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REVISITING IVERMECTIN SAFETY: INSIGHTS AND LESSONS AFTER COVID-19 PANDEMIC

REVISITANDO A SEGURANÇA DA IVERMECTINA: INSIGHTS E LIÇÕES APÓS A PANDEMIA DE COVID-19

REVISANDO LA SEGURIDAD DE LA IVERMECTINA: PERSPECTIVAS Y LECCIONES TRAS LA PANDEMIA DE COVID-19

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ABSTRACT

Ivermectin is a macrocyclic lactone extensively used to treat parasitic infections in humans and animals. Although considered safe at therapeutic doses, its off-label use during the COVID-19 pandemic raised significant safety concerns. This chapter discusses ivermectin's pharmacological properties, mechanisms of antiparasitic action, and emerging toxicological evidence, with emphasis on neurotoxicity and hepatotoxicity. High doses, inappropriate formulations, or genetic vulnerabilities may compromise blood–brain barrier integrity or liver metabolism, leading to severe adverse effects. The rise in poisoning reports during the pandemic highlights the dangers of unsupervised use. Environmental impacts of ivermectin residues are also addressed, emphasizing the need for cautious, evidence-based use.

Keywords: Ivermectin. Antiparasitic. Adverse Effects. Neurotoxicity. Hepatotoxicity.

RESUMO

A ivermectina é uma lactona macrocíclica amplamente utilizada no tratamento de infecções parasitárias em humanos e animais. Embora considerada segura em doses terapêuticas, seu uso off-label durante a pandemia de COVID-19 levantou preocupações significativas de segurança. Este capítulo discute as propriedades farmacológicas da ivermectina, os mecanismos de ação antiparasitária e as evidências toxicológicas emergentes, com ênfase na neurotoxicidade e hepatotoxicidade. Altas doses, formulações inadequadas ou vulnerabilidades genéticas podem comprometer a integridade da barreira hematoencefálica ou o metabolismo hepático, levando a efeitos adversos graves. O aumento nos relatos de intoxicação durante a pandemia destaca os perigos do uso não supervisionado. Os impactos ambientais dos resíduos de ivermectina também são abordados, enfatizando a necessidade de um uso cauteloso e baseado em evidências.

Palavras-chave: Ivermectina. Antiparasitário. Efeitos Adversos. Neurotoxicidade. Hepatotoxicidade.

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RESUMEN
La ivermectina es una lactona macrocíclica ampliamente utilizada para tratar infecciones parasitarias en humanos y animales. Si bien se considera segura en dosis terapéuticas, su uso fuera de indicación durante la pandemia de COVID-19 planteó importantes preocupaciones de seguridad. Este capítulo analiza las propiedades farmacológicas de la ivermectina, sus mecanismos de acción antiparasitaria y la evidencia toxicológica emergente, con énfasis en la neurotoxicidad y la hepatotoxicidad. Las dosis altas, las formulaciones inadecuadas o las vulnerabilidades genéticas pueden comprometer la integridad de la barrera hematoencefálica o el metabolismo hepático, provocando efectos adversos graves. El aumento de los informes de intoxicaciones durante la pandemia pone de relieve los peligros del uso sin supervisión. También se abordan los impactos ambientales de los residuos de ivermectina, enfatizando la necesidad de un uso cauteloso y basado en la evidencia.

Palabras clave: Ivermectina. Antiparasitario. Efectos Adversos. Neurotoxicidad. Hepatotoxicidad.

1 INTRODUCTION

Ivermectin is a semi-synthetic macrocyclic lactone derived from avermectins. Originally isolated from the bacterium *Streptomyces avermitilis* in the 1970s, it has been widely used in the treatment of human and veterinary parasitic diseases, noted for its efficacy and safety at therapeutic doses (Campbell et al., 1983; Crump, 2017). However, its off-label use during the COVID-19 pandemic reignited discussions about its potential toxic effects, especially when administered in high doses or in veterinary formulations (Chaccour et al., 2021). Recent reports have indicated cases of neurotoxicity, associated with high doses and with blood–brain barrier dysfunction and P-glycoprotein deficiency (Geyer et al., 2005; Lespine et al., 2012), gastrointestinal symptoms, musculoskeletal complaints and hepatotoxicity. This review aims to present the development of ivermectin and summarize some reports and available evidence in the literature regarding its toxicity observed in clinical and experimental studies, especially after COVID-2019 pandemic.

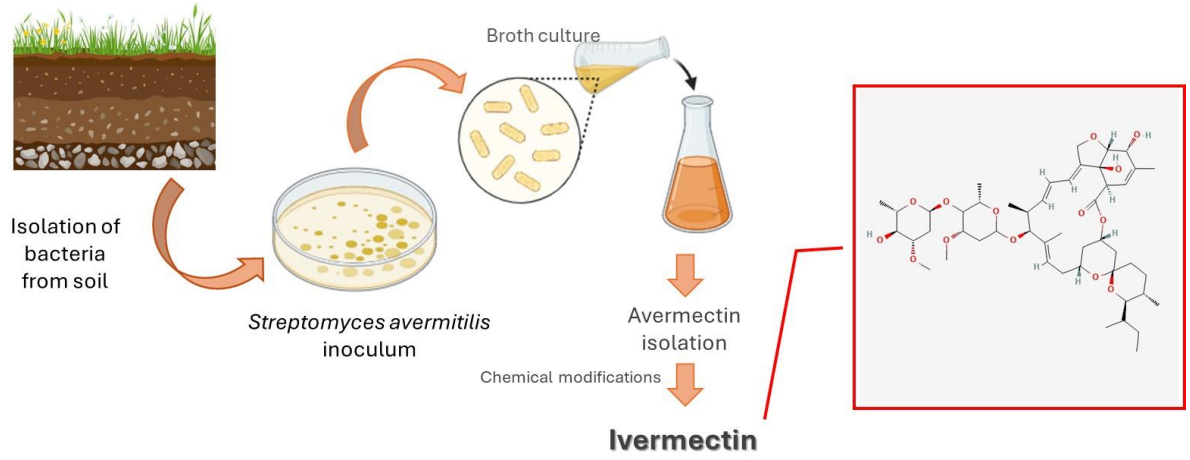
1.1 HISTORY OF IVERMECTIN

Discovered in the 1970s through a collaboration between the Kitasato Institute in Japan and the pharmaceutical company Merck, ivermectin represented a breakthrough in the treatment of parasitic diseases affecting millions of people worldwide (Burg et al., 1979). Derived from chemical modifications of avermectins, this semi-synthetic macrocyclic lactone inaugurated a new class of antiparasitic drugs, characterized by broad-spectrum activity and high efficacy, surpassing the agents available at the time, marking a milestone in antiparasitic pharmacology (Bennett; Williams; Dave, 1988). The process began with the isolation of *Streptomyces avermitilis* from Japanese soil, which was sent for evaluation at Merck Sharp & Dohme (MSD) laboratories in the USA. The fermentation broth of this culture showed significant antiparasitic activity in various biological models. The active compound was isolated in 1975 and named avermectin. Subsequent studies confirmed its effectiveness against a wide range of nematodes, insects, and arachnids. Avermectin exhibited a distinct mechanism of action, primarily acting on glutamate-gated chloride channels. Further chemical modifications led to the synthesis of ivermectin (Figure 1), a more stable and effective version with excellent pharmacokinetic properties and a broad spectrum of activity against parasites of medical and veterinary importance (Omura, 1986; Campbell et al., 1983). In recognition of its importance, Satoshi Ōmura and William C. Campbell were awarded the

2015 Nobel Prize in Physiology or Medicine, alongside Youyou Tu, for discoveries in therapies against parasitic infections (The Nobel Prize, 2015).

Figure 1

Production and chemical structure of ivermectin



Ivermectin has the molecular formula $C_{48}H_{74}O_{14}$ and a molecular mass of approximately 875.1 g/mol. Its structure comprises a 16-membered macrocyclic lactone ring, as well as several functional groups including hydroxyls, ethers, and conjugated double bonds. These confer high lipophilicity and a specific three-dimensional conformation to the molecule (National Center for Biotechnology Information, 2025).

Antiparasitic Use

Ivermectin was introduced to the market in 1981 and revolutionized parasite control by offering a unique combination of potency, broad-spectrum activity, and persistence, which opened new markets and opportunities in livestock production. It also became prominent in the prevention of heartworm disease in dogs and in treating parasitic infections in cattle, sheep, pigs, and horses, benefiting hundreds of millions of animals. In 1985, ivermectin began to be used in human medicine after it was found to prevent symptoms of *Onchocerca volvulus* infection, a disease transmitted by the bite of *Simulium blackflies* (Geary, 2005). Ivermectin is effective against various parasites beyond onchocerciasis. It is used in the treatment of worm infections, parasitic skin diseases, insect infestations, lymphatic filariasis, strongyloidiasis, scabies, fleas, and lice (Crump, 2017). Perhaps the most striking feature of ivermectin's nematode and arthropod action is its potency. This potency varies considerably

among parasite species and stages; however, in all cases, the minimum effective dose is significantly lower than that of other anthelmintics (Campbell et al., 1983).

Initial studies suggested that gamma-aminobutyric acid (GABA)-gated chloride channels were the main targets of ivermectin in parasites, given GABA's role as an inhibitory neurotransmitter in the somatic neuromuscular system of nematodes. However, further evidence has shown that glutamate-gated chloride channels (GluCls), located in nerve and muscle cells of invertebrates, are the primary physiological targets of the drug (Geary, 2005). Ivermectin binds with high affinity to these channels, preventing their closure and increasing membrane permeability to chloride ions, leading to significant influx into cells. This causes neuronal membrane hyperpolarization, which inhibits neural transmission, resulting in paralysis of somatic muscles, especially the pharyngeal pump, ultimately causing parasite death. Although ivermectin also interacts with GABA-gated channels, its affinity for mammalian receptors is much lower, and its ability to cross the blood–brain barrier is limited at therapeutic doses. These factors contribute to its relative safety in vertebrate hosts (Ōmura & Crump, 2004). Additionally, ivermectin may exert immunomodulatory effects on the host, such as neutrophil activation and increased inflammatory mediators like C-reactive protein and interleukin-6, which may enhance its antiparasitic action (Onyeaka et al., 2022).

1.2 PHARMACOKINETICS

Oral administration is the only route approved for ivermectin use in humans. Parenteral administration, as a subcutaneous injection, is possible in veterinary medicine only. Its pharmacokinetic profile after oral administration is characterized by rapid absorption, which is enhanced when taken with food. Plasma peak concentration is typically reached within 4 to 5 hours after administration, and the drug is widely distributed in tissues, especially the liver and adipose tissue (González Canga et al., 2008). With a plasma protein binding rate of approximately 93%, ivermectin undergoes limited biotransformation. Its half-life is around 19 hours, and it is metabolized in the liver by cytochrome P450 enzymes CYP1A and CYP3A4, producing 10 metabolites mainly through demethylation and hydroxylation. The drug is primarily excreted in feces, with only about 1% eliminated via urine (Juarez; Schcolnik-Cabrera; Dueñas-González, 2018).

Ivermectin is excreted also in milk. Healthy women administered 150 μg/kg of ivermectin had a maximum concentration in milk of 14.1 $ng \cdot ml^{-1}$, reached in 6.5 h.

Considering that, a breast-fed child would receive an average dose of 2.75 µg/kg via milk (Ogbuokiri; Ozumba; Okonkwo, 1993).

1.3 TOXICITY

In humans, ivermectin is well tolerated at therapeutic doses. The established dosing regimen ranges from 150 µg/kg to 200 µg/kg administered orally, with a one- to two-dose administration generally being effective (Ashour, 2019). Most patients do not experience serious adverse effects, only immune or inflammatory reactions against intense parasite death, such as fever, itching, rashes, and malaise (Juarez; Schcolnik-Cabrera; Dueñas-González, 2018). However, adverse effects were reported during mass ivermectin treatment for endemic onchocerciasis, including increased pruritus, swelling, headaches, and worsening of skin rashes (Chijioke; Okonkwo, 1992).

Toxicity is especially frequent in cases of overdose, prolonged use, drug interactions, or in individuals with genetic predispositions. Adverse effects can be acute or chronic, presenting with severe neurotoxicity, as well as gastrointestinal, cardiovascular, and dermatological symptoms (Baudou et al., 2020; Chandler, 2017).

During COVID-19 pandemic, ivermectin has been shown to inhibit the replication of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in cell cultures (Caly et al., 2020). From the pharmacokinetic and pharmacodynamic point of view, however, the plasma concentrations necessary for the antiviral efficacy require administration of doses up to 100-fold higher than those approved for use in humans (Chaccour et al, 2020). Because ivermectin is used primarily in veterinary medicine, many people around the world acquired veterinary products in the early phase of uncertainty about targeted anti COVID-19 treatment, which massively increased the risk of overdosing and toxicity.

The Oregon Poison Center (Portland, USA) reported a sharp increase in ivermectin-related calls during COVID-19 pandemic (Temple et al., 2021). A retrospective analysis of the cases of ivermectin exposures from the Oregon Poison Center over a period of 24-week (14 August 2021 − 31 January 2022) resulted in a total of 37 cases of ivermectin intoxication. Most cases involved adults over 60 years old who used veterinary formulations for COVID-19 prevention or treatment. Clinical effects included neurotoxicity (30 patients), gastrointestinal symptoms (14 patients), and musculoskeletal complaints (7 patients) (Hoang et al., 2022).

2 NEUROTOXICITY

Neurotoxicity is considered one of the most serious adverse effects of ivermectin, particularly when protective mechanisms of the blood–brain barrier are compromised or in cases of overdose. Animal studies have provided important data on this issue. In mice, single doses between 0.3 and 0.8 mg/kg caused neurotoxicity—manifested as tremors, lack of coordination, and lethargy—within 2 to 8 hours of administration, affecting approximately 25% of randomly selected animals (Umbenhauer et al., 1997). Moreover, although ivermectin has a higher affinity for glutamate-gated chloride channels in parasites, at elevated concentrations it can also interact with mammalian GABA receptors. This interaction facilitates an excessive influx of chloride ions, resulting in hyperpolarization and neuronal inhibition, which contributes to the neurodepressive effects observed in toxicity cases (Lespine et al., 2012).

A key factor in ivermectin neurotoxicity is the integrity of the blood–brain barrier, particularly the activity of P-glycoprotein (P-gp), a transmembrane protein encoded by the ABCB1 gene (also known as MDR1). P-gp functions as a biological barrier by actively extruding toxins and xenobiotics from cells, thereby preventing the accumulation of potentially harmful substances in the central nervous system (Edwards, 2003). In animal models with deficient or absent P-gp function, ivermectin more readily crosses the blood–brain barrier, accumulates in brain tissue, and induces neurological symptoms even at doses considered safe in individuals with functional P-gp (Geyer et al., 2005). For instance, Collie dogs exhibited signs of neurological toxicity after receiving a single oral dose of ivermectin (120 µg/kg), including apparent depression, ataxia, mydriasis, and salivation. This study identified a genetic mutation leading to a truncated, non-functional P-glycoprotein, which normally protects the brain from xenobiotic penetration (Mealey et al., 2001). Additionally, drugs that act as substrate for P-gp, such as HIV protease inhibitors and the antibiotic cyclosporine A, can lead to accumulation of ivermectin in the brain that might further increase its toxicity (Kwei et al., 1999; El-Saber Bathia et al., 2020). The latter reported effects highlight the possibility of potentially dangerous drug interactions.

In humans, several polymorphisms have been described in the ABCB1 gene encoding P-gp (Kroetz et al., 2003). Many of these are associated with reduced expression or function of P-gp and have been correlated with increased sensitivity to neuroactive drugs such as antidepressants and antipsychotics (Vendelbo et al., 2018). Although the relationship between P-gp polymorphisms and ivermectin toxicity in humans remains uninvestigated,

evidence from animal models strongly suggests that impaired P-gp function could increase susceptibility to adverse neurological effects.

Clinical reports in humans have also raised concerns about ivermectin-induced neurotoxicity under specific conditions. An unprecedented case was reported in Slovakia involving a 50-year-old woman who developed severe neurological symptoms minutes after receiving an intravenous infusion of veterinary ivermectin intended for COVID-19 treatment. The neurotoxicity was attributed primarily to the intravenous route of administration, while moderate elevation of liver enzymes and lymphopenia may have resulted from the combination of COVID-19 and ivermectin use. The patient required hospitalization in the Intensive Care Unit; although neurological damage was not permanent, symptom resolution was slow but ultimately complete (Porubcin et al., 2022).

Additionally, it has been reported that patients who used veterinary ivermectin formulations and received higher doses experienced higher rates of altered mental status than those who used prescription tablets. Notably, patients who took ivermectin chronically, with smaller daily doses (13.5 mg) over a prolonged period (median 3.8 weeks), developed milder neurotoxicity compared to those with acute ingestion. These findings indicate a direct relationship between ivermectin dose and the severity of neurotoxic effects (Hoang et al., 2022).

2.1 HEPATOTOXICITY

The liver, being the primary site of ivermectin metabolism, is particularly vulnerable when the drug is administered in high doses or over extended periods. Before the COVID-19 pandemic, ivermectin induced liver injury was considered very rare, consisting mostly of mild to moderate elevations in liver enzyme levels (LiverTox, 2012). Few cases of severe acute liver injury linked to ivermectin use were reported before 2020. For example, in 2006, Veit et al. reported the first case of ivermectin-induced liver injury in a 20-year-old woman originally from Cameroon who was infected by the *Loa loa* parasite, in which a liver biopsy showed intralobular inflammatory infiltrates, confluent necrosis and apoptosis (Veit et al., 2006). In 2011, Hirote et al. (2011), in Japan, reported another case of ivermectin-induced liver injury in an 85-year-old homeless man with scabies who received a dose of 0.2 mg/Kg of body weight in 2 doses with an interval of 15 days, where alanine aminotransferase levels were up to 1081 (Normal value: 100-325 IU/L); transaminase and bilirubin levels returned to normal levels only 10 weeks after the start of therapy (Hirote et al., 2011).

The number of related cases of hepatotoxicity increased after 2020. A case published in 2022 describes a 61-year-old patient who developed fulminant hepatic failure after ingesting veterinary ivermectin in an attempt to treat COVID-19. The patient exhibited jaundice, hepatic encephalopathy, and markedly elevated transaminases, consistent with drug-induced liver injury (Sidhu et al., 2022). Furthermore, a pharmacovigilance study in VigiBase - a database that registers all individual case safety reports entered by the National Pharmacovigilance Centers of more than 130 countries around the world - described six cases of serious hepatic disorders in adults who used ivermectin for SARS-CoV-2 infection, including hepatitis, hepatocellular injury, cholestasis, increased alanine aminotransferase and/or aspartate aminotransferase levels and abnormal liver function tests (Oscanoa et al., 2022). Another significant case was reported in Brazil involving a 70-year-old woman who used ivermectin prophylactically for COVID-19. After several weeks of continuous use, she developed jaundice, pruritus, and fatigue, with lab tests showing elevated transaminases and a total bilirubin of 9.4 mg/dL (Sonderup et al., 2023). The mechanisms involved in hepatotoxicity, however, are not fully elucidated.

3 IVERMECTIN AS AN ENVIRONMENTAL POLLUTANT

Ivermectin widespread use as antiparasitic drug, both in human and in livestock production, due to its effectiveness in controlling internal and external parasites, can eventually lead to contamination of soil and water bodies (Adeleye et al., 2023). The accumulation of ivermectin residues over time in the environment represents a potential risk of contamination to non-target organisms (Vokrál et al., 2019). Ivermectin is highly toxic to a wide range of invertebrates, including beneficial soil-dwelling organisms like earthworms and insects (Halley; Vandenheuvel, 1993). This disrupts soil ecosystems and harms non-target organisms (Bloom. Matheson, 1993). In water bodies, ivermectin can negatively impact fish and aquatic invertebrates, and lead to ecological imbalances (Adeleye et al., 2023). Additionally, ivermectin persistence in the environment can lead to long-term accumulation and further affect aquatic biodiversity (Verdú et al., 2018). The environmental concentrations, however, are low, minimizing the risk of human contamination and toxicity (Adeleye et al., 2023).

4 CONCLUSION

Ivermectin remains a valuable therapeutic agent for parasitic diseases, with a well-established safety profile under approved conditions. However, this review highlights that its use outside those parameters—particularly indiscriminate and scientifically unsupported—can pose considerable health risks. Manifestations of neurotoxicity, especially in individuals with P-glycoprotein deficiency, and hepatotoxicity show that ivermectin's safety margin can be exceeded by overdose or genetic predisposition. The increase in intoxication reports during the COVID-19 pandemic, driven by self-medication and veterinary formulations, underscores the dangers of unsupervised off-label use. Public and professional education on the rational use of medications is essential to prevent serious adverse events. Ivermectin must continue to be used responsibly, strictly for approved indications and under medical guidance. Future studies are needed to deepen understanding of its toxic mechanisms, identify risk biomarkers, and ensure even greater safety in clinical use. These data highlight the risks of improper ivermectin use without medical supervision and reinforce the need for toxicological monitoring in self-medication contexts.

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