Review Article

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Insights on the therapeutic use of ivermectin: Mechanism of action and histopathological effects

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ABSTRACT

Ivermectin is a broad-spectrum antiparasitic drug with outstanding efficacy and a wide margin of safety. This drug has been widely utilized in veterinary medicine since 1987, and its use in humans has grown. Ivermectin is a broad-spectrum anti-parasitic agent licensed by the FDA. Ivermectin is a mixture of 80% or more avermectin B1a (AB1a) analogue and 20% or less avermectin B1b analogue. Iverzine has been proven to have widespread antiviral action in recent years. Ivermectin has also a broad-spectrum activity against the viruses that cause dengue, Zika, HIV, and yellow fever in vitro. Despite this in vitro action, no clinical trials have shown that ivermectin has a therapeutic benefit in patients with these viruses. Some ivermectin studies have also revealed potential anti-inflammatory qualities, which may be beneficial in persons with COVID-19. However, the use of ivermectin in animals was also associated with some histopathological effects in the internal organs including the liver, kidney, spleen, and brain. The purpose of this review was to provide light on the mechanism of action of ivermectin and its related histopathological consequences in various animal species.

Introduction

Ivermectin is an antiparasitic medication that has a broad spectrum of activity, excellent efficacy, and a wide margin of safety. Since 1987, this chemical has been widely used in veterinary medicine, and its use in humans has been expanded. Ivermectin is an FDA-approved broad-spectrum anti-parasitic agent (González Canga *et al*., 2008). Ivermectin is a mixture of 80% or more of an analog of avermectin B1a (AB1a) and 20% or less of an analog of avermectin B1b (Wagner and Wendlberger, 2000). In recent years, it was shown that iverzine has wide activity against a broad range of viruses (Götz *et al*., 2016). Okumuş *et al*. (2021) investigated the efficiency of using ivermectin in treating COVID-19 cases.

In the present review, we threw the light on the mechanism of action of ivermectin and its associated histopathological effects in different animal species.

Mechanism of action of ivermectin

Mastrangelo *et al*. (2012) mentioned that ivermectin is an antiparasitic drug that has broad-spectrum activity in vitro against the viruses that cause dengue, Zika, HIV, and yellow fever. Despite this in vitro activity, no clinical trials have reported a clinical benefit for ivermectin in patients with these viruses. Some studies of ivermectin have also reported potential anti-inflammatory properties, which have been postulated to be beneficial in people with COVID-19. They added that ivermectin is a potent inhibitor of flavivirus replication specifically targeting NS3 helicase activity. GabAllh *et al*. (2017) mentioned that ivermectin inhibits the host from importing alpha/beta-1 nuclear transport proteins, which are part of a key intracellular transport process that viruses hijack to enhance infection by suppressing the host's antiviral response. Besides, Adegboro *et al*. (2021) reported that ivermectin may have antiviral effects by inhibiting the importing (IMP) a/b1 receptor, which is responsible for transmitting viral proteins into the host cell nucleus. It may also affect SARS-CoV-2 replication through IMP a/b1 inhibition. When all these data were evaluated, it was thought that ivermectin may also be effective in COVID-19 patients.

Side effects of ivermectin

Rohrer and Evans (1990) recorded that the median lethal dose (LD50) of ivermectin for beagle dogs has been reported to be about 80 mg/kg. Moreover, Brooks and Grace (2002) recorded that the side effects of ivermectin intense itching, skin edema, arthralgia, bone pain, severe headache, and severe fever with joint and bone pains and striking. The most common of these include myalgia, rash, node tenderness, swelling of nodes, joints, limbs, or face, itching, fever, and chills. In dogs, Hopper *et al*. (2002) recorded that the clinical signs associated with ivermectin toxicity were ataxia, disorientation, obtundation, bradycardia, mydriasis, and hypersalivation. In addition, Otaki *et al*. (2005) recorded that of the side effects of ivermectin is decreasing platelet counts. Chosidow (2006) recorded that the side effects of ivermectin itching may be intense during early administration. Besides, Fujimoto *et al*. (2014) recorded that serious side effects of ivermectin have been reported where acute toxicities, such as convulsions were induced in an overdose study in animals. Ashour (2019) demonstrated that ivermectin induces neurologic disorders that can be fatal. Few cases of neurologic disorders after ivermectin treatment have been reported in humans, and data are lacking on such a deleterious mutation in the human gene ABCB. Baudou *et al*. (2020) recorded that after the administration of a usual dose of ivermectin. The seriousness

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of the intoxication in the child implies that caution is warranted regarding medical prescriptions of ivermectin and other ABCB1 substrates. Our findings highlight the importance of pharmaco-vigilance and the benefit of ABCB1 genotyping in identifying clinically significant ABCB1 mutations related to a well-circumscribed phenotype and explaining an unexpected response to a drug. Okumuş *et al*. (2021) recorded that the side effects of ivermectin were fever, headache, dizziness, pruritus, and rash, but neurological side effects were encephalopathy, confusion, and coma. None of the adverse reactions were considered life-threatening.

Histopathological changes due to ivermectin

At a therapeutic dose of ivermectin

In the liver, Ali (1990) said that the investigated rabbit liver obtained at 24h post last injection of ivermectin revealed congestion of hepatic blood vessels and blood sinusoids in association with vacuolated cytoplasm of hepatocytes characterized by multiple variably sized discrete empty vacuoles that distend the cell cytoplasm, Meanwhile, the commonly hepatic changes in liver obtained at 7-days post last injection of TD of ivermectin (0.2 mg/kg BW) represented mainly in congestion of the central veins and blood sinusoids with activation of Von Kupffer's cells, Additionally, mild degenerative changes in the form of vacuolar degeneration in hepatocytes were also demonstrated in some cases.

In the kidney, Lifschitz *et al*. (2004) recorded that the microscopical examination of the kidney acquired at 24h post-last injection of TD of ivermectin revealed congestion of the renal blood vessels and intertubular capillaries. The renal cortex showed hypercellularity of glomerular tufts with proliferation of the lining endothelial cells of glomerular capillaries. Moreover, the Bowman's capsule was filled with glomerular tuft with the absence of the subscapular space. Moreover, the accumulation of homogenous structureless eosinophilic fluid in Bowman's space was also observed. The lining epithelium of the convoluted tubules in the renal cortex showed vacuolar and hydropic degeneration. However, individual epithelial cells were shrunken with pyknosis of the nuclei. Furthermore, mild cystic dilatation of some renal tubules was also noticed. Besides, Arise *et al*. (2012) recorded that the investigated kidney obtained 7 days after the last injection of TD of ivermectin showed mild congestion of the renal blood vessels and intertubular capillaries. Additionally, the lining epithelium of the convoluted tubules mostly appeared vacuolated as well as vacuolation of the endothelial lining of the glomerular tuft.

In the spleen, Lifschitz *et al*., (2000) recorded that spleen showed thickening in the splenic capsule with lymphoid depletion in white pulp associated with hemosiderosis in therapeutic dose.

In the brain, Arise and Malomo, (2012) mentioned that the brain suffered degenerative changes in neurons in the form of tygrolysis, satilletosis, and neuronophagia with meningitis in receiving a therapeutic dose for 8 weeks. These degenerative changes are accompanied by focal mononuclear leukocytic cellular infiltration and perivascular cuffing with an area of malacia among brain substances.

At a double therapeutic dose of ivermectin

In the liver, Alvinerie *et al*. (1993) mentioned that the liver obtained at 24h post-last injection DTD of ivermectin showed congestion of the hepatic blood vessels and blood sinusoids. Additionally, the proliferation of the biliary epithelium and newly formed bile ductules in association with fibrous connective proliferation around the portal area admixed with few leukocytic cellular infiltrations were seen. Besides, Nayak *et al*. (2011) mentioned that female rats received a therapeutic dose to a severe degree of degeneration in a double therapeutic dose which extend to form a focal necrotic area in hepatic parenchyma after 8 weeks from this dose. Moreover, hyperplasia of epithelial cells lining the bile duct with periductal mononuclear leukocytic cellular infiltration and fibrosis were observed in all rabbits that received ivermectin either in therapeutic or double therapeutic doses. Fibrous connective tissue takes greenish coloration with Crossman's trichrome stain. Arise *et al*. (2012) demonstrated that the livers of treated rats obtained at 7-days post last injection of DTD of ivermectin (0.4mg/kg BW) showed congestion of the hepatic blood vessels and blood sinusoids with degenerative changes in the hepatocytes represented mainly in hydropic degeneration characterized by, pale, vacuolated cytoplasm. Furthermore, Rabab *et al*. (2015) mentioned that various pathological changes in the liver, kidney, and testes were also detected. The severity of these changes varied from mild to severe changes according to the dose as histopathological changes were more severe in male rats injected with a double therapeutic dose than that injected with the therapeutic one.

In the kidney, Webb *et al*. (2004) recorded that the investigated kidneys obtained at 24h post-last DTD of ivermectin revealed congestion of renal blood vessels and inter-tubular capillaries. Multifocally, the cortical interstitium, predominantly around cortical blood vessels and glomeruli was occasionally expanded by edema admixed with inflammatory cells mainly lymphocytes and fewer macrophages. Besides, Kramer *et al*. (2011) recorded that severe vacuolation of the lining epithelium of the renal tubules as well as vacuolation of the endothelial lining of the glomerular tufts was detected in association with mononuclear leukocytic cellular infiltration in the interstitial tissue. In some cases, desquamation of the lining epithelium of the renal tubules with destruction of the basement membrane of some renal tubules was also observed. Additionally, Gonzalez *et al*. (2012) recorded that the investigated kidneys obtained at 7 days post-last injection of DTD of ivermectin revealed congestion of the renal blood vessels and intertubular capillaries. Moreover, peri-glomerular leukocytic cellular infiltration mainly lymphocytes was also observed. Vacuolar and hydropic degeneration of the lining epithelium of some convoluted tubules. Additionally, lytic necrotic changes of the cortical renal tubules that are characterized by loss of renal tubules and replaced by erythrocytes and a few mononuclear leukocytes into the free space were observed in some cases. Abou-Elghar *et al*. (2013) recorded that kidneys showed congestion of renal blood vessels that ranged from mild to severe depending on the dose of drug administration. Additionally, the glomerular tufts shrink and become completely degenerated in the case of females receiving daily ivermectin at a therapeutic dose from day 6th till day 28th of pregnancy. Eosinophilic homogenous substance in the Bowman's space was noticed in daily therapeutic doses and after 8 weeks of administration of double therapeutic doses. Recently, El-Shobokshy *et al*. (2023) recorded that the renal tubules showed a severe degree of degeneration as vacuolation of the cytoplasm of affected renal tubules in males and females received therapeutic dose while double therapeutic dose induced degeneration, necrosis, and desquamation of affected epithelium. It was noticed that hyaline casts were found in cases of long periods of drug administration in both therapeutic and double-therapeutic doses. Additionally, some renal tubules showed cystic dilatation daily.

In the spleen, Farrag *et al*. (2011) mentioned that a double therapeutic dose showed the same lesions with high severity, and subcapsular leukocytic cellular infiltration and vacuolation in the wall of the splenic arteriole were also noticed.

In the brain, Li *et al*. (2013) reported that in vitro, ivermectin exhibited apparent cytotoxicity and triggered apoptosis in neurons of King pigeons in a dose-dependent manner. After 24 hours of treatment with avermectin at doses of 0, 2.5, and 5 μg/L, cell viability was 99.93 8.52%, 82.02 4.99%, and 78.23 5.67%, respectively, which fell to 56.36 2.17% at 10 μg/L. Apoptosis morphological alterations in treated cells included cytoplasmic vacuolation, chromatin condensation, an unclear nuclear membrane, and decreased/swollen mitochondria. Furthermore, Ji-Ming *et al*. (2014) mention that long administration of ivermectin either in females treated daily till day 28th of pregnancy or in males treated for 8 weeks with a double therapeutic dose showed vesiculation of brain substance. The lesions in the brain were directly related to the dose and frequency of administra-

tion.

Conclusion

This review highlighted the effective role of ivermectin as an anti-parasitic drug used efficiently in the veterinary field. Recently, antiviral effects for the ivermectin were proposed. However, more investigations are still needed before confirming such effects. The use of ivermectin at therapeutic or double therapeutic doses might lead to several adverse and histopathological effects in the internal organs like the liver, kidney, spleen, and brain. Therefore, ivermectin should be used strictly with the prescribed doses.

Conflict of interest

The authors declare that they have no conflict of interest

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