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Mini-Review

The Pharmacokinetics and Interactions of Ivermectin in Humans—A Mini-review

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Abstract. Ivermectin is an antiparasitic drug with a broad spectrum of activity, high efficacy as well as a wide margin of safety. Since 1987, this compound has a widespread use in veterinary medicine and it use has been extended in humans. Here we present a brief review of the information availabile regarding the pharmacokinetics and interactions of ivermectin in humans. Awareness of these characteristics could improve the clinical efficacy of Ivermectin. All Authors declare that they do not have any Conflict of interest and that the work is original. All Authors agree that the contents of the manuscript are confidential and will not be copyrighted, submitted, or published elsewhere (including the Internet), in any language, while acceptance by the Journal is under consideration.

KEY WORDS: humans; interactions; ivermectin; pharmacokinetics.

INTRODUCTION

Ivermectin is a semisynthetic derivative of avermectin B_1 and consists of an 80:20 mixture of the equipotent homologous 22,23 dehydro B_{1a} and B_{1b}. This antiparasitic agent, developed by Merck & Co., is frequently used in veterinary medicine, due to its broad spectrum of activity, high efficacy and wide margin of safety (1,2).

The first formulation destined to humans was launched in 1987, when Merck Laboratories had enough data to register ivermectin for use against onchocerciasis. The company announced that the drug would be provided at no cost to treat onchocerciasis, anywhere in the world, for as long as it was needed (3).

To control onchocerciasis, the *Onchocerciasis Control Programme in West Africa* was launched in 1974. The main goal of this program is to interrupt the parasite transmission cycle. Since 1987, the use of ivermectin in combination with aerial larviciding has had a remarkable impact on the transmission of the disease and greatly reduced the effect on humans. This led to the development, in 1992, of the *Onchocerciasis Elimination Programme in the Americas*, launched in 6 countries and, in 1995, of the *African Programme for Onchocerciasis Control*, both based mainly on distribution and treatment with ivermectin (4). In 1998, the *Global Programme to Eliminate Lymphatic Filariasis*, based on the regular mass administration of albendazole with either ivermectin or diethylcarbamazine, was initiated, confirming the safety and efficacy of the drug combinations (5).

Presently, ivermectin is approved for use in humans in several countries (Australia, France, Japan, The Netherlands, USA, etc.), to treat onchocerciasis, lymphatic filariasis, strongiloidiasis and/or scabies.

Ivermectin is exceptionally potent, with effective dosages levels that are unusually low. In the treatment of onchocerciasis, the optimal dose of ivermectin is 150 μg/kg, but the frequency of administration is still controversial, ranging from 150 μg/kg once to three times yearly. The optimal duration of treatment has not been established (6). It is effective in most patients with scabies after a single oral dose of 200 μg/kg, but often the regimen involves two or three repeated doses, separated by interval of 1 or 2 weeks (7).

Due to the extended use of this compound in humans, the knowledge of ivermectin pharmacokinetic behavior becomes essential. Nevertheless, little is known about the kinetics and interactions of ivermectin in humans compared to animals (even if the majority of fundamental work is veterinary, there is little evidence that such knowledge has helped to inform clinicians).

Thus, in this paper, we review the literature concerning the absorption, distribution, metabolism and excretion of ivermectin in man, as well as the interactions of the compound.

PHARMACOKINETICS

The oral route is the only approved for ivermectin administration in humans. The one-compartmental model (8, 9), as well as the two-compartmental model (10) have been used to describe ivermectin kinetic behavior after its oral administration. In the rest of the studies cited here,

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pharmacokinetic parameters were determined using a model-independent method.

Absorption

In healthy subjects that received 12 mg of ivermectin as oral solution, tablets or capsules, it was shown that the solution had approximately twice the systemic availability as either of the solid forms (tablets and capsules showed similar systemic availability; Table 1). The oral solution was given as an ethanolic solution. This may affect bioavailability and could explain why the solution resulted in a twice as high availability as tablets and capsules. Nevertheless, the rate of absorption was similar in the three cases (11).

In healthy and onchocerciasis volunteers treated with 150 μg/kg, no significant differences were found in the pharmacokinetic parameters calculated. After an initial decrease, both groups showed a tendency for a second rise in plasma levels (mostly occurring between 6 and 12 h after the dose) suggesting an enterohepatic recycling of the drug (12).

It was also investigated whether diminished ivermectin absorption could explain the fact that some severely infected onchocerciasis patients experience relatively few adverse effects following ivermectin treatment, although the occurrence and extent of adverse reactions have been related to infection intensity (17). According to this study, there was no observable relation between the plasma concentration after a single oral dose (150 μg/kg) and the occurrence of adverse reactions. Neither parasite load nor ivermectin concentrations had an influence on the occurrence of adverse reactions in the entire group of patients.

The ability to achieve adequate levels of ivermectin after oral administration in patients with disseminated strongyloidiasis may be impaired, highlighting the need for alternative routes of administration of ivermectin in these patients. Thus, ivermectin levels, in a patient with disseminated strongyloidiasis, were below the average of those reported by other authors following oral administration (1.1 $ng \cdot ml^{-1}$ after ingesting a total dosage of 1,000 μg/kg over 3 consecutive days). This was followed by the administration of three subcutaneous doses (200 μg/kg), injected every 2 days, increasing ivermectin levels to 7.9 $ng \cdot ml^{-1}$ at 1 week after the last dose, with evidence of additional metabolite accumulation and also a sustained antiparasitic effect. Thus, in these patients, who are unable to absorb oral medication, parenteral ivermectin (not licensed for use in humans) is a better option (18). In another report, a man with disseminated strongyloidiasis, severe hypoalbuminemia and paralytic ileus, received ivermectin by the oral route. Three hours after the third daily dose, the serum ivermectin concentration was only 0.8 $ng \cdot ml^{-1}$, but it increased to 5.8 $ng \cdot ml^{-1}$ 16 hours after the first subcutaneous dose. Over the next 15 days, subcutaneous ivermectin (200 μg/kg, once a day) produced serum ivermectin levels between 11.4 and 17.2 $ng \cdot ml^{-1}$ with no significant accumulation (19).

Distribution

Due to the high lipid solubility of ivermectin, this compound is widely distributed within the body.

In healthy men, the volume of distribution in the central compartment, V_c, was 3.1 and 3.5 $l \cdot kg^{-1}$, after ingesting 6 and 12 mg of ivermectin, respectively (8). In onchocerciasis patients, with 6 mg (tablet), the volume of distribution of the area (V_λ) was 9.9 $l \cdot kg^{-1}$ and the mean residence time (MRT) was 3.7 days (16).

The tissue distribution of ivermectin was similar in healthy and onchocerciasis volunteers treated orally. So,

Table 1. Pharmacokinetic Parameters Obtained after Ivermectin Oral Administration

Reference	Dose	Absorption			Elimination	
		C_{max} ($ng \cdot ml^{-1}$)	t_{max} (h)	$t_{1/2(abs)}$ (h)	$t_{1/2}$ (h)	Cl ($1\ kg^{-1} \cdot day^{-1}$)
Healthy subjects						
9[a]	12 mg (tablet)	–	–	–	12	–
8[a]	6 mg (tablet)	23.1	4.3	0.5	12.6	4.28
8[a]	12 mg (tablet)	30.4	10.3	2.5	13.4	4.03
9[a]	6 mg (tablet)	20.2	4.7	1.4	11.1	7.57
9[a]	12 mg (tablet)	23.5	5.3	1.4	21.1	6.53
9[a]	18 mg (tablet)	31.2	5.1	1.7	16.7	10.6
11	12 mg (solution)	81	3.6	–	–	–
11	12 mg (tablet)	50	3.4	–	–	–
11	12 mg (capsule)	46	3.6	–	–	–
12	150 μg/kg	54.4	4.9	–	36.6	–
13	150 μg/kg	37.9	–	–	–	–
14	150 μg/kg	33.8	–	–		4.70 (♂) 8.40 (♀)
Onchocerciasis patients						
12	150 μg/kg	52.2	5.2	–	35.0	–
15	150 μg/kg	39	5.6	–	16	–
16	6 mg (tablet)	38.2	4.7	–	54.5	3.1
17	150 μg/kg				19.9	–

– Unknown data; C_{max} maximum plasma concentration; t_{max} time to reach C_{max}; $t_{1/2abs}$ absorption half-life; $t_{1/2}$ elimination half-life; *Cl* total body clearance

[a] One-compartment model

infection with *Onchocerca volvulus* does not appear to affect the distribution of this drug. The compound was present in fat, skin, subcutaneous fascia and nodules and in worm fragments. Fat showed the highest and most persistent levels, whilst values for skin, nodular tissues, and worms were comparable, being the lowest concentrations found in the subcutaneous fascia (12). In patients with *Onchocerca volvulus* infection treated orally with ivermectin (150 μg/kg), Elkassaby (15) also detected the drug in the nodular tissue of the parasite and in worm fragments. After subcutaneous administration (500 μg/kg) to cattle with nodules of *Onchocerca ochengi* (a cattle parasite that can be used as a model of *O. volvulus*), high concentrations were detected in the capsule wall and inside the nodule (55 and 45 $ng \cdot g^{-1}$ on day 2; 60 and 30 $ng \cdot g^{-1}$ on day 7). So, the poor penetration of ivermectin into the nodules could not explain the lack of efficacy against adult filariae (20).

In the skin, the peak concentration of the drug in squames, sebum and sweat on the forehead and the antithenar was 8 h after a 12 mg oral dose and decline quickly beyond 24 h (21).

Ivermectin binds strongly to plasma proteins in healthy subjects (93.2%) (22). It was also high in onchocerciasis patients (93.1%), with a specific binding for serum albumin. There were two binding sites, with an association constant of 2×10^8 mol^{-1} at the primary site. Such avid binding assumes great importance as the drug is administered in world areas where malnutrition and hypoalbuminemia are common, so in these patients a decrease in plasma proteins and, consequently, a higher free fraction of ivermectin could be expected. Nevertheless, acetylsalicylic acid does not interfere with ivermectin binding (16).

Ivermectin was not detected in the cerebrospinal fluid of a man with disseminated strongyloidiasis, severe hypoalbuminemia and paralytic ileus, after five subcutaneous doses of ivermectin, when the serum level was 12.1 $ng \cdot ml^{-1}$ (18).

Elimination

Studies regarding the *metabolism* of ivermectin in humans are scarce. This drug is extensively metabolized by human liver microsomes by cytochrome P450. The predominant isoform responsible for the biotransformation of this compound in the liver of humans is cytochrome P-4503A4, converting the drug to at least 10 metabolites, most of them hydroxylated and demethylated derivatives (23). In plasma, radioactive metabolites were reported after the oral administration of ivermectin to healthy volunteers (10).

Data concerning *excretion* can be observed on Table 1. No differences in the elimination half-life were detected among healthy and onchocerciasis subjects (12). It was also suggested that the kinetics of ivermectin (its elimination half-life is around a day) were somewhat disconnected from its pharmacodynamics (antiparasitic events persisting for several months after a single dose of the drug) (11).

A significant effect of gender was found in ivermectin pharmacokinetics in healthy volunteers orally treated with 150 μg/kg, with a lower total body Cl/F in males compared to females (see Table 1) (14).

In connection with the excretion pathways, ivermectin and its metabolites were excreted mainly in faeces and only 1% in urine. Positive identification was obtained for the presence of 3"-*O*-desmethyl-H_2B_{1a}, and 22,23-dihydroavermectin B_{1a} monosacharide in urine and faeces, respectively [10]. Other authors who tried to determine ivermectin in urine (8, 9, 16) did not find the parent drug nor its metabolites.

Finally, in the milk of healthy women administered 150 μg/kg, the maximum concentration (14.1 $ng \cdot ml^{-1}$) was reached in 6.5 h (13). On the basis of this information, a breast-fed child would receive an average dose of only 2.75 μg/kg via milk. Thus, these authors did not recommend excluding breastfeeding mothers from mass ivermectin therapies, as they only represent 5–10% of the population in the areas hyperendemic with onchocerciasis.

INTERACTIONS

Several authors evaluated the effect of ivermectin coadministration with different drugs employed to control helminthes. To interrupt the transmission of onchocerciasis in humans, the combination of ivermectin and doxycycline is highly effective as, in infested patients, the ingestion of the anthelmintic (200 μg/kg, single dose) and the antibacterial (100 mg/kg, daily for 6 weeks), kept the microfiladermia levels low more time than did ivermectin alone. Doxycycline enhanced ivermectin-induced suppression of microfiladermia, as it sterilize adult female worms for a few months by depletion of symbiotic endobacteria of filariae, *Wolbachia* spp. (24) (essential for their survival and reproduction). Other studies showed that, to control onchocerciasis, the combination of ivermectin with other drugs offers no advantage over ivermectin alone. Thus, in infected patients, the ingestion of ivermectin had no effect on the kinetics of an oral dose of albendazole and there was no additive effect of both drugs against the parasite compared to ivermectin given alone (25, 26, 27). Albendazole (400 mg) did not modify the kinetic behavior of a single oral ivermectin dose (12 mg) (27). Also in onchocerciasis patients, the antiparasitary efficacy was similar when administering a single ivermectin dose (150 μg/kg, on day 1) followed by amorcazine (3 mg/kg twice daily, on days 8, 9 and 10) than when administering ivermectin alone (28). Similarly, the combination of ivermectin (200 μg/kg) and levamisole (2.5 mg/kg) was neither macrofilaricidal nor more effective against the microfilariae and the adult worms than ivermectin alone, although levamisole increased ivermectin plasma bioavailability in these patients (29).

The efficacy of drugs available for the treatment of infection with *Trichuris trichiura* is low in humans. Nevertheless, single-dose treatment with albendazole (400 mg)-ivermectin (200 μg/kg) appears to be highly effective against trichuriasis, being higher than when administering albendazole alone or with diethylcarbamazine (6 mg/kg) (30).

Thus, ivermectin interactions with another concurrently administered drugs can occur. This issue becames important, as combination chemotherapy is being used with increasing frequency as resistance to antiparasitic agents is becoming more widespread.

Regarding bleeding disorders, haematomatous swellings were reported in 2 out of 28 onchocerciasis patients treated with ivermectin (150 μg/kg), and prothrombin times were significantly above baseline by one week to one month after

drug ingestion, suggesting an antagonist effect against vitamin K (31). Nevertheless, in other 20 subjects, no changes were observed in prothrombin nor in thromboplastin times compared with baseline results, during 13 days after the ingestion of 220–420 μg/kg of ivermectin (32); bleeding disorders were not found in 15,000 patients treated with ivermectin (150 μg/kg) (33). Moreover, prolonged prothrombin ratios were observed in 148 subjects given ivermectin orally. Although no patients suffered bleeding complications, factor II and VII levels were reduced in most of them, suggesting interference with vitamin K metabolism. Ivermectin has a minimal effect on coagulation and concern about mass treatment for this reason appears to be unjustified (34). Finally, a man that had been on long-term oral anticoagulant therapy with acenocoumarol showed a persistent, excessive hypocoagulability while using insecticides (ivermectin and metidation) without protection to treat trees. So, it is to be taken into account that these types of interactions can exist and could cause hemorrhagic complications (35).

Information about the influence of foods in the pharmacokinetics of ivermectin is scarce. The knowledge of the influence of alcohol in ivermectin kinetic behaviour is scarce; co-ingestion of alcoholic drinks however is not recommended, because of ivermectin association with GABA receptors and the effect of alcohol in the central nervous system. In healthy volunteers administered ivermectin orally (150 μg/kg), plasma levels were significantly higher when coadministered with 750 ml of beer than with 750 ml of water; the plasma concentrations were significantly higher in patients who drank beer (66.3, 109, and 97.2 ng/ml at 1, 3 and 4 h, respectively) *vs*. those who drank water (44.0, 67.5, and 58.7 ng/ml, respectively, $P<0.01$ at each time point) (36).

Finally, ivermectin (150 μg/kg) was administered to 16 individuals with water or orange juice (750 ml). Orange juice decreased AUC (15.7 $ng \cdot d \cdot ml^{-1}$) and C_{max} (20.7 $ng \cdot ml^{-1}$) (water: 33.8 $ng \cdot ml^{-1}$; 24.3 $ng \cdot d \cdot ml^{-1}$), possibly because fruit juices and constituents are potent inhibitors of certain drug transporters (14).

CONCLUSION

Although the efficacy of ivermectin has been established in humans against several parasite diseases, the pharmacokinetic properties of this compound are less well known in humans compared to animals. Potential drug-drug interactions and drug-food interactions exist for ivermectin, which should be considered during therapeutic use of this drug.

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