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Ivermectin

21st Century "Snake Oil" or Safe and Effective for COVID-19?

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Snake oil refers to deceptive information with claims that a product is a "cure all" and/or a panacea for illness or disease and/or promotes health.[1]

Oral ivermectin is a powerful anthelmintic and insecticide for ruminants, pigs, horses, or humans with action against gastrointestinal parasitic nematodes (roundworms), lung worms, lice, and mange. The current trend of "repurposing ivermectin" lies in claims that this drug has possible antiviral, antimalarial, antimetabolic, and anticancer actions and offers preventative and illness treatment of COVID-19. The emphasis here is possible.[2]

Ivermectin is widely used across the world. Nearly 3·7 billion doses of ivermectin have been distributed globally for the past 30 years. Global demand is expected to remain robust because of its approval to treat *Strongyloides*, as well as its use with other agents to treat lymphatic filariasis, and possible use in reducing transmission of malaria.[3]

Ivermectin is derived from the avermectins, a class of highly active broad-spectrum, antiparasitic agents primarily metabolized by CYP3A4. Depending on the in vitro method used, CYP2D6 and CYP2E1 were also shown to be involved in the metabolism of ivermectin but to a significantly lower extent compared with CYP3A4. Ivermectin binds selectively and with high affinity to glutamate-gated chloride ion channels in invertebrate nerve and muscle cells, which leads to an increase in the permeability of cell membranes to chloride ions with hyperpolarization of the nerve or muscle cell. The result is paralysis and death of the parasite. Ivermectin is indicated for the treatment of intestinal (ie, nondisseminated) strongyloidiasis caused by the nematode parasite *Strongyloides stercoralis* and for the treatment of onchocerciasis caused by the nematode parasite *Onchocerca volvulus*. Ivermectin has no activity against adult *O. volvulus* parasites living in subcutaneous nodules, which are often removed by surgical excision to eliminate the microfilariae-producing parasite.[4]

Ivermectin is also used worldwide for onchocerciasis (river blindness, lymphatic filariasis-parasitic thread worms), strongyloidiasis (parasitic intestinal infection), human sarcoptic scabies (human itch mite), acarodermatitis (dermatitis), and rosacea. Beginning in the 1990s, reports emerged that ivermectin could induce severe encephalopathies in some persons.[5]

THE CURRENT TIDAL WAVE OF COVID-19 RESEARCH REPORTS

As the COVID-19 pandemic continues, articles continue to flood the literature. Scientists, clinicians, patients, and governments face significant challenges in interpreting evidence to drive practices. In addition, disconcerting is the rise in false information in social media as well as the literature that continues to drive vaccine hesitancy, fear, and use of unproven products for the prevention and treatment of COVID-19. Claims for ivermectin's safety and efficacy in COVID-19 are more of an opinion than evidence.[6]

For example, a recent meta-analysis of randomized trials evaluated the effects of hydroxychloroquine, ivermectin combined with iota-carrageenan, and ivermectin alone in subjects having a high risk for developing COVID-19. Thus, 35 106 titles and abstracts were screened and included 671 full texts. Only 9 trials were deemed eligible for analysis: 6 evaluated hydroxychloroquine, 2 evaluated ivermectin, and 1 each evaluated ivermectin combined with iota-carrageenan, ramipril, and bromhexine hydrochloride. Results for hydroxychloroquine revealed no benefit with regard to reducing rates of infection, hospitalization, or death, and evidence supporting the use of ivermectin was also absent. None of the trials reported symptom or clinical improvement in subjects with severe acute respiratory syndrome coronavirus 2 infection.[6]

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In another meta-analysis, trials using ivermectin for COVID-19 reported statistically significant infection prevention, reduced mortality, shortened time to clinical recovery, and shorter time to viral clearance with regular use of ivermectin. Study locations included Brazil, Peru, Paraguay Bangladesh, Egypt, Argentina, France, Spain, and the Dominican Republic. Although this analysis of worldwide reports of outcomes of ivermectin used for prophylaxis, treatment, and prevention of COVID-19 at first look is remarkable, these conclusions regarding the efficacy of ivermectin may be seriously overstated. Most of the studies reported were observational, and "controlled" trials seem to use convenience samples. (Controlled may be overstated.) Sample sizes were small with significant dosing variance. With all of the factors considered, this evaluation suggests a significant bias in the analysis of results. Finally, the favorable outcomes reported from public health data before and after use of ivermectin do not control for viral history in the population or historical events in the areas during the timeline that could significantly impact outcomes.[7]

In a recent meta-analysis, the authors wrote, "Ivermectin is likely to be an equitable, acceptable, and feasible global intervention against COVID-19. Health professionals should strongly consider its use, in both treatment and prophylaxis" (p e455). These recommendations are deeply problematic considering the sources of data for this analysis, which included preprint and unpublished studies. Many of the sources had significant limitations in design, small sample sizes, variable treatment protocols, and lack of peer review. Furthermore, the author's positive recommendations for ivermectin seem to be a function of multiple complex statistical procedures that cannot attenuate bias, poor design, and variances in recruitment and treatment protocols as well as the care provided for subjects in India, the Middle East, Turkey, Bulgaria, Bangladesh, Mexico, Spain, South America, and Nigeria.[8]

Not all meta-analyses report favorable outcomes with ivermectin use. One French study examined analyzed antinematodal-related serious adverse drug reactions (sADRs) reported after ivermectin use. Data were obtained from VigiBase (https://www.who-umc.org/vigibase/vigibase/), the global safety report database of the World Health Organization. The investigators evaluated the frequency of sADRs relative to the frequency of events after use of antinematodal drugs reported in Africa and other areas of the world.

Analysis revealed 2041 persons with sADRs post treatment had more reports of toxidermias, encephalopathies, and confusional disorders after ivermectin use compared with benzimidazole administration. Furthermore, encephalopathies occurred within and outside African loiasis endemic regions (adjusted reporting odds ratio, 6.30; 95% confidence interval, 2.68-14.8). How serious postivermectin encephalopathies manifest requires further study, as well as study of emerging reports of 2 serious toxidermias: Drug reaction with eosinophilia and systemic symptoms syndrome and acute generalized exanthematous pustulosis.[5]

A safety analysis of ivermectin and doxycycline monotherapy as well as in combination in the treatment of COVID-19 was recently published.[9] Two hundred articles were screened, which included 19 studies (6 retrospective cohort studies, 7 randomized controlled trials [RCTs], 5 nonrandomized trials, 1 case series, and preprinted) with 8754 unique patients in various stages of COVID-19. Safety profile was addressed in only 6 studies. Analysis revealed that there is little evidence to either promote or refute the efficacy of ivermectin, doxycycline, or their combination in the management of COVID-19 and that there are significant gaps in safety profile information.[9]

Particularly absent in the literature is evidence for the safety of ivermectin in pregnancy. One study evaluated existing evidence for serious and nonserious adverse events after ivermectin exposure in pregnant women. Relevant databases and trial registry platforms without language or date restrictions were searched for RCTs or observational studies reporting adverse events. Outcomes examined were spontaneous abortions, stillbirths, congenital anomalies, neonatal death, maternal morbidity, preterm births, and low birth weight.[3] Sources of data included MEDLINE, SCOPUS, Toxline, US Food and Drug Administration (FDA) List of Pregnancy Exposure Registries, World Health Organization's International Clinical Trials Registry Platform, ClinicalTrials.gov, and the Cochrane Central Register of Controlled Trials. One hundred forty-seven records were identified, which included only 5 observational studies and 1 RCT published between 1990 and 2008 in 6 African countries. The sample include 893 patients, of which 496 pregnant women received ivermectin inadvertently during treatment campaigns. For the observational studies, 397 pregnant women purposely received ivermectin as part of the open-label RCT. No study reported neonatal deaths, maternal morbidity, preterm births, or low birth weight. However, there was insufficient evidence to determine whether ivermectin is safe during pregnancy. Until safety evidence is available, treatment campaigns should focus on the prevention of providing ivermectin to pregnant women.[3]

REPURPOSING IVERMECTIN

Across the world, scientists are working to develop vaccines and drug therapies for COVID-19. Certainly, the discovery of low-cost and available agents would significantly reduce many of the hardships of the pandemic. Ivermectin does have broad antiviral activity through the inhibition of viral proteins. Studies using only tissue cultures with high concentrations of ivermectin have revealed possible antiviral, antimalarial, antimetabolic, and anticancer actions.[2] Caly and colleagues have found in in vitro studies that ivermectin reduced viral load nearly 100% at 48 hours and have suggested that ivermectin could reduce viral loads in infected

patients with possible suppression of disease progression and spread. However, there is no evidence that ivermectin doses used by Caly and colleagues in their in vitro severe acute respiratory syndrome coronavirus-2 research can be replicated in vivo.[10,11] Potential paths for repurposing ivermectin to treat COVID-19 may lie in developing inhaled formulations to provide high local concentrations in the lung while minimizing systemic exposure.[11]

Multiple current registered clinical trials (ClinicalTrials.gov) are in progress evaluating ivermectin for the treatment of COVID-19. During this time, it is necessary to remember pharmacological principles in the design and process of in vitro and clinical testing to safely repurpose drugs for use in the COVID-19 pandemic.[12]

RISKS OF IVERMECTIN ABSENT ON SOCIAL MEDIA

Ivermectin provided at 10 to 100 times the approved human dose is a known teratogen in mammals.[3] Use of ivermectin for the prevention or treatment of COVID-19 has demonstrated harmful effects. Calls to poison control centers due to ivermectin ingestion have increased 5-fold from the prepandemic baseline. Healthcare professionals should counsel patients against use of ivermectin as a treatment of COVID-19, emphasizing the potential toxic effects of this drug, including nausea, vomiting, and diarrhea. Overdoses are associated with hypotension and neurologic effects such as decreased consciousness, confusion, hallucinations, seizures, coma, and death.[13]

IVERMECTIN USE

The American Medical Association encourages patients and prescribers to consult the FDA's Consumer Update ("Why You Should Not Use Ivermectin to Treat or Prevent COVID-19") and the Centers for Disease Control and Prevention Health Alert Network Advisory ("Ivermectin Prescriptions and Reports of Severe Illness Associated with Products Containing Ivermectin to Prevent or Treat COVID-19").[13–15]

Ivermectin has approval from the US FDA for human use to treat infections caused by internal and external parasites. Ivermectin is not approved to prevent or treat COVID-19.[14] The World Health Organization recommends not to use ivermectin in patients with COVID-19, except in clinical trials.[4] The American Medical Association, American Pharmacists Association, and American Society of Health-System Pharmacists also object to the ordering, prescribing, or dispensing of ivermectin to prevent or treat COVID-19 outside a clinical trial.[13]

Ivermectin is available for defined veterinary conditions, and these products formulated for use in animals should never be used by humans.[4,13] Exposure to unknown doses of veterinary formulations of ivermectin in humans, either by ingestion, inhalation, injection, or exposure to body surfaces, is frequently associated with significant adverse events. Reports include rash, edema, headache, dizziness, asthenia, nausea, vomiting, diarrhea, seizure, ataxia, dyspnea, abdominal pain, paresthesia, urticaria, and contact dermatitis.[4] Animal ivermectin is highly concentrated and highly toxic for humans.[16] In addition, inactive ingredients found in animal ivermectin have not been evaluated for use in humans. Therefore, it is also unknown how the inactive ingredients impact ivermectin absorption in the human body.[14,16]

When using ivermectin to treat specific parasitic infections, for example, patients with onchocerciasis and severe *Loa loa*, patients may develop serious or even fatal encephalopathy either spontaneously or after treatment. Additional reported adverse events include neck and back pain, red eye, conjunctival hemorrhage, dyspnea, urinary and/or fecal incontinence, difficulty in standing/walking, mental status changes, confusion, lethargy, stupor, seizures, or coma. Again, with no adequate and well-controlled studies in pregnant women, ivermectin should not be used during pregnancy. Because ivermectin has been registered overseas, other ADRs that have been reported include hypotension, worsening of bronchial asthma, toxic epidermal necrolysis, Stevens-Johnson syndrome, seizures, elevation of liver enzymes, and bilirubin.[17]

For persons with exposure to unknown quantities of ivermectin or veterinary ivermectin products through ingestion, inhalation, injection, or exposure, supportive therapy should include parenteral fluids and electrolytes, respiratory support (oxygen and mechanical ventilation if necessary), and vasoactive agents for significant hypotension. Gastric lavage should occur as soon as possible followed by purgatives and routine antipoison measures, to prevent absorption.[15]

In summary, clinicians should strongly counsel patients against use of ivermectin as a treatment of COVID-19, including emphasizing the potentially toxic effects without treatment benefits. Use of animal ivermectin products must also be strongly discouraged related to significant risk of overdose.[16–18]

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