Ivermectin as a potential COVID-19 treatment from the pharmacokinetic point of view

Georgi Momekov[1]*, Denitsa Momekova[2]

[1]*Lab of Experimental Chemotherapy and Molecular Pharmacology, Department of Pharmacology, Pharmacotherapy and Toxicology, Faculty of Pharmacy, Medical University of Sofia, Bulgaria*

[2]*Department of Pharmaceutical Technology and Biopharmaceutics, Faculty of Pharmacy, Medical University of Sofia, Bulgaria*

Corresponding author: Georgi Momekov, DSc, *Lab of Experimental Chemotherapy and Molecular Pharmacology, Department of Pharmacology, Pharmacotherapy and Toxicology, Faculty of Pharmacy, Medical University of Sofia, 2 Dunav Str., 1000 Sofia, Bulgaria; e-mail: gmomekov@gmail.com;*

Abstract

The broad-spectrum antiparasitic agent ivermectin has been very recently found to inhibit SARS-CoV-2 *in vitro* and proposed as a candidate for drug repurposing in COVID-19. In the present report the *in vitro* antiviral activity end-points are analyzed from the pharmacokinetic perspective. The available pharmacokinetic data from clinically relevant and excessive dosing studies indicate that the SARS-CoV-2 inhibitory concentrations are not likely to be attainable in humans.

Key words: ivermectin; SARS-CoV-2; COVID-19; Drug repurposing

Introduction

The COVID-19 pandemics has fuelled much research efforts towards repurposing of existing drugs as possible antiviral agents, whereby the therapeutic strategies have been largely based on preexisting data for the preceding coronaviral outbreaks TORS and MERS[1-3]. The drug regulatory agencies, health authorities, key opinion leaders and policy decision makers have been significantly strained by the dilemma of evidence-based medicine and good clinical practice versus the prompt need for safe and effective treatment[4]. Unfortunately we have been witnessing huge public and political pressure for legitimation of drug-repurposing and off-label use worldwide, which nonetheless could be regarded as an acceptable compromise, pending the emergency of the current situation, but only in case of drugs with well-defined safety profiles and at least some clinical evidence in COVID-19[4,5]. Conversely most of the treatment protocols are based on observational studies and anecdotic reports[4,6-9], albeit with a hope that the promptly emerging data from randomized studies will enable switching COVID-19 treatment back to the avenues of evidence-based medicine[10]. An exceptionally alarming phenomenon however is the public communication of drugs with preliminary *in vitro* activities against SARS-CoV-2 as

potential therapeutics for COVID-19 eventually causing malignant reverberation in social media. Such example is the otherwise very interesting study of Caly et al., recently published in Antiviral Research[11].

This paper is describing the *in vitro* antiviral activity of the antiparasitic agent ivermectin in a model of Vero/hSLAM cells infected with a SARS-CoV-2 isolate (Australia/VIC01/2020)[11]. The authors have performed a pilot experiment using continuous exposure of the cells to ivermectin at 5 μmol/L and found time-dependent decrease of cell associated and supernatant viral RNA. Thereafter the antiviral activity was assessed following continuous exposure to serial dilutions of ivermectin, which caused concentration-dependent antiviral effects with practically total eradication at 5 μmol/L and half-maximal inhibition at approximately 2.5 μmol/L[11].

The academic, virological and pharmacological impact of the newly discovered antiviral effects of ivermectin against SARS-CoV-2 is beyond any doubt, but nevertheless the notion for possible clinical translation and repurposing, which has generated enormous media coverage, needs to be carefully addressed with reference to the pharmacokinetics of ivermectin. In this paper we sought to analyze the dosing regimens of the drug, the available maximal plasma concentration levels to allow detailed juxtaposition with the SARS-CoV-2 inhibitory effects and to question the paradigm for the plausibility of ivermectin repurposing in COVID-19.

Materials and methods

A literature survey was performed in order to analyze the published dose regimens and to collect human exposure data for ivermectin, following clinically relevant (150 – 800 μg/kg) or excessive dosing (up to 2000 μg/kg). The available pharmacokinetic data for ivermectin in patients with parasitic infection and healthy volunteers were pooled and the maximal plasma concentration levels (C_{max}) used as surrogates for juxtaposition with the *in vitro* SARS-CoV-2 inhibitory findings. The published concentrations shown antiviral activity were recalculated in ng/ml to allow direct comparison with the pharmacokinetic data.

Results and discussion

Ivermectin has a valuable clinical role for the management of different parasitic diseases whereby the described therapeutic regimens, could be summarized as follows: 150 μg/kg once yearly for treatment of onchocerciasis, 200 μg/kg as a single dose for strongyloidiasis, 150 to 200 μg/kg twice yearly or alternatively 300 to 400 μg/kg once yearly in endemic areas for lymphatic filariasis, and 200 μg/kg in conjunction with topical drugs for hyperkeratotic, also known as crusted or 'Norwegian' scabies[12-14].

Ivermectin is a semisynthetic analogue of the natural product avermectin B_{1a}, a lipophilic macrolide isolated from *Streptomyces avermitilis* developed as a crop management insecticide. Ivermectin affects

a plethora of ivertebrate species, incl. parasitic nematodes, arachnids, and insects. Its mode of action on target species is by potentiating GABA-mediated neurotransmission and by binding to glutamate-gated Cl^- channels, found only in invertebrates[13]. The drug induces tonic paralysis of the musculature of susceptible parasites, and eventually death[13]. At the recommended doses, ivermectin does not readily penetrate the CNS of mammals, where GABA functions as a neurotransmitter[13,15]. Conversely in healthy volunteers and infected patients the drug is usually well tolerated at the therapeutic dose ranges[12-14]. A recent meta-analysis has shown that even larger doses (up to 800 μg/kg) with a several years period of follow-up could be well tolerated in patients with parasitic infections[16]. The largest dose intensity with registered pharmacokinetic parameters in healthy subjects is 120 mg, corresponding to up to 2000 μg/kg[12].

As evident form the analyzed pharmacokinetic data both the clinically applied dosage schedules and the aforementioned excessive 120 mg dose yield blood levels at the nanogram/ml i.e. nanomolar range (Table 1). These concentrations are orders of magnitude lower, as compared to the *in vitro* antiviral end-points, described in the study of Caly et al[11]. Table 2 summarizes the *in vitro* inhibitory concentrations, recalculated in ng/ml (based on a molecular weight of 875.1) to allow direct juxtaposition with the pharmacokinetic parameters in Table 1. Moreover the *in vitro* data have been compared to the C_{max} values, obtained after 36 mg and 120 mg doses corresponding to dose intensities of up to 700 μg/kg[17] or 2000 μg/kg[12] respectively, with calculation of the corresponding exposure ratios.

The analyzed data show that at least at the clinically relevant dose ranges of ivermectin the published *in vitro* inhibitory concentrations and especially the 5 μmol/L level causing almost total disappearance of viral RNA are virtually not achievable with the heretofore known dosing regimens in humans. The 5 μmol/L concentration is over 50 times higher than the levels obtainable after 700 μg/kg[17] and 17 times higher *vs*. the largest C_{max} found in the literature survey (247.8 ng/ml)[12]. Moreover the authors` claim for achieving viral inhibition with a single dose is inappropriate because practically the infected cells have been continuously exposed at concentrations that are virtually unattainable even with excessive dosing of the drug. With other words the experimental design is based on clinically irrelevant drug levels with inhibitory concentrations whose targeting in a clinical trial seems doubtful at best.

Table 1. Published pharmacokinetic parameters for ivermectin following clinically relevant and excessive dosing

Pharmacokinetic study	Dose	Absorption parameters				Elimination	
		C_{max} **(ng/ml)**	C_{max} **(nmol/L)**	t_{max} (h)	$t_{1/2(abs)}$ (h)	$t_{1/2}$ (h)	Cl ($1\ kg^{-1}\cdot day^{-1}$)
Krishna et al., 1993[18]	6 mg (tablets)	23.1	26.4	4.3	0.5	12.6	4.28
Krishna et al., 1993[18]	12 mg (tablets)	30.4	34.7	10.3	2.5	13.4	4.03
Long et al., 2001[19]	6 mg (tablets)	20.2	23.1	4.7	1.4	11.1	7.57
Long et al., 2001[19]	12 mg (tablets)	23.5	26.9	5.3	1.4	21.1	6.53
Long et al., 2001[19]	18 mg (tablets)	31.2	35.7	5.1	1.7	16.7	10.6
Edwards et al., 1988[20]	12 mg (solution)	81	92.6	3.6	–	–	–
Edwards et al., 1988[20]	12 mg (tablets)	50	57.1	3.4	–	–	–
Edwards et al., 1988[20]	12 mg (capsules)	46	52.6	3.6	–	–	–
Ogbuokiri et al., 1993[21]	150 µg/kg	37.9	43.3	–	–	–	–
Baraka et al.,1996[22]	150 µg/kg	52.2	59.7	5.2	–	35.0	–
Elkassaby, 1991[23]	150 µg/kg	39	44.6	5.6	–	16	–
Okonkwo, et al., 1993[24]	6 mg (tablets)	38.2	43.7	4.7	–	54.5	3.1
Njoo, et al. 1995[25]	150 µg/kg	-	-	-	-	19.9	–
Muñoz, et al., 2018[17]	36 mg (550 - 700 µg/kg)	96.2	109.9	3.64	-	91.77	
Guzzo et al., 2002[12]	90 mg	158.1	180.7	4.9	-	18.8	-
Guzzo et al., 2002[12]	120 mg (1404 - 2000 µg/kg)	247.8	283.2	4.2	-	19.1	-

Table 2. Comparison between the in vitro inhibitory concentration of ivermectin[11] with exemplar published C_{max} values of the drug[12,17]

In vitro end-points[11]	Inhibitory concentrations (µmol/L)	Inhibitory concentrations recalculated in µg/ml	Inhibitory concentrations recalculated in ng/ml	Ratio between the inhibitory concentrations and clinically relevant C_{max} (96.2 ng/ml)	Ratio between the inhibitory concentrations and C_{max} after excessive dosing 247,8 (ng/ml)
IC_{50} - cell associated (E gene)*	2.8	2.45	2450	25.5	9.9
IC_{50} - supernatant (E gene)	2.4	2.1	2100	25.9	8.5
IC_{50} -cell associated (RdRp gene)**	2.5	2.19	2190	27.0	8.8
IC_{50} - supernatant (RdRp gene)	2.2	1.95	1950	24.1	7.9
Average IC_{50}	2.475	2.166	2450	**30.6**	**10**
$IC_{90\text{-}100}$ (highest and most effective concentration tested)	5.0	4.3755	4375	**55.0**	**17.7**

*E - envelope protein gene; ** RdRp - RNA-dependent-RNA-polymerase gene.[11]

The repurposed antimalarial drugs hydroxychloroquine and chloroquine that have been included in numerous COVID-19 treatment protocols also have micromolar inhibitory concentrations against SARS-CoV-2[26] and nanomolar C_{max} values[27]. Nevertheless these agents have enormous apparent volumes of distribution and presumably disproportionally larger tissue levels relative to the plasma concentrations, which makes the translation of the *in vitro* data plausible[27-29]. The other very promising agent tested in clinical trials and applied as compassionate use for COVID-19 is remdesivir[1,30]. This broad-spectrum antiviral drug originally developed for Ebola shows potent inhibitory effects against SARS-CoV-2 with an IC_{50} of 0.77 µmol/L (464 ng/ml)[31]. This concentration is readily attainable as the drug is given as venous infusion. The typical dosing schedule for remdesivir - initial infusion of 200 mg, followed by 100 mg/daily for a total of 5 days yields maximal plasma concentrations of 5440 ng/ml in the first day and 2610 on day 5 [30].

In case of ivermectin, however, the potential repurposing plausibility if any is at present not very likely, because the antiviral concentrations would be attainable only after massive overdose. The therapeutic

application of ivermectin is usually not associated with significant toxicity, whereby the majority of documented adverse effects, such as: nausea, rash, dizziness, itching, eosinophilia, abdominal pain, fever, tachycardia, could be generally attributable to the gross lethality of invading microfilarias giving rise to Mazzotti-like reactions[13,14,32]. Nevertheless at large doses the drug could penetrate the blood-brain barrier and could affect GABA-ergic transmission causing CNS depression and potentiation of the effects of benzodiazepines[15]. Human exposures at doses multifold higher than the therapeutic is expected to give rise to side effects similar to those documented in preclinical mammalian testing[13,15]. Human overdoses have been associated with vomiting, tachycardia and ECG abnormalities, significant blood pressure fluctuations, CNS effects (drowsiness, ataxia) and visual disturbances (mydriasis). Accidental self-injection of a veterinary medicinal product has produced signs of clinical toxicity, albeit the drug was applied at therapeutically relevant dose (approximately 200 μg/kg)[15].

It has to be emphasized that general public communication of drugs as potential COVID-19 therapeutics, based solely on *in vitro* data, is neither scientifically nor ethically appropriate. Ivermectin has been previously shown to exert antiviral activity *in vitro* against Dengue fever virus (DENV)[33], influenza virus[34], West Nile Virus[35], Venezuelan equine encephalitis virus[36], and heralded as possible antiviral drug, but so far there has not been any clinical translation of these data. Noteworthy a clinical trial for the treatment of Dengue fever in Thailand failed to show clinical benefits[11]. In light to the aforementioned pharmacokinetic considerations this is not surprising given the published inhibitory concentrations against DENV1-4 ranged 1.66 - 2.32 μM[33].

Conclusion

The world has already seen epidemics of self-medication, drug shortages and even overdoses with chloroquine and hydroxychloroquine[37,38]. Unfortunately the Caly et al. study which prompted enormous public interest has the potential to evoke similar tragic sequels, especially having in mind that in many countries the drug is only available as solutions for injection for veterinary use, whose potential for serious toxicological outcomes in humans is unanimous. In Bulgaria in particular this study has prompted the National Veterinarians` Union to share their concerns about the hysteria this study has evoked and to firmly discourage self-medication with ivermectin, which in this country is only available for use in animals[39]. In a 10th April letter to stakeholders FDA has similarly shared its concerns on this issue and explicitly advised against any attempts for self-medication with ivermectin for COVID-19[40].

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