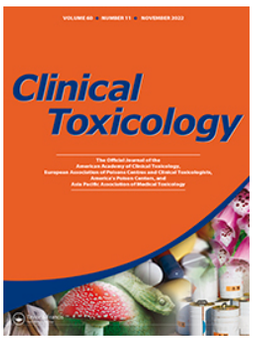

Clinical Toxicology

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/ictx20

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To cite this article: Ruby Hoang, Courtney Temple, Matthew S. Correia, Joseph Clemons & Robert G. Hendrickson (2022): Characteristics of ivermectin toxicity in patients taking veterinary and human formulations for the prevention and treatment of COVID-19, Clinical Toxicology, DOI: 10.1080/15563650.2022.2134788

To link to this article: https://doi.org/10.1080/15563650.2022.2134788

CLINICAL TOXICOLOGY
https://doi.org/10.1080/15563650.2022.2134788

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POISON CENTRE RESEARCH

Characteristics of ivermectin toxicity in patients taking veterinary and human formulations for the prevention and treatment of COVID-19

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ABSTRACT

Background: US poison control centers reported increased cases of ivermectin toxicity during the COVID-19 pandemic. Previous descriptions of ivermectin toxicity have evaluated heterogeneous groups with a variety of ivermectin sources and dosage patterns. We sought to compare the clinical effects of ivermectin toxicity in patients taking human- vs. veterinary-formulations and acute- vs. chronic-ingestion patterns.

Methods: We performed a retrospective analysis of cases from the Oregon Poison Center of ivermectin exposures for the prevention or treatment of COVID-19 that resulted in a healthcare visit over a 24-week period (14 August 2021 – 31 January 2022).

Results: We identified 37 cases of ivermectin toxicity. The median age of patients was 64 years, and most patients were male. The majority of patients were hospitalized (21) or treated in an emergency department (13). A minority were treated in an outpatient setting (3) and one patient died. Seventeen ingested veterinary formulations and fifteen ingested prescription tablets. Patients reported taking ivermectin for treatment (23) and prevention (14) of COVID-19. Clinical effects included neurotoxicity (30), gastrointestinal symptoms (14), and musculoskeletal complaints (7). Patients taking veterinary products took higher doses of ivermectin and had higher rates of altered mental status than those taking prescription tablets. Patients taking ivermectin chronically took smaller doses (daily dose of 13.5 mg) over a prolonged period (median 3.8 weeks) and developed toxicity that was milder than those with acute ingestions.

Conclusion: Ivermectin toxicity developed in predominantly male patients >60 years old who ingested higher than recommended doses and developed neurologic symptoms. Patients who took a veterinary formulation of ivermectin ingested large single doses or large daily doses for several days and developed rapid onset of neurotoxicity. Patients with chronic toxicity developed milder symptoms and tended to take typical therapeutic doses, but continued therapy for weeks rather than days.

ARTICLE HISTORY
Received 9 August 2022
Revised 1 October 2022
Accepted 6 October 2022

KEYWORDS
Ivermectin; toxicity; COVID; veterinary; overdose

Introduction

For much of the COVID-19 pandemic in 2021, there were few therapeutic options for treating COVID-19 or preventing infection after exposure. As a result, the public resorted to a variety of therapies including veterinary formulations or supratherapeutic doses of ivermectin. In August 2021, the Centers for Disease Control and Prevention issued a warning statement highlighting the large increase of outpatient prescriptions of ivermectin for COVID-19, despite not being approved by the U.S. Food and Drug Administration [1]. During this same month, poison centers reported increased cases of ivermectin toxicity [2].

Ivermectin is FDA approved for the treatment of intestinal strongyloidiasis and onchocerciasis as a single 150–200 mcg/kg oral dose (12 – 16 mg in an 80 kg patient) [3,4]. Ivermectin is also indicated for the topical treatment of rosacea and pediculosis [4]. Veterinary ivermectin is used for the treatment of internal and external parasites in many species and commonly for gastrointestinal worms in horses [5,6]. Previous studies suggest that ivermectin inhibits cell replication of SARS-CoV-2 *in vitro* at plasma concentrations 10 times higher than concentrations obtained with recommended dosing [7]. Subsequent human studies do not support its use for COVID-19 outside of ongoing clinical trials [8]. At therapeutic ivermectin doses, adverse effects include headache, myalgia, arthralgia, diarrhea, vomiting, and weakness [3,9]. In overdose, seizures, hypotension, and obtundation have occurred [2,9]. Ivermectin is available in tablets by prescription or online and in paste or liquid veterinary formulations that are readily available for purchase through animal feed stores or online (Figure 1).

Previous descriptions of ivermectin toxicity for the prevention and treatment of COVID-19 have reported a variety of ivermectin sources and dosage patterns [2,10]. We sought to compare the clinical effects of ivermectin toxicity in patients

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Figure 1. Different formulations of ivermectin (from left to right: solution, equine paste, and tablets).

taking human or veterinary formulations and acute or chronic ingestion patterns.

Methods

This is a retrospective series of patients for whom the Oregon Poison Center was consulted over a 24-week period from 14 August 2021 – 31 January 2022 (figure 2). The start date was the onset of a quality improvement project in which we obtained additional medical records. We have previously reported some information from 13 patients included in this study [2]. Their data were included here because additional dosing and clinical information were available after medical record chart review. We searched the Poison Center medical record (Toxicall®, Aurora, CO) for all cases with "ivermectin" in the "substance" data field. We excluded non-human exposures, information cases, ivermectin exposures for reasons other than the prevention or treatment of COVID-19, accidental exposures, if the patients did not present to a health care facility, if the presenting symptoms were attributed to COVID, if patients did not develop symptoms of toxicity, or charts with incomplete data. As part of a previous quality improvement project, a complete hospital medical record was requested for all cases of suspected ivermectin toxicity during this time period. These records were used to augment the Poison Center medical records and included ingested dose, patient weight, complete physical examination findings, medical history, vital signs, and medication list.

Cases were reviewed and the following data extracted: age, sex, ingestion history (dose, formulation, frequency, duration), exposure to COVID-19, purpose of ingestion (prevention or treatment), time to symptom onset, clinical presentation, examination, consultations, laboratory, and imaging tests when available. All cases were assigned to two medical toxicology fellows for review. Differences in data were resolved by consensus and assigned to a third reviewer if not resolvable.

Ivermectin for veterinary purposes is available in 1% (w/v) solution and 1.87% (w/v) paste (see Figure 1) [5,6]. A click of 1.87% ivermectin equine paste is the dose intended for a 250 lb animal. We converted the dose into micrograms using 91 mcg/lb dose in patients who described taking a certain "pound" dose of ivermectin. For example, a patient who reported taking a dose intended for a 250 lb animal (1 click) would have ingested 22.75 mg (250 lb × 91 mcg/lb) of ivermectin. We then reviewed the daily dose and calculated dose/weight for patients with weight and dose available. Dichotomous outcomes were analyzed using Chi-square and Fisher exact test when data were sparse. Continuous variables were compared using Mann-Whitney *U* test.

In patients who tested positive for COVID during their evaluation, we excluded symptoms commonly caused by COVID-19 or deemed to be due to infection: cough, dyspnea, fever, or chills. Home medications were reviewed for every case with special denotation for known p-glycoprotein inhibitors. Altered mental status was noted for any patient presenting neurocognitively different than their known baseline,

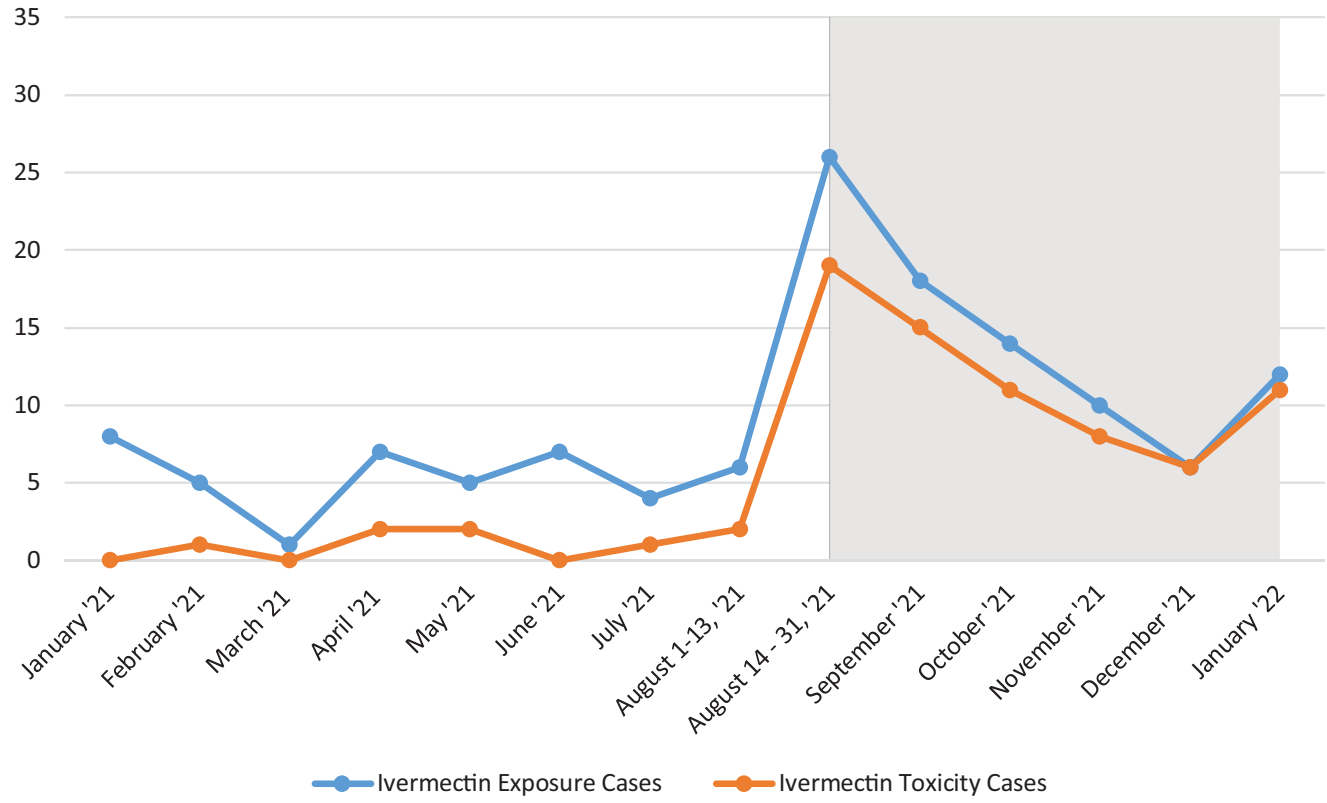

Figure 2. Ivermectin cases reported to the Oregon Poison Center over a year. The highlighted portion indicates our study interval from 14 August 2021 to 31 January 2022.

including but not limited to confusion, encephalopathy, obtundation, etc. We further defined severe altered mental status if the patient was unable to meaningfully communicate, sit upright, or was unconscious. Disposition was described as home, outpatient setting, emergency department (ED), inpatient admission, and death, and were coded to the highest level of care that the patient received.

We defined single ingestions as a one-time ivermectin ingestion occurring within a 24-h period prior to health care facility presentation. Multiple ingestions taken over 1–7 days were considered acute ingestions. We considered acute-on-chronic ingestions as an ingestion of a steady dose with an increase in dose over the preceding 1–7 days before seeking medical care. We defined chronic ingestions as ingestion of a steady dose of ivermectin for greater than 7 days without a dose increase. The Oregon Health & Science University Institutional Review Board approved the study.

Results

Eighty-six cases met initial inclusion criterion, and we excluded 49 cases, leaving 37 cases of ivermectin toxicity available for analysis. Reasons for exclusion: information cases (6), ivermectin exposures for reasons other than the prevention or treatment of COVID-19 (2), accidental exposures (7), patients who did not present to a health care facility (16), symptoms that were attributed to COVID-19 (7), patients who did not develop symptoms of toxicity (6), and incomplete data (5). There were no discrepancies between the reviewers. Figure 2 depicts the timeline of Ivermectin cases over a year reported to the Oregon Poison Center. Twenty-nine (83%) cases had poison center charts that were supplemented with complete hospital records. The remainder had sufficient documentation for inclusion.

Comprehensive results are displayed in Table 1. The median age of patients was 65 years (32–81) for males and 62 years (16–77) for females. Most patients were male (23). Most patients were either hospitalized (21) or treated in an emergency department (13), a minority were treated in an outpatient setting (3), and one died. Seventeen patients ingested veterinary formulation and fifteen ingested prescription ivermectin, and two used both. Three patients took unknown formulations of ivermectin. Twenty-three patients reported taking ivermectin for treatment of COVID-19 symptoms and fourteen patients were taking ivermectin to prevent COVID-19.

Neurotoxicity was the most common complaint in patients taking ivermectin regardless of COVID status, formulation, dosage, or chronicity. Most patients reported symptoms were neurological (30), gastrointestinal (14), and musculoskeletal (7) (Table 1). Overall, the mean total dose ingested was 277.8 mcg/kg and the mean daily dose was 57.1 mg. Of the 32 patients with reported heart rates and blood pressures, seven patients had tachycardia, two had bradycardia, sixteen had elevated blood pressure, and three had hypotension (Table 1).

Table 1. Clinical effects of ivermectin ingestion by formulation, chronicity, dose, and organ system effects.

			Formulation			Chronicity			
	All $N = 37$	COVID negative $n = 11$	Human product (tablets) $n = 15$	Veterinary product (paste or liquid) $n = 17$	Both $n = 2$	Single ingestion <24 h $n = 5$	Acute 1–7 day $n = 19$	Acute on chronic $n = 2$	Chronic >7 day $n = 4$
Demographics									
Sex									
Males	23	8	9	11	1	2	12	2	1
Females	14	3	6	6	1	3	7	0	3
Age (median)									
Males (years)	65	64	64	58	73	54	61	53	58
Females (years)	62	60	55	62	69	62	60	–	72
Dose									
Daily mean (mg)	57.1	32.3	19.2	**95.1***	–	212.5	31.2	18.4	13.5
Daily mean (μg/kg)	277.8	358.6	230.4	325	–	–	302.2	231.2	52.8
Symptoms									
Neurologic	30	10	11	16	1	5	15	2	4
Ataxia	6	4	2	3	0	0	3	0	1
Altered mental status	15	6	3	**11***	1	1	7	1	1
Severe altered mental status	5	1	2	3	0	1	3	0	0
Agitation	2	0	1	0	0	0	1	0	0
Seizure	2	1	1	1	0	1	0	1	0
Tremors	3	1	2	1	0	0	2	0	0
Weakness	12	5	4	6	1	1	6	0	3
Paresthesia	1	1	0	0	0	0	1	0	0
Vision changes	5	1	1	4	0	3	1	1	0
Hallucinations	2	0	0	2	0	1	0	1	0
Dizziness	1	2	0	0	0	0	4	0	1
Gastrointestinal	14	3	5	8	0	3	7	0	2
Abdominal pain	3	0	3	0	0	0	2	0	2
Vomiting	7	2	2	5	0	2	5	0	0
Diarrhea	10	1	4	4	0	2	3	0	2
Musculoskeletal	7	2	5	2	1	0	5	0	1
Myalgia	5	1	3	2	0	0	4	0	0
Rash	2	1	1	0	1	0	2	0	1
Heart rate (bpm)	$n = 32$								
Bradycardia (<60)	2	2	1	1	0	0	1	0	0
Normal (60–99)	23	9	10	10	2	0	5	0	0
Tachycardia (>=100)	7	0	3	2	0	0	5	0	0
Blood Pressure	$n = 32$								
Hypotension < 90/60	3	0	1	2	0	0	0	0	2
Normotension	13	1	6	3	0	0	8	0	1
Hypertension > 140/80	16	10	7	8	2	2	8	2	1
Disposition, % (*n*)									
Outpatient	3	0	0	3	0	2	1	0	0
Emergency Department	13	5	9	4	1	2	7	1	1
Hospitalization	21	6	6	10	1	1	11	1	3
Deaths	1	0	1	0	0	0	1	0	0

*= $p < 0.05$.

COVID status

To ensure that we were not attributing COVID-19 symptoms to ivermectin toxicity, we compared patients who had a currently positive SARS-CoV-2 test and were taking ivermectin to treat COVID symptoms with those who were attempting to prevent COVID and had a negative SARS-CoV-2 test. There were no statistically significant nor clinically relevant differences (Table 1).

Formulation

Compared to those who ingested prescription medications, patients who ingested veterinary products had higher rates of altered mental status (11/17 v. 3/15, $p = 0.01$), ingested higher doses per day (95.1 mg/day vs. 19.2 mg/day, $p = 0.02$), and were all acute ingestions (100% v. 44%, $p = 0.05$) (Table 1).

Chronicity

All five patients who ingested a single, large veterinary formulation of ivermectin developed varying degrees of neurotoxicity with severe altered mental status (1), seizure (1), visual changes (3), and hallucinations (1). All single ingestions were from veterinary products. Patients taking ivermectin chronically developed toxicity despite taking smaller doses (daily dose 13.5 mg/day) over a prolonged period (median 3.8 weeks). Patients with chronic ingestions had milder toxicity with no cases of severe altered mental status. The acute-on-chronic cohort reported taking a consistent dose of ivermectin for weeks without symptoms then acutely increasing the dose (mean of 10-fold increase) over the days prior to developing toxicity after an exposure to COVID.

P-glycoprotein

Six patients were previously prescribed p-glycoprotein inhibitors including macrolides, proton pump inhibitors, and beta

blockers. Five patients taking p-glycoprotein inhibitors took acute ingestions that were higher than recommended doses (range 21–136.5 mg). Patients co-ingesting p-glycoprotein inhibitors reported symptoms of generalized weakness, gastrointestinal distress, or musculoskeletal complaints.

Discussion

We describe toxicity related to ivermectin that was used to treat COVID-19 symptoms or to prevent COVID-19 infection. Most patients developed a variety of neurologic symptoms from obtundation to encephalopathy to ataxia to visual disturbances. This finding is similar to previous studies of ivermectin and avermectin toxicity and constitutes more severe features of toxicity [9,10].

More than half of our patients ingested veterinary ivermectin paste or liquid (19) that is readily available in feed stores and on the internet. The difficulty in dosing this formulation may have contributed to the very large doses taken by our patients with single ingestions (mean 212.5 mg). This dose is 13–18 times higher than the 12–16 mg (150–200 mcg/kg) for human antiparasitic treatment. All patients who presented after a single ingestion took a veterinary formulation of ivermectin. Patients taking veterinary formulations were more likely to develop altered mental status.

We found that all single ingestions were of veterinary formulations and constituted large doses of ivermectin leading to rapid onset of neurotoxicity. Patients with acute and acute-on-chronic toxicity tended to take ivermectin doses that were three to eight times higher than recommended for several days before developing toxicity. Patients with chronic ivermectin toxicity reported a mean 13.5 mg daily dose, which is typical for the one-time dosing for onchocerciasis and strongyloidiasis, but continued to take this dose for a median of 3.8 weeks. Chronic toxicity patients developed mild neurologic and gastrointestinal symptoms such as weakness, dizziness, diarrhea, and dehydration, which are similar to those described in clinical trials and with therapeutic use [3].

P-glycoprotein inhibitors may augment neurotoxicity in patients taking ivermectin. Previous case reports illustrate the development of neurotoxicity despite small dosages as the p-glycoprotein inhibitors prevent the neuronal efflux of ivermectin [11]. We were unable to determine a relationship between p-glycoprotein inhibitors and neurotoxicity due to our small sample size ($n = 6$).

There are several limitations in this study. The data arise from voluntary reporting to a single poison center. This limits the generalizability as the dosages and formulations of ivermectin may differ in other areas. Some charts lacked certain data points like a patient's weight and therefore limited our ability to calculate a dose per weight. Dosing was obtained by patients and reported in unconventional measurements such as clicks, teaspoons, or estimated volume of solution that required conversion to milligrams of ivermectin.

Conclusion

Ivermectin toxicity developed in predominantly male patients over 60 years old who ingested higher than recommended doses and developed neurologic symptoms, gastrointestinal symptoms, and elevated blood pressure. Patients who took a veterinary formulation of ivermectin ingested large single doses or large daily doses for several days and developed rapid onset of neurotoxicity. Patients with chronic toxicity developed milder symptoms and tended to take typical therapeutic doses, but continued therapy for weeks rather than 1–2 days. Despite evidence that ivermectin is ineffective at treating or preventing COVID-19 [8], prescriptions increased during the pandemic suggesting a greater need for providing rapid and accurate information to prescribers in both local and national arenas.

Author contributions

All authors have participated in the data collection, analysis, drafting, and preparation of the manuscript. They have approved, reviewed, and revised of the manuscript as submitted. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Funding

The author(s) reported there is no funding associated with the work featured in this article.

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