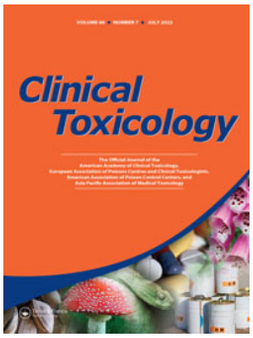

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CLINICAL RESEARCH

Ivermectin associated adverse events in the treatment and prevention of COVID-19 reported to the FACT pharmacovigilance project

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ABSTRACT

Background: In August 2021, the Centers for Disease Control and Prevention (CDC) released a health alert following the rapid increase in ivermectin prescriptions and reports of severe illness associated with use of products containing ivermectin for the prevention or treatment of COVID-19 infections. The United States Food and Drug Administration (FDA) and the CDC have explicitly discouraged the use of ivermectin in the prevention or treatment of COVID-19 outside of clinical trials. The study aims to describe the adverse events (AEs) related to ivermectin use for the prevention or treatment of COVID-19.

Methods: This is a prospective case series of adverse events related to therapeutics used in the prevention or treatment of COVID-19 submitted to the FDA ACMT COVID-19 ToxIC (FACT) Pharmacovigilance Project sub-registry between October 2020 and December 2021. This is an ongoing toxico-surveillance system at 15 major academic medical centers in 12 states. Data collected included sociodemographics, exposure related information including dose, frequency, route, duration, and reason for taking ivermectin as well as a clinical description of the adverse event and the outcome.

Results: A total of 40 patients who developed AEs following ivermectin use were reported to FACT over 15 months. Self-medication with veterinary formulations were reported in 18/40 patients Thirty-three patients presented to emergency departments and nineteen patients were admitted to the hospital. Patients reported using ivermectin for prevention (24/40), treatment of symptoms (19/40), and for treatment of documented COVID-19 (8/40). Neurological toxicity was the most frequent finding. Fifteen patients had minor symptoms while 25 developed severe toxicity.

Conclusions: Ivermectin use for the attempted treatment of COVID-19 has potential adverse health effects primarily related to neurological function. This is especially true when patients are self-treating with this medication and when they are using formulations intended for non-human use.

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COVID-19; ivermectin; treatment; prevention; adverse event; veterinary formulation

Introduction

The World Health Organization (WHO) declared the novel coronavirus disease 2019 (COVID-19) a pandemic on March 11, 2020 [1]. The rapid increase in COVID-19 cases worldwide has posed an unprecedented challenge to healthcare professionals and the public health community. While vaccines are the cornerstone of curbing the pandemic, it remains critical to develop therapeutic countermeasures to reduce the morbidity and mortality of the disease. In the absence of approved and authorized medications to treat severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections, there has been an interest in repurposing currently available pharmaceuticals that may have therapeutic efficacy for this purpose. Ivermectin (IVM) has attracted the attention of researchers and laypeople since the beginning of the COVID-19 pandemic [2]. Currently, IVM is approved by the United States (US) Food and Drug Administration (FDA) for the treatment of onchocerciasis (river blindness), intestinal strongyloidiasis, rosacea, and pediculosis capitis [3].

Ivermectin is available as an oral tablet (3 mg), topical cream (1%) and lotion (0.5%) for human use. It is also available for animal use in several forms including tablet, paste (1.87%), topical solution (5 mg/ml), and liquid for parenteral administration (1%). Several clinical trials have been undertaken to assess the efficacy and safety of IVM against the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). While IVM has been shown to have an inhibitory effect on *in vitro* SARS-CoV-2 replication in the early stages of infection [4]; overall, the reliable evidence available does not support the use ivermectin for treatment or prevention of COVID-19 outside of well-designed randomized trials [5]. To date, the US Centers for Disease Control and Prevention (CDC), FDA, WHO, and the European Medicines Agency have explicitly discouraged the use of IVM in the prevention or treatment of COVID-19 outside of clinical trials [6–9]. The US National institutes of Health (NIH) COVID-19 Treatment

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Guidelines Panel states that "there is insufficient evidence … to recommend either for or against the use of ivermectin for the treatment of COVID-19" [10]. The NIH further stated a need for adequately powered, well-designed, and well-conducted clinical trials in order to reach evidence-based guidance on the role of IVM in the treatment of coronavirus 2 (SARS-CoV-2).

Ivermectin dispensing by retail pharmacies increased 10 to 24-fold during the COVID-19 pandemic [11]. A recent study showed that in a single week of August 2021, private and Medicare plans paid an estimated total of $2 493 716.16 for IVM prescriptions for COVID-19 [12]. The use of veterinary formulations of IVM that are available over the counter (OTC) has also greatly increased [7].

On August 26, 2021, the CDC released a health advisory after a number of poison control centers (PCCs), reported about the use of IVM, including veterinary formulations, to treat or prevent COVID-19 [7]. The health advisory states that PCCs across the U.S. experienced a three-fold increase in the number of calls for human exposures to IVM in January 2021 and a five-fold increase in July 2021 compared to the pre-pandemic baseline.

In September 2020, the American College of Medical Toxicology's Toxicology Investigators Consortium entered into a contract with the FDA to form the FDA ACMT COVID-19 ToxIC (FACT) Pharmacovigilance Project Sub-registry to prospectively identify adverse events (AEs) for drugs and substances associated with the treatment or prevention of COVID-19. Herein, we describe 40 cases of IVM exposures reported to the FACT Pharmacovigilance Project Sub-registry.

Methods

This is a prospective case series of AEs submitted to the FACT Pharmacovigilance Project Sub-registry [13] between October 2020 and December 2021. The FACT Pharmacovigilance Project is an ongoing toxico-surveillance system at 15 major academic medical centers in 12 states (Arizona, California, Colorado, Washington D.C., Georgia, Massachusetts, Minnesota, Missouri, New York, Pennsylvania, Oregon and Texas). Participating sites report suspected AEs related to therapeutics used in the prevention or treatment of COVID-19 into an online REDCap-based data collection interface specifically constructed for this project [14]. Medical toxicologists at each site, with the assistance of FACT research assistants, assessed each case and rated the likelihood of the relatedness of the IVM to the AE as definitive, probable, possible or doubtful. The classification was based on the clinical judgement of the medical toxicologists. The type of data collected is summarized in Table 1. Data were communicated to the FDA in real time as cases were identified and assessed. Cases were included if the implicated substance of the AE was identified as IVM. We chose to classify patients as experiencing minor symptoms if they experienced gastrointestinal symptoms or and the following neurological symptoms: dizziness, headache and paresthesia. Central nervous system (CNS) depression, seizure, confusion, agitation, visual disturbances/visual hallucinations, delirium/toxic psychosis and syncope were classified as severe neurological symptoms. Categorical variables were described using frequency and percentages, and continuous variables were described using medians and interquartile ranges. This study was approved by the Western Internal Review Board (IRB) and by each participating institutions IRB.

Results

A total of 40 patients who developed AEs following the use of IVM were reported to the FACT Pharmacovigilance Project between October 2020 and December 2021. The median age was 53 years [range 39–65] and 19/40 were female (Table 2). Self-medication with veterinary formulations intended to treat parasitic worms in horses and cattle were reported in 18/40 patients, 5 patients reported purchasing IVM on the internet without further information. The source of IVM could not be identified in 17 patients. Veterinary paste and injectable IVM were the most frequently reported forms. Doses ranged from 12 mg to 1360 mg. Patients reported using IVM for prevention (24/40), treatment of symptoms in undocumented COVID-(19/40), and for treatment of documented COVID-19 (8/40).

Thirty-three patients presented to emergency departments and nineteen were admitted to the hospital. Three patients called the PCC following their exposure and were recommended to stay at home while four patients refused to go to the ED and chose to stay at home. The outcome in these four patients was unknown as they did not return poison specialists calls on follow up. In 33 patients, IVM was the only reported drug used to treat or prevent COVID-19, while two patients reported using a combination of IVM and azithromycin, and another two reported using a combination of IVM and hydroxychloroquine to treat documented COVID-19. One patient reported using a combination of IVM with clorsulon for prevention.

Neurological toxicity was the most frequent finding, followed by gastrointestinal (GI) adverse reactions. Three patients, who took a veterinary parenteral preparation orally, developed lactic acidosis, hypotension and tachycardia. These preparations contained propylene glycol (50%–60%) (Table 3). Out of 40 patients, 15 had minor symptoms (GI symptoms, minor neurological symptoms or a combination of both), while 25/40 developed severe toxicity. The distribution of patients by type and severity of AEs is summarized in Table 4. The time to onset of symptoms ranged from less than 12 h to up to 5 days since the first dose of IVM.

Discussion

This pharmacovigilance case series identifies potential hazards of inappropriate use of IVM for the prevention or treatment of COVID-19. This is particularly important due to the off-label use of veterinary formulations by the public. Although, our study does not aim at assessing quantitatively self-medication with IVM or the use of veterinary formulations, our findings, the CDC's health advisory, and the marked increase in sales of veterinary formulations compared

Table 1. Data collected by the FACT Pharmacovigilance Project.

	Variables
Sociodemographic	Age, sex, race, pregnancy status
Past medical history	Co-morbidities
	Chronic and current medications
Exposure	Agents involved: dose, frequency, route, duration, source
	Reason for exposure
Adverse event	Place of occurrence
	Time to onset of adverse events from initiation of exposure
	Signs and symptoms by system
	Outcome

Table 2. Summary of patients' characteristics ($N = 40$).

Characteristics	Number
Gender (Female)	19
Age, in years (Median, interquartile range)	53 (39–65)
Reason for exposure	
Prevention	24
Treatment of symptoms in undocumented COVID-19	7
Treatment of documented COVID-19	8
Missing	1
Outcome	
ED visit	33
Hospital admission	19
Minor effect (patients kept at home)	3
Unknown†	4
Agent	
Ivermectin	33
Ivermectin + azithromycin	2
Ivermectin + hydroxychloroquine	2
Ivermectin + Clorsulon	1
Missing	2

†Patients refused PCC recommendations to visit ED.

Table 3. Distribution of adverse events.

Signs and symptoms	Number (%)
Gastrointestinal	
Nausea/Vomiting/Diarrhea	13 (33)
Anorexia	2 (5)
Neurological	
Confusion	11 (28)
CNS depression	8 (20)
Dizziness	7 (18)
Visual disturbances/visual hallucinations	6 (15)
Seizure	4 (10)
Somnolence	4 (10)
Headache	4 (10)
Delirium/toxic psychosis	4 (10)
Paresthesia	2 (5)
Tremors	2 (5)
Agitation	2 (5)
Syncope	1 (3)
Skin	
Pruritus and rash	2 (5)
Metabolic	
Lactic acidosis	3 (8)
Cardiovascular	
Hypotension	4 (10)
Bradycardia	3 (8)
Tachycardia	3 (8)
Respiratory	
Dyspnea	2 (5)

CNS: Central Nervous System.

to pre-pandemic levels reveal that in the absence of straightforward medical treatment, people will self-medicate with dangerous remedies.

Despite the FDA and WHO's efforts in alerting the public on several occasions to avoid self-medication [8,15], IVM has been promoted by media outlets and online sites. The wide accessibility of IVM through the internet, tractor supply, tackle and feed shops, likely contributes to the continued reports of toxic exposures. Therefore, there is an urgent need for rapid dissemination of information to the health community and general public regarding the potential for deleterious effects associated with IVM use in the treatment and prevention of COVID-19 [9,15,16].

The FDA human approved labeling for oral IVM identifies adverse reactions including GI symptoms of anorexia (0.9%), constipation (0.9%), diarrhea (1.8%), nausea (1.8%), vomiting (0.9%), neurological events of dizziness (2.8%), somnolence (0.9%), vertigo (0.9%), and tremor (0.9%) and skin manifestation of pruritus (2.8%), rash (0.9%), and urticaria (0.9%) were observed in human clinical trials for the treatment of strongyloidiasis and assessed as, at least possibly related to IVM [3]. Similarly, headache (0.2%) was observed with treatment of onchocerciasis [3]. These symptoms are consistent with those reported in the majority of our patients reporting less severe outcomes. This could be explained by the underreporting of less severe symptoms in more clinically serious cases. The severe neurological AEs we identified are consistent with those reported in public health programs aiming to eliminate onchocerciasis in Africa. Chandler (2018) analyzed IVM reports received from national pharmacovigilance centers in 125 countries participating in the WHO Program for International Drug Monitoring [17], and reported cases of encephalopathy, confusion, stupor, and coma in community-based IVM campaigns to treat onchocerciasis. Several criteria in favor of causal inference between the exposure to IVM and the occurrence of severe neurological AEs were cited: the cessation of exposure reversed the symptoms, the reoccurrence of symptoms on repeated exposures, and the identification of IVM in brain tissue in one case [17]. Ivermectin is a CYP3A4 substrate and P-glycoprotein substrate and inhibitor. At therapeutic doses, IVM does not penetrate the CNS well; however, increased CNS penetration can occur with genetic polymorphisms in the MDR1 protein or overdoses saturating P-glycoprotein (P-gp) efflux pumps, which could result in increased CNS penetration and neurotoxicity. Also, co-administration of IVM with P-glycoprotein or CYP3A4 inhibitors can increase IVM plasma concentration and decreases metabolism. Therefore drug-drug interactions and polymorphism may contribute to toxicity [18].

The recommended therapeutic doses of IVM for onchocerciasis and strongyloidiasis are 150 mcg/kg and 200 mcg/kg of body weight, respectively. The calculated therapeutic dose for a 70-kg individual is 10–14 mg, equivalent to 4–5 oral tablets of IVM intended for human use, 0.6–0.84 grams of

Table 4. Distribution of patients by type and severity of AEs.

Symptoms	*N* (%)
GI symptoms	7 (18)
Severe neurological symptoms†	11 (28)
Severe neurological symptoms with metabolic, cardiovascular, or respiratory symptoms	5 (12)
Minor neurological symptoms§	6 (15)
Minor neurological symptoms§ & GI symptoms	2 (5)
Combination of symptoms	9 (22)

†Seizure, confusion, delirium, agitation, visual disturbances, visual hallucinations syncope and CNS depression, §Headache, dizziness, somnolence, tremors and paresthesia.

horse paste formulation (1.87%), 2–3 ml of a 5 mg/ml veterinary topical solution and 1–1.4 ml of parenteral formulation (1%). Given the higher concentration of veterinary formulations compared to human oral tablets, patients ingesting veterinary products are at higher risk of experiencing overdose related toxicity.

Limitations

The data related to individual cases have been incomplete due to the inherent limitations of the database we used. For example, we could not assess patients' home medications, herbal products, and supplements in the majority of the cases. Therefore, we might have missed drug-drug or food-drug interactions that could have explained the occurrence of AEs. Furthermore, we were unable to collect IVM doses and body weight in all cases which prevented us from exploring the potential association of higher doses with more severe outcomes. Additionally, cases were assessed by a heterogeneous group of medical toxicologists. Finally, our database is based on 15 sites in the United States and is not a complete nationally representative sample. However, recent alerts sent by other PCCs confirm that several states are facing the same problem [19,20].

Conclusions

Despite its lack of documented efficacy, IVM use for the attempted treatment and prevention of COVID-19 has the potential for serious adverse health effects. This is especially true when patients are self-treating with this medication and when they are using formulation intended for non-human use. In addition to raising awareness among health care providers about these hazards, a large public awareness campaign is warranted to educate about these potential risk

Disclaimer

This article reflects the views of the authors and should not be construed to represent FDA's views or policies.

Disclosure statement

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

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