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Approaches to Treatment of Human Strongyloidiasis

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Background:

Strongyloides stercoralis is an important human parasite found in tropical and subtropical regions of the world. It can also be found in temperate areas where migrants have travelled from impoverished tropical regions to more affluent countries (Genta, Weesner *et al.* 1987; de Silva, Saykao *et al.* 2002). *Strongyloides fuelleborni* is a related species that can also cause strongyloidiasis and has been described in infants living in Papua New Guinea and sub-Saharan Africa (Ashford 1978). In some locations *S. fuelleborni* has a higher prevalence than that of *S. stercoralis* (Pampiglione and Ricciardi 1971; Pampiglione and Ricciardi 1971).

Estimates of 30 to 100 million infected people, worldwide, have been reported (Bethony, Brooker *et al.* 2006), but the true global prevalence of human strongyloidiasis is unknown, because of its chronic subclinical nature, coupled with the difficulty of making a diagnosis (Genta, Weesner *et al.* 1987). People can remain infected years after the original exposure to this parasite due to its ability to reinfect the same host.

The life cycle of *S. stercoralis* is complex, alternating between free living and parasitic cycles including potential for auto infection within the host (See full life cycle: <http://www.dpd.cdc.gov/dpdx>). Poor sanitation and hygiene resulting in faecal contamination of the soil and warm moist tropical conditions are optimal for the survival of *S. stercoralis*.

Hyperinfection Syndrome:

Although parasite numbers are kept low in immunocompetent hosts, worms can multiply unchecked in those who are immunosuppressed leading to a life-threatening condition known as the hyperinfection syndrome. Neva *et al.* (1986) showed that patients receiving corticosteroid medication had increased risk of developing hyperinfection with *S. stercoralis*. Other immunocompromised conditions in which *S. stercoralis* hyperinfection has been reported include other immunosuppressive therapies (Fardet, Genereau *et al.* 2006), HTLV-1 infection (Verdonck, Gonzalez *et al.* 2007), immune reconstitution syndrome associated with HIV infection (Brown, Cartledge *et al.* 2006), haematological malignancies

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Seminar on Pandemic Influenza: What happened last winter?

Wednesday 25 November 2009

Westmead Education & Conference Centre, Westmead Hospital

The Centre for Infectious Diseases and Microbiology-Public Health is hosting a one day seminar on Pandemic Influenza, which will outline how the pandemic unfolded in Australia and NSW, and its effects on various medical services (eg. ICU, transplantation, paediatrics). The laboratory issues found identified during the pandemic will be addressed, as well as infection control and vaccination. The seminar is aimed at scientists, medical & nursing staff, public health officials and anyone with an interest in pandemic influenza. **Speakers include:** Professor Dominic Dwyer, Dr Kerry Chant, Professor Anne Kelso, Professor Peter McIntyre, Dr Ian Chambers, Professor Raina MacIntyre, Dr Bin Wang, Professor Elizabeth Elliott, A/Professor Jon Iredell, Dr Biju George, Mala Ratnamohan and Linda Hueston.

For more information on speakers, program and registration, please visit the CIDM-Public Health website at www.cidmpublichealth.org or contact Lou Orszulak@wsahs.nsw.gov.au

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(Nucci, Portugal *et al.* 1995), cadaveric transplantation, tuberculosis, and malnutrition (Terashima, Alvarez *et al.* 2002). Hyperinfection has also been reported following heart transplantation (Schaeffer, Buell *et al.* 2004) and in chronic alcoholism (de Oliveira, Ribeiro *et al.* 2002).

Treatment:

Many of the older anthelmintics were shown to be ineffective before the benzimidazoles group of drugs were used against strongyloidiasis (Grove 1989). Ivermectin, which is highly effective against onchocerciasis, has more recently become the drug of choice for treatment of strongyloidiasis also.

Action of Drugs on *Strongyloides*:

Both groups of drugs currently available for treatment of human strongyloidiasis were initially developed for the livestock and agriculture industry.

a. Benzimidazole Group:

Albendazole replaced thiabendazole in the benzimidazole group for treating strongyloidiasis because it has fewer unwanted side effects. This anthelmintic is almost insoluble in water restricting absorption through the gut (Grove 1989). It has a broad spectrum anthelmintic activity where metabolic sites of the parasite are disrupted interfering with energy production. In common with the other benzimidazoles, albendazole inhibits polymerase activity associated with cytoplasmic microtubule production (Lacey 1988).

b. Ivermectin:

Ivermectin is a macrocyclic lactone derived from a microorganism, *Streptomyces avermectinius*. It is active against a range of ecto and endo parasites (nematodes, arachnids and insects) but has no antimicrobial effect on protozoa, bacteria and fungi (Omura 2008). The drug acts by opening the glutamate-gated chloride channels causing hyperpolarisation at the neuromuscular synapses thus causing paralysis of the worm.

Treatment of Uncomplicated Strongyloidiasis:

Early studies on the treatment of strongyloidiasis show the variable success of benzimidazoles in clearing the parasite from infected patients. The efficacy is also affected by the dose regimen and the patient's immune status. Since both albendazole and ivermectin have poor solubility in water, absorption of these drugs into patients will depend upon gut contents at the time of medication and the state of the gastrointestinal tract. Perhaps improved bioavailability would be achieved if these drugs were formulated as an emulsion with oil based additives. These anthelmintics need to be absorbed sufficiently to reach therapeutic levels in all organs and tissues to either kill or paralyse all migrating larvae for an effective cure. Both drugs however also rely on an intact immune system for this to occur.

The recommended dose for albendazole is 400 mg daily for 3 days with reported cures of 62.2% after 2-3 weeks (Horton 2000). In some countries (e.g. Thailand and Bangladesh) albendazole is the only available anthelmintic for treating strongyloidiasis; ivermectin remains to be registered in these countries. Moreover, ivermectin is not recommended for children under five years so albendazole remains the only drug available for treatment of this group.

Ivermectin is consistently better than albendazole at clearing the parasite (Datry, Hilmarsdottir *et al.* 1994; Toma *et al.* 2000) and is the drug of choice in Australia. There is a diverse range of recommended dosages for uncomplicated strongyloidiasis. Therapeutic Guidelines on Antibiotics recommend a single dose of 200 µg/kg (URL: <http://www.tg.com.au>). Others suggest dose regimens of 200 µg/kg given twice, one week apart (Currie *et al.* 2003). Those who are concerned with the difficulty of removing the autoinfective stage in patients advise that three single doses be given 4 weeks apart (URL: <http://rrh.deakin.edu.au>). The dose regimen for ivermectin recommended by the parasitologists at the National Institute of Health in USA is 200 µg/kg for 2 days and repeated after 2 weeks (Keiser and Nutman 2004). None of these dose regimens has been thoroughly tested by randomised control trials and have relied on clinical experience. Studies directed at finding optimal dose regimens for ivermectin and albendazole are lacking; whether these drugs can act in synergy to remove this parasite is uncertain.

A new drug, tribendimidine (50 mg/kg), reduced larval numbers in the stools by 90% and completely removed adult worms in rats infected with *S ratti* (Keiser, Thiemann *et al.* 2008). In an open-label randomised trial with this new drug in human adults (n=11) with a stat dose of 400 mg showed that 54.5% (6/11) had no detectable larvae in coprological examination 2 weeks after treatment (Steinmann *et al.* 2008). In China, tribendimidine is a registered anthelmintic for both adults and children with reported minimal adverse side effects. More studies with this drug are underway.

Treatment of Hyperinfection Syndrome

Patients with inadequate immunity can succumb to hyperinfection with strongyloidiasis and the danger is that diagnosis is not rapid enough to save the patient from an uncontrollable fatal septicaemia (Marcos, Terashima *et al.* 2008). Mortality rate in 89 hyperinfected patients, who were immunosuppressed because of corticosteroid therapy, was 59% (Fardet 2007). Different immunocompromised states will have different treatment outcomes because effective treatment with anthelmintics is dependant on an at least partially intact immune system to remove this parasite.

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Refractory patients whose immune system is unable to effect 100% removal of the parasite even with anthelmintics will continue to pass larvae and autoinfect. These cases may require ongoing monitoring and treatment for a prolonged periods of time (Hauber, Galle *et al.* 2005). Furthermore, these patients frequently do not have detectable antibodies to strongyloidiasis requiring fortnightly monitoring by faecal culture and microscopy.

As for uncomplicated infection, the optimal choice and dose of drugs is unknown. A report of a patient recovering from hyperinfective strongyloidiasis after receiving combined albendazole (400 mg/day) and ivermectin (200-400 µg/kg/day) for 2 weeks (Pornsuriyasak *et al.* 2004) supports the use of these drugs in combination. Higher doses of ivermectin may be able to eliminate both the parasitic larvae and adults. This has been demonstrated when a single oral dose of ivermectin at 500 µg/kg. was given to rats infected with *S. ratti* (Keiser, Thiemann *et al.* 2008). All adults and 90% reduction of larvae were cleared from these infected rats. Veterinary preparations have been given parentally in hyperinfected patients with paralytic ileus who were unable to absorb oral medication (Chiodini *et al.* 2000; Hauber *et al.* 2005). Subcutaneous injections at a dose of 6 mg were given daily for 22 days in one case report and 170 µg/kg/day (12 mg/day) were given in the other. Although both cases had fatal outcomes (due to the underlying condition), parental treatment was successful in removing the parasite. Neither patient showed any signs of toxicity from injections. An enema preparation of ivermectin given at 200 µg/kg/day for 7 days in a patient who was suffering from paralytic ileus successfully cleared the parasite (Tarr *et al.* 2003). The patient improved 3 days after treatment and made a full recovery from the hyperinfection. Obviously, use of either injectable or rectal ivermectin preparations needs more detailed studies on toxicity and monitoring of therapeutic drug levels in humans.

Conclusion:

Strongyloidiasis is listed as a neglected disease found mainly in tropical and sub tropical regions where sanitation and hygiene are poor. This parasitic nematode can infect patients for decades and go undetected in those who are immunocompetent. When the immune system is weakened either by debilitating disease, malnutrition or immunosuppressive therapy, an ensuing hyperinfection with *S. stercoralis* can occur. Successful treatment of this infection depends on an early diagnosis and removal of this worm before sepsis develops. Optimal treatment regimens have not been properly studied and there is a need to determine the best chemotherapeutic dose to permanently remove this parasite from its human host.

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