivermectin in healthy volunteers (fasted: n=12, fed: n=11). Miyajima *et al.*[11] reported a more modest increase (1.25×) in AUC in 13 Japanese patients with scabies. Homeida *et al.*[6] reported no effect of either food or alcohol intake on bioavailability.

Patients and methods

Data were included from two clinical trials conducted by our group.[5,12] Both trials were performed in healthy volunteers taking a single oral dose of 12 mg ivermectin (four tablets of Stromectol® 3 mg; MSD France, Courbevoie). In the first trial,[5] 12 subjects [6 female and 6 male, median age (range) 23 (20–36) years, median weight (range) 65 (57–94) kg] were dosed 30 min after a high-fat breakfast; in the second trial, three male subjects [median age (range) 39 (34–64) years, median weight (range) 91 (78–119) kg] were dosed in a fasted state.[5,12]

We performed the population PK analysis using NONMEM (Version 7.4.3; Icon Development Solutions, http://www.iconplc.com) and data checkout in GNU R (Version 3.3.3; http://www.R-project.org). As a starting point for our analysis, we used our previously published two-compartment model with absorption through a chain of transit compartments; allometric scaling was applied with a factor of ¾ for clearance (flux and elimination) and 1 for volume (central and peripheral) on total body weight.[5] We fitted

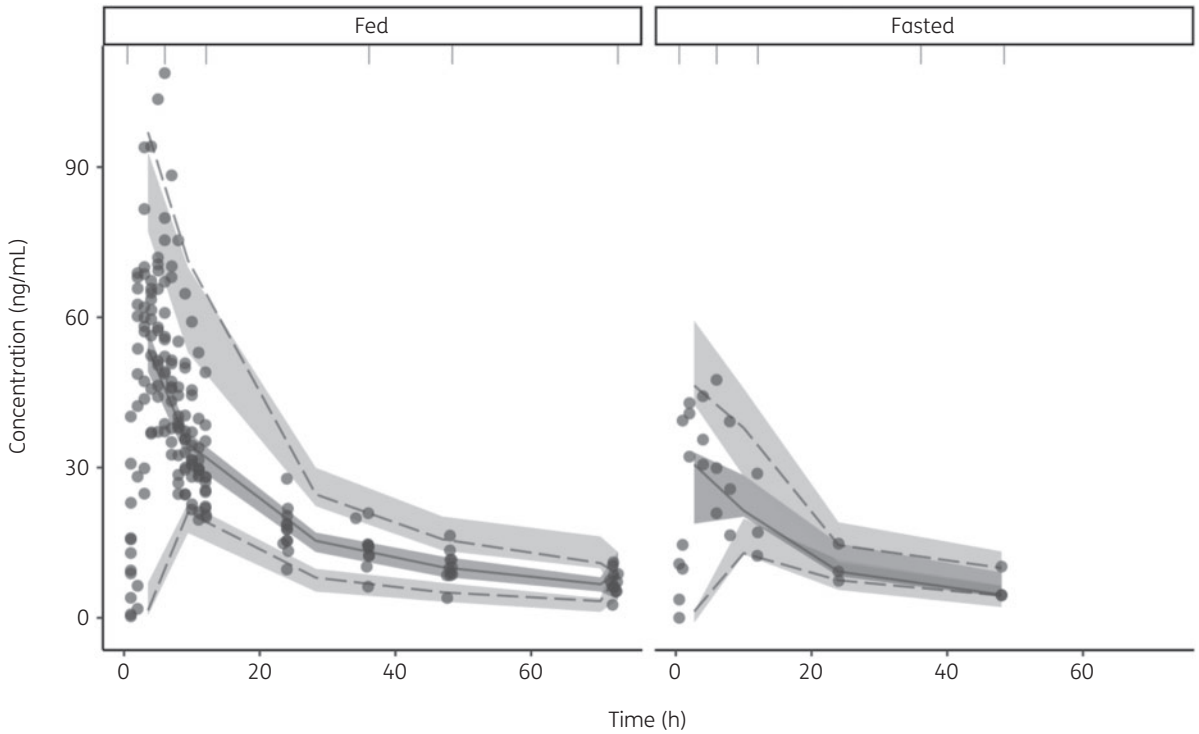

Figure 1. VPC (n=500 simulations) with 80% CI bands (10th and 90th percentiles shaded light grey, median shaded dark grey) and observed data (dashed lines, 10th and 90th percentiles; solid line, median).

the pooled data to this structural model and explored potential covariates as well as effects of fed state on the transit compartment model and the absorption rate (k_a). We conducted model diagnostic and covariate testing using the Xpose and PsN software packages; first-order conditional estimation with eta–epsilon interaction (FOCE-I) was used throughout all runs. We selected models based on goodness-of-fit statistics, graphical analysis with visual predictive checks (VPCs, n=500 simulations) and model plausibility. Finally, we used non-parametric bootstrap analysis stratified by study (n=1000 runs) to determine the precision of parameters of the final model.

Results and discussion

After excluding two plasma samples that had been drawn incorrectly, we were left with a total of 348 post-dose measurements from 15 volunteers (n=294 from Duthaler *et al.*[5]; n=54 from Duthaler *et al.*[12]); no values were below the lower limit of quantification. The incorporation of additional covariates brought no improvement, as was the case in our previously published model.[5]

The VPC (Figure 1) shows a good agreement between model predictions and observed data. Basic goodness-of-fit plots are given in Figure S1 (available as Supplementary data at *JAC* Online). Parameter estimates (Table 1, Table S1) are similar to our previous study,[5] which is not surprising as model parameters from fasted-state dosing are scaled by the bioavailability term F1 and the inclusion of transit compartments adequately accounts for differences in absorption.[13] The model discussed here captures peak concentrations better. This could be owing to the presence of an early sampling timepoint (0.5 h post-dose), which was not part of the schedule in Duthaler *et al.*[5]

The model-based estimate of relative bioavailability (F1) was 0.84, i.e. oral availability is reduced in the fasted state. This corresponds to a food effect of 1.18 (95% CI 1.10–1.67, from non-parametric bootstrap analysis). Fed-state dosing, in particular with high-fat meals, is thought to increase systemic exposure by enhancing bile secretion. This would lead to better dissolution by wetting and micellar solubilizing and an increased absorption of hydrophobic drugs such as ivermectin. Some authors have speculated that the higher levels of plasma lipids seen postprandially could also improve solubility.[11] This could potentially facilitate uptake into chylomicron lipoproteins and lymphatic transport, leading to the increase in bioavailability observed here.

Our findings are similar to the recent publication by Miyajima *et al.*,[11] who also administered a dose of 12 mg, but much lower than the value of 2.6 reported by Guzzo and colleagues.[10] A possible reason for this discrepancy may be the high doses (30 mg) given in the latter trial.[10] This could be due to ivermectin being a good substrate for active efflux pumps such as P-glycoprotein (P-gp, MDR1, ABCB1).[4] P-gp is prominently expressed in the gastrointestinal tract, and at higher doses, along with an exposure increased by meals, concentrations could saturate the active efflux process. This in turn would lead to greater systemic concentrations.

An important shortcoming of this analysis is the small number of volunteers, especially for the fasted-state condition. Also, subjects in the latter condition were slightly older, all male and had a higher body weight (which was corrected for by allometric scaling). Overall, however, no considerably larger trials have addressed the food effect in ivermectin.

Table 1. Final parameter estimates and results from non-parametric bootstrap analysis and sampling importance resampling (SIR, n=1000)

			Bootstrap analysis		SIR	
	Estimate	%RSE	median	95% CI	median	95% CI
Fixed effects						
CL/F (L/h)	7.7	7.9	7.6	6.7–8.8	7.7	6.6–9.1
V_c/F (L)	101	11.1	97	37–120	102	81–118
V_p/F (L)	229	7.5	234	203–280	228	201–265
Q/F (L/h)	18.7	14.3	18.8	15.0–24.0	18.6	13.9–24.5
k_a (h^{-1})	0.68	17.5	0.65	0.30–0.96	0.69	0.51–0.88
NN	6 (fixed)					
MTT (h)	0.93	16.8	0.92	0.71–1.23	0.93	0.67–1.25
$F1_{fasted}$	0.84	3.5	0.83	0.60–0.91	0.84	0.76–0.92
Interindividual variability (ω)						
CL/F	0.31	16.9	0.29	0.19–0.39	0.32	0.22–0.43
V_c/F	0.10	44.7	0.08	0.01–0.45	0.11	0.03–0.18
V_p/F	0.21	37.1	0.20	0.01–0.31	0.22	0.08–0.34
Q/F	0.52	18.6	0.47	0.28–0.65	0.53	0.38–0.75
MTT	0.63	16.1	0.60	0.41–0.78	0.64	0.47–0.86
Residual errors (σ)						
proportional	0.09	9.4	0.09	0.07–0.10	0.09	0.08–0.11
additive (ng/mL)	0.92	36.7	0.80	0.16–1.98	0.93	0.58–1.38

CL/F, clearance; V_c/F, central volume of distribution; V_p/F, peripheral volume of distribution; Q/F, intercompartmental transfer; k_a, absorption rate; MTT, mean transit time; NN, number of transit compartments; $F1_{fasted}$, relative availability with fasted dosing; %RSE, relative standard error [%RSE=100 × (standard error/parameter estimate), as provided by NONMEM].

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Transparency declarations

None to declare.

Supplementary data

Figure S1 and Table S1 are available as Supplementary data at *JAC* Online.

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