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TOXICITY STUDIES OF IVERMENTIN- A REVIEW

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ABSTRACT

The avermectins are a newly discovered class of macrocyclic lactones isolated from Streptomyces avermitilis that have insecticidal, acaricidal, and anthelmintic activity. Ivermectin (MK-0933) is a parasiticide that is the -dihydro derivative of avermectin Bl. It is used in a variety of animal species, including humans. Ivermectin is a semisynthetic derivative of ivermectin B1 that is made up of an 80:20 mixture of the equipotent homologous. When IVM acts as a bacteriostatic agent, it is advantageous because bacteriostatic antibiotics can avoid some of the drawbacks associated with bactericidal drugs. For example, when bactericidal drugs kill bacteria, endotoxins are released that may be toxic to the host, whereas bacteriostatic drugs inhibit bacterial growth, allowing the host to elicit protective immunity and thus result in immunological clearance of the bacteria Although the efficacy of ivermectin against several parasitic diseases has been established in humans, the pharmacokinetic properties of this compound in humans are less well understood than in animals. Ivermectin has potential drug-drug interactions and drug-food interactions that should be considered during therapeutic use.

Keywords: Ivermectin, Anthelminthic drug, Bacteriostatic.

INTRODUCTION

The ivermectin's are a newly discovered class of macrocyclic lactones isolated from Streptomyces overtitles that have insecticidal, acaricidal, and anthelmintic activity [1]. Ivermectin (MK-0933) is a parasiticide that is the 22, 23-dihydro derivative of ivermectin Bl. It is used in a variety of animal species, including humans. Ivermectin is a semisynthetic derivative of ivermectin B1 that is made up of an 80:20 mixture of the equipotent homologous 22, 23 dehydrin B1a and B1b. Merck & Co. developed this antiparasitic agent, which is widely used in veterinary medicine due to its broad spectrum of activity, high efficacy, and wide margin of safety [1,2]. When Merck Laboratories had enough data to register ivermectin for use against onchocerciasis, they launched the first human formulation in 1987. The company stated that the drug would be provided free of charge for the treatment of onchocerciasis anywhere in the world for as long as it was required. [3] Ivermectin's antiparasitic activity is due to the drug binding to high-affinity receptors. This causes an increase in chloride ion conductance as well as the suppression of action potentials in invertebrate nerve and muscle tissue, resulting in paralysis and death of the organism. Mammalian central nervous systems contain ivermectin receptors with much lower affinity. The relative inability of ivermectin to cross the mammalian blood-brain barrier, combined with the lower affinity of mammalian receptors, results in a markedly lower sensitivity of mammals to the toxic effects of this group of compounds when compared to invertebrates. Oral administration of ivermectin, on the other hand, has resulted in neurotoxicity in at relatively high dose levels. Ivermectin's are a new chemical class of anthelmintic agents with a novel mode of action against a wide range of animal nematode and arthropod parasites.

They also work against plant parasites, free-living nematodes, and arthropods. Ivermectin's are fermentation products produced naturally by the morphologically distinct soil organism Streptomyces overtitles [1, 2]. Early research on this mold's broth culture revealed the presence of a substance with unrivalled anthelmintic potency [3]. Furthermore, in its natural state and without

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chemical modification, this new substance demonstrated very high potency and safety. Early chromatographic studies yielded four distinct entities, which were identified as compounds with varying degrees of anthelmintic efficacy using thin layer chromatography [4]. The complex was discovered to have four components labelled A1, A2, B1, B2 in varying proportions. These major components were available in two variants, a and b. The b series was the lower homologue of the corresponding major a component (that is, Ala was more potent than Alb). Component B1a performed exceptionally well against nematodes in sheep at a dosage rate of 0.025 mg/kg. The ivermectin's have the basic chemical structure of a macrocyclic lactone with two sugars attached [3]. The removal of the sugar fraction from the molecule results in a significant decrease in potency and anthelmintic activity. Analogues have been created chemically, and they can be compared to the parent compound in terms of activity and safety. The most interesting derivative in this context is 22, 23-dihydroavermectin B1, also known as ivermectin. This compound demonstrated good efficacy and safety characteristics in early laboratory and in vivo studies, and was thus chosen for further research and development [5, 6, 7]. Ivermectin is made up of at least 80% 22, 23-dihydroavermectin Bla and more than 20% of the Blb homologue. The Onchocerciasis Control Programmed in West Africa was established in 1974 to combat onchocerciasis. This program's main goal is to break the parasite transmission cycle. Since 1987, the use of ivermectin in conjunction with aerial larviciding has had a significant impact on disease transmission and has greatly reduced the effect on humans. This resulted in the creation, in 1992, of the Onchocerciasis Elimination Programmed in the Americas, which was launched in six countries, and, in 1995, of the African Programmed for Onchocerciasis Control, both of which were based primarily on ivermectin distribution and treatment [4]. The Global Programmed to Eliminate Lymphatic Filariasis, based on regular mass administration of albendazole with either ivermectin or diethylcarbamazine, was launched in 1998, confirming the drug combinations' safety and efficacy [5].

Ivermectin is currently approved for use in humans in a number of countries (including Australia, France, Japan, the Netherlands, and the United States) to treat onchocerciasis, lymphatic filariasis, strongyloidiasis, and/or scabies. Ivermectin is extremely potent, with unusually low effective dosage levels. The optimal dose of ivermectin for the treatment of onchocerciasis is 150 g/kg, but the frequency of administration is still debatable, ranging from 150 g/kg once to three times yearly. The optimal duration of treatment has yet to be determined [6]. It is effective in most scabies patients after a single oral dose of 200 g/kg, but the regimen usually consists of two or three repeated doses separated by one or two weeks [7].

Action Mechanism

GABA is a neurotransmitter substance that mediates the transmission of inhibitory signals from antineutrons to motor neurons in the ventral nerve cord of parasites. Ivermectin is now known to act as a GABA agonist [8, 9, 10, 11]. This GABA transmitter's function is to open the chloride channels on the postsynaptic junction, allowing Cl - ions to enter and inducing the resting potential. Ivermectin enhances this effect by stimulating presynaptic GABA release and increasing GABA binding to postsynaptic receptors [1, 11]. When ivermectin is present, the chloride channels open when they should close, resulting in the recipient cell not receiving signals and impulses. Although both motor neurons and muscle cells are capable of individual excitation, electrical impulse passage across the synapse is blocked. GABA is used as a neurotransmitter in arthropods, but not between two sets of nerve cells, as in nematodes, but between nerve and muscle cells [7]. Ivermectin's effects are sustained and irreversible when GABA release is prolonged [6]. This causes neuromuscular blockade, paralysis, and death in the majority of parasites. The overall GABA-mediated chloride ion conductance effect could be attributed to (a) ivermectin acting as a GABA agonist at the GABA binding site or elsewhere on the protein, (b) stimulation of presynaptic GABA release, or (c) potentiation of GABA binding to its receptors [1]. It was also discovered in experiments that washing neurons with picrotoxin (a GABA antagonist) stopped the ivermectin-induced paralysis [1, 11, 12]. Ivermectin's most visible effect in parasites is paralysis, but it has also been shown to suppress reproductive function in ticks [1, 2, 6]. Ivermectin has no effect on cestodes or trematodes because these parasites do not use GABA as a neurotransmitter [1]. This is consistent with the mode of action hypothesis.

Pharmacokinetics

In humans, only the oral route is approved for ivermectin administration. The one-compartmental model [8, 9] and the two-compartmental model [10] have been used to describe the kinetic behavior of ivermectin after oral administration. The remaining studies cited here used a model-independent method to determine pharmacokinetic parameters.

Absorption

In healthy subjects given 12 mg of ivermectin as an oral solution, tablets, or capsules, the solution had roughly twice the systemic availability as either of the solid forms. An ethanolic solution was used to administer the oral solution. This could affect bioavailability and explain why the solution had twice the availability of tablets and capsules. Nonetheless, the rate of absorption was comparable in all three cases [11]. There were no significant differences in the pharmacokinetic parameters

calculated in healthy and onchocerciasis volunteers treated with 150 g/kg. Following an initial decrease, both groups demonstrated a tendency for a second rise in plasma levels (mostly occurring between 6 and 12 h after the dose), indicating enterohepatic drug recycling [12]. It was also investigated whether decreased ivermectin absorption could explain why some severely infected onchocerciasis patients have relatively few adverse effects after ivermectin treatment, despite the fact that the occurrence and severity of adverse reactions have been linked to infection intensity [17]. There was no discernible relationship between plasma concentration after a single oral dose (150 g/kg) and the occurrence of adverse reactions, according to this study. Neither parasite load nor ivermectin concentrations were found to have an effect on the occurrence of adverse reactions in the entire group of patients. In patients with disseminated strongyloidiasis, the ability to achieve adequate levels of ivermectin after oral administration may be impaired, highlighting the need for alternative routes of ivermectin administration in these patients. Thus, ivermectin levels in a patient with disseminated strongyloidiasis were lower than the average reported by other authors following oral administration (1.1 ngml1 after ingesting a total dosage of 1,000 g/kg over three days). This was followed by three subcutaneous doses (200 g/kg) injected every two days, increasing ivermectin levels to 7.9 ngml1 one week later, with evidence of additional metabolite accumulation and a sustained antiparasitic effect. As a result, in these patients who are unable to absorb oral medication, parenteral ivermectin (not approved for human use) is a better option [18]. In a separate report, a man with disseminated strongyloidiasis, severe hypoalbuminemia, and paralytic ileus was given ivermectin orally. The serum ivermectin concentration was only 0.8 ngml1 three hours after the third daily dose, but it increased to 5.8 ngml1 16 hours after the first subcutaneous dose. Subcutaneous ivermectin (200 g/kg, once daily) produced serum ivermectin levels ranging from 11.4 to 17.2 ngml1 over the next 15 days, with no significant accumulation [19].

DISTRIBUTION

Ivermectin is widely distributed throughout the body due to its high lipid solubility. After ingesting 6 and 12 mg of ivermectin, the volume of distribution in the central compartment, Vc, in healthy men was 3.1 and 3.5 lkg1, respectively [8]. With 6 mg (tablet), the volume of distribution of the area (V) in onchocerciasis patients was 9.9 lkg1 and the mean residence time (MRT) was 3.7 days [16]. Ivermectin tissue distribution was similar in healthy and onchocerciasis volunteers treated orally. So,issue Ivermectin Disposition When administered orally or parenterally, ivermectin is well absorbed. The route of administration and formulation used influence its disposition profile; ivermectin concentrations in body fluids are maintained for long periods of time [13]. A halflife of 70 hours per total radioactive residue in plasma was reported in cattle dosed subcutaneously with ivermectin at 0.3 mg/kg [14]. A terminal half-life of 178 hours was observed in sheep after intravenous administration of 0.2 mg/kg ivermectin [15]. This relatively long half-life is related to the compound's extremely high potency, as studies with other anthelmintics have shown that the kinetic profile has a significant impact on efficacy [16]. When ivermectin was administered into the rumen of sheep, it was found to have a low bioavailability [12]. This decreased bioavailability could be attributed to rumen degradation. The parent drug's monosaccharide and aglycone derivatives (two possible metabolites or rumenal degradation) are less potent than the monosaccharide and aglycone derivatives [5]. The lower efficacy and shorter duration of action of orally administered ivermectin (compared to parenteral dosing) may explain the less potent effect in cattle [17] against certain ticks (Boophilus spp.) and body lice in sheep [18]. The majority of the ivermectin administered is excreted in the faeces, with the remainder excreted in the urine [1]. The presence of residues is minimal in the muscle and kidneys, with the highest concentrations found in the liver and fat tissues [1]. In nature, all tissues' residues are extractable, with little or no macromolecularly bound drug or metabolite present. The unaltered parent drug is the most abundant single component in the edible tissues of cattle, sheep, and pigs [1]. Although mammals use gammaaminobutyric acid as a central neurotransmitter, ivermectin has little effect on them. This is because, as a macrolide with a high molecular weight, ivermectin does not easily cross the mammalian blood-brain barrier to affect GABA levels in the central nervous system [19]. Radioactive residue assays revealed only trace amounts of ivermectin in cattle brain concentration tests. This was the lowest concentration of any of the tissues examined [1]. A number of purebred and crossbred longhaired Collies have developed central nervous system depression [20]. The cause of this breed's susceptibility is unknown. It has been proposed that the Collie's bloodbrain barrier is more permeable to ivermectin than in other species, allowing ivermectin to enter the central nervous system [2, 21, 22]. There have been few studies on the metabolism of ivermectin in humans. This drug is extensively metabolised by cytochrome P450 in human liver microsomes. The predominant isoform responsible for this compound's biotransformation in human liver is cytochrome P-4503A4, which converts the drug to at least ten metabolites, the majority of which are hydroxylated and demethylated derivatives [23]. After giving ivermectin to healthy volunteers orally, radioactive metabolites were found in their plasma [10]. There were no differences in the elimination half-life between healthy and onchocerciasis subjects [12]. It was also suggested that ivermectin's kinetics (its elimination halflife is around a day) were somewhat disconnected from its

pharmacodynamics (antiparasitic events lasting several months after a single dose of the drug) [11]. Gender had a significant effect on ivermectin pharmacokinetics in healthy volunteers orally treated with 150 g/kg, with males having a lower total body Cl/F than females [14]. In terms of excretion pathways, ivermectin and its metabolites were mostly excreted in faeces and only 1% in urine. Positive identification was obtained for the presence of 3"-O-desmethyl-H2B1a monosacharide in urine and 22, 23-dihydroavermectin B1a monosacharide in faeces, respectively 10. Other researchers who attempted to detect ivermectin in urine [8, 9, 16] found neither the parent drug nor its metabolites.

Finally, the maximum concentration (14.1 ngml1) was reached in 6.5 hours in the milk of healthy women given 150 g/kg [13]. Based on this data, a breast-fed child would receive an average dose of 2.75 g/kg via milk. As a result, these authors did not recommend excluding breastfeeding mothers from mass ivermectin therapies because they only make up 5–10% of the population in onchocerciasis-endemic areas.

Interactions

Several authors investigated the effect of ivermectin coadministration with various helminthes control drugs. To prevent the spread of onchocerciasis in humans, the combination of ivermectin and doxycycline is highly effective, as infested patients, the anthelmintic (200 g/kg, single dose) and antibacterial (100 mg/kg, daily for 6 weeks) kept microfiladermia levels lower for longer than ivermectin alone. Doxycycline improved ivermectin-induced suppression of microfiladermia by sterilising adult female worms for a few months by depleting filariae symbiotic endobacteria, Wolbachia spp. [24] (essential for their survival and reproduction).

Other studies have shown that combining ivermectin with other drugs has no advantage over ivermectin alone in controlling onchocerciasis. Thus, in infected patients, ivermectin had no effect on the kinetics of an oral dose of albendazole, and there was no additive effect of both drugs against the parasite when compared to ivermectin alone [25, 26, 27]. Albendazole (400 mg) had no effect on the kinetics of a single oral ivermectin dose (12 mg) [27].

In onchocerciasis patients, the antiparasitary efficacy of a single ivermectin dose (150 g/kg, on day 1) followed by amorcazine (3 mg/kg twice daily, on days 8, 9, and 10) was comparable to that of ivermectin alone [28]. Similarly, the combination of ivermectin (200 g/kg) and levamisole (2.5 mg/kg) was not macrofilaricidal or more effective against microfilariae and adult worms than ivermectin alone, despite the fact that levamisole increased ivermectin plasma bioavailability in these patients [29].

In humans, the efficacy of available drugs for treating Trichuris trichiura infection is low. Nonetheless, a single-dose treatment with albendazole (400 mg)-ivermectin (200 g/kg) appears to be more effective against trichuriasis than albendazole alone or with diethylcarbamazine (6 mg/kg) [30].

As a result, ivermectin interactions with other drugs taken at the same time are possible. As antiparasitic drug resistance spreads, this issue has grown in importance.In terms of bleeding disorders, haematomatous swellings were reported in 2 of 28 onchocerciasis patients treated with ivermectin (150 g/kg), and prothrombin times were significantly higher one week to one month after drug ingestion, indicating an antagonist effect against vitamin K.. However, no changes in prothrombin or thromboplastin times were observed in the other 20 subjects 13 days after ingestion of 220–420 g/kg of ivermectin [30]; bleeding disorders were not found in 15,000 patients treated with ivermectin (150 g/kg) .Furthermore, prothrombin ratios were found to be prolonged in 148 subjects who were given ivermectin orally. Although no patients experienced bleeding complications, factor II and VII levels were reduced in the majority of them, indicating a disruption in vitamin K metabolism. Ivermectin has a negligible effect on coagulation, so widespread treatment appears to be unnecessary. Finally, a man who had been on long-term oral anticoagulant therapy with acenocoumarol demonstrated persistent, excessive hypocoagulability while treating trees with insecticides (ivermectin and metidation) without protection. As a result, it is important to remember that these types of interactions can occur and may result in hemorrhagic complications. at the standard dose rate, completely removed , Swine Ivermectin is available as a one percent injection for subcutaneous administration at a dosage of 0.3 mg/kg for routine use in swine. The adult and larval stages of Ascaris suum [26], Hyostrongylus rubidus [5, 7], Oesophagostomum spp. [3], Trichuris spp. [27], and the lungworm Metastrongylus aprior are all active in this species [6]. The treatment of pregnant sows can prevent the transmission of Strongyloides ransomi to piglets. Ivermectin is extremely effective against the porcine mange mite Sarcoptes scabiei as well as the sucking louse. Horses with Haematopinus suis Ivermectin has a greater-than-98 percent efficacy in equine species as an oral paste against Gastrophilus spp., Trichostrongylus axei, Parascaris equorum, Osyuris equi, Strongylus vulgaris,. Although an intramuscular formulation was initially used for the equine species, the oral paste formulation containing 1.87 percent active ingredient is now the only preparation approved for use in horses. In terms of efficacy against Oxyuris equi, the oral route is claimed to be marginally more effective than the parenteral route According to other reports, the parenteral route extends the efficacy of ivermectin in reducing strongyle egg production and subsequent pasture contamination by about two weeks.

Strongylus vulgaris arterial larval stages are resistant to most equine anthelmintic agents. Intensive

therapy with certain benzimidazole members has been reported to be effective against these migratory pathogenic strongyle stages .Many studies have shown that a single dose of ivermectin at the recommended dosage rate is 100 percent effective against arterial larvae. This type of treatment has been shown to reduce the size of cranial mesenteric aneurysms and increase circulation to arteries distal to the aneurysm .Following such treatments, there has been reported resolution of arteritis and thrombosis, as well as a return of the smooth contour of the arteries [9]. Ivermectin therapy is equally effective against the ubiquitous but less pathogenic "small strongyles" [30]. Given its distinct structure and mode of action, this is to be expected. Ivermectin is particularly effective against adults and larval stages of Ancylostoma caninum and Uncinaria stenocephala in dogs Hookworkms, with efficacy of 96-100 percent demonstrated at 0.002 mg/kg orally [1]. Adult Ascaris, Strongyloides, and Trichuris species require doses of 0.2 mg/kg to be controlled .Ivermectin is ineffective against the adult stage of Dirofilaria immitis but effective against microfilariae and precardiac stages of the heartworm at 0.005 mg/kg orally or 0.2 mg/kg subcutaneously. According to reports, dosages of 0.1 mg/kg or higher expel more than 99 percent of Trichuris vulpis infections, and 0.2 mg/kg removes 90 percent of all adult stages and 97 percent of the intestinal larval stages of Toxocara canis. In dogs [2] and mice, high doses (1-2 mg/kg) are required to produce an effect against tissue dwelling stages of Toxocara canis. A single dose of ivermectin at 0.2 mg/kg gave complete cure of natural infection of Otodectes cynotis and Sarcoptes scabiei in dogs Two treatments at 14-day intervals have been recommended in severe cases of sarcotic mange

Safety Cattle as a Target

Bull breeding performance, including sperm quality, was assessed before and after ivermectin dosing at 0.4 mg/kg (twice the normal dosage level) for 70 days. There were no negative effects observed [6]. In cows treated at a similar dosage, no adverse effects were observed during early, mid, or late pregnancy [6]. Oral dosages of 2 mg/kg had no adverse effects [2], but subcutaneous administration of 8 mg/kg resulted in listlessness, ataxia, and death in some cases [2]. During an ivermectin efficacy trial, one calf died as a result of bloat. An eosinophilic esophagitis appears to have developed as a result of the death of Hypoderma spp. larvae [28].
Other infected cattle developed posterior paresis as a result of spinal cord haemorrhages following treatment.

Sheep

Sheep given 4.0 mg/kg ivermectin in propylene glycol developed ataxia and depression, with hemoglobinuria evident in several cases. The control animals, on the other hand, showed similar effects when only given the vehicle [2]. In calves, propylene glycol can cause hemoglobinuria

Dogs:

The safety of ivermectin in dogs after off-label use should not be assumed. Canine toxicity states are caused by both overdosage and breed susceptibility. Ivermectin has a negative effect on Collies, causing depression, muscle weakness, blindness, coma, and death [21]. Many cases of ataxia progress to paralysis and loss of consciousness [21, 22] Collies have higher ivermectin concentrations in their brains than Beagles, mice, cattle, sheep, and pigs [10]. As a result, the Collie has greater blood-brain barrier penetration [21]. According to reports, picrotoxin infusion may be a useful antidote in such cases [10]. Anaphylactic reactions in dogs have been linked to polysorbate 80 in the injectable formulation [2]. In the United States, a specific oral formulation for the prevention of heartworm disease was recently licenced. This product is administered monthly in tablet form at a minimum dosage level of 0.006 mg/kg. There is a scarcity of data on the effect of foods on the pharmacokinetics of ivermectin. The influence of alcohol on ivermectin kinetic behaviour is poorly understood; however, co-ingestion of alcoholic beverages is not recommended due to ivermectin's association with GABA receptors and the effect of alcohol on the central nervous system. When ivermectin (150 g/kg) was administered orally to healthy volunteers, plasma levels were significantly higher when coadministered with 750 ml of beer than with 750 ml of water; plasma concentrations were significantly higher in patients who drank beer (66.3, 109, and 97.2 ng/ml at 1, 3, and 4 h, respectively) vs. those who drank water (44.0, 67.5, and 58.7 ng (36).Finally, ivermectin (150 g/kg) was given to 16 people with water or orange juice (750 ml). Orange juice reduced AUC (15.7 ngdml1) and Cmax (20.7 ngml1) (water: 33.8 ngml1; 24.3 ngml1), possibly because fruit juices and constituents are potent inhibitors of specific drug transporters [14]. Because of the long-term use of this compound in humans, understanding ivermectin pharmacokinetic behaviour is critical. Nonetheless, compared to animals, little is known about the kinetics and interactions of ivermectin in humans (even though the majority of fundamental work is veterinary, there is little evidence that such knowledge has helped to inform clinicians).

Ivermectin Tissue Disposition

When administered orally or parenterally, ivermectin is well absorbed. The route of administration and formulation used have an impact on its disposition profile. Ivermectin concentrations in body fluids are maintained for long periods of time [13]. A halflife of 70 hours per total radioactive residue in plasma was reported in cattle dosed subcutaneously with ivermectin at 0.3 mg/kg [14]. A terminal half-life of 178 hours was

observed in sheep after intravenous administration of 0.2 mg/kg ivermectin [15]. This relatively long half-life is related to the compound's extremely high potency, as studies with other anthelmintics have shown that the kinetic profile has a significant impact on efficacy [16]. When ivermectin was administered into the rumen of sheep, it was found to have a low bioavailability [12]. This decreased bioavailability could be attributed to rumen degradation. The parent drug's monosaccharide and aglycone derivatives (two possible metabolites or rumenal degradation) are less potent than the monosaccharide and aglycone derivatives [5]. The lower efficacy and shorter duration of action of orally administered ivermectin (compared to parenteral dosing) may explain the less potent effect in cattle [17] against certain ticks (Boophilus spp.) and body lice in sheep (18). The majority of the ivermectin administered is excreted in the faeces, with the remainder excreted in the urine [1]. The presence of residues is minimal in the muscle and kidneys, with the highest concentrations found in the liver and fat tissues [1]. In nature, all tissues' residues are extractable, with little or no macromolecularly bound drug or metabolite present. The unaltered parent drug is the most abundant single component in the edible tissues of cattle, sheep, and pigs [1]. Although mammals use gammaaminobutyric acid as a central neurotransmitter, ivermectin has little effect on them. This is because, as a macrolide with a high molecular weight, ivermectin does not easily cross the mammalian blood-brain barrier to affect GABA levels in the central nervous system [19]. Radioactive residue assays revealed only trace amounts of ivermectin in cattle brain concentration tests. This was the lowest concentration of any of the tissues examined [1]. A number of purebred and crossbred longhaired Collies have developed central nervous system depression [20]. The cause of this breed's susceptibility is unknown. It has been proposed that the Collie's bloodbrain barrier is more permeable to ivermectin than in other species, allowing ivermectin to enter the central nervous system [2, 21, 22].

Application in Clinical Practice :

Cattle:

Ivermectin is effective against all pathogenic or economically important gastrointestinal nematodes in cattle [23, 24, 25, 26]. Ivermectin has been shown to be highly effective against at least seven species of gastrointestinal nematodes at a dosage of 0.2 mg/kg, including the adult and larval stages of Ostertagia spp. [27, 28], Trichostrongylus spp. [27, 28], Oesophagostomum spp. [28], Haemonchus spp. [27, 28], and the lungworm Dictyocaul [25, 27]. Immature larvae, hypobiotic fourth stage larvae, and strains with established resistance to other anthelmintics are also susceptible [2]. When administered orally or parenterally, the drug is equally effective against nematodes. For field conditions, a dosage rate of 0.2 mg/kg via subcutaneous injection is used commercially. Poor or variable activity against early hypobiotic fourth stage Ostertagia spp. larvae is a feature of many anthelmintics. Ivermectin is effective against these parasites by either the oral or parenteral route at the recommended dosage rate [24, 30]. The persistent efficacy of parenteral treatment in cattle against the immature stages of certain nematodes is a useful feature This period of protection is determined by the nematode species' susceptibility to Clinical Use.

DISCUSSION:

The time-kill kinetics data indicated that the effects of IVM were most likely bacteriostatic rather than bactericidal. When IVM acts as a bacteriostatic agent, it is advantageous because bacteriostatic antibiotics can avoid some of the drawbacks associated with bactericidal drugs. For example, when bactericidal drugs kill bacteria, endotoxins are released that may be toxic to the host, whereas bacteriostatic drugs inhibit bacterial growth, allowing the host to elicit protective immunity and thus result in immunological clearance of the bacteria [24]. Torres et al. [25] found that IVM was effective against S. aureus biofilm formation. Our findings expand on previous findings about IVM's antibacterial efficacy against S. aureus. S. aureus infections have been reported all over the world. The emergence of antibiotic resistance has made treating infections caused by S. aureus infections difficult. As a result, new drugs other than traditional antibiotics should be introduced immediately to address the problem and reduce selection pressure on resistant isolates. To that end, we tested the antibacterial activities of anthelmintics on S. aureus isolates and discovered that IVM had antibacterial activity against two of the twenty S aureus isolates tested. It would be interesting to investigate why other isolates were not sensitive to this drug. IVM is known to be a good substrate of P-glycoprotein (efflux pumps) in helminthes The evidence of drug efflux pumps' involvement clearly necessitates further investigation. In humans and animals, IVM is given at a dose rate of 200 g/kg body weight. The maximum plasma concentration of IVM at this dosage is 52 ng/ml . The concentration at which IVM's anti-staphylococcal activity was observed in this study was higher than the concentration used in its current therapeutic use, which may explain why this mechanism has not previously been reported. However, the lethal dose 50 (LD50) of IVM has been reported as high as 50 mg/kg, indicating that IVM has a broad therapeutic index. At this dosage, IVM concentration in tissue is in the low micromolar range. As a result, we report anti-staphylococcal activity of IVM against MRSA and MSSA isolates at pharmacologically relevant concentrations. Given that IVM is already approved for the treatment of various parasites in humans and animals, its development as a potential antimicrobial agent to kill S. aureus, particularly MRSA, is an appealing option.

CONCLUSION:

Although the efficacy of ivermectin against several parasitic diseases has been established in humans, the pharmacokinetic properties of this compound in humans are less well understood than in animals. Ivermectin has potential drug-drug interactions and drug-food interactions that should be considered during therapeutic use.

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