Etiological Treatment for Chagas Disease

The National Health Foundation of Brazil

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A panel of 13 experts from several states of Brazil (see Box 1) met in Brasilia to discuss the etiological treatment of American trypanosomiasis.

Treatment of Chagas Disease

Acute phase. By definition, acute phase (which lasts up to 60 days) is the stage of Chagas disease in which the parasite Trypanosoma cruzi is easily detected by direct examination of peripheral blood (by wet smear, or after staining, with or without previous concentration methods). A suggestive clinical picture along with the detection of IgM anti-T. cruzi antibodies also permits the diagnosis of the acute phase. No matter by which mechanism Chagas disease was acquired, all patients must be treated, since the cure rate (parasitological and serological) with acute-phase treatment is around 60%.

Congenital infection. The same diagnostic criteria of acquired acute phase hold for the congenital mechanism of transmission. A congenital infection may be suspected from the offspring of any mother known to be infected. The infection of the child is often diagnosed once the child is in the chronic phase. Positive serological reactions six months after birth are indicative of congenital transmission. The search for the parasite may be done by xenodiagnosis or by haemoculture. Specific treatment should be started, and is more efficient closer to delivery.

Chronic phase. Treatment is indicated in recent chronic infections (i.e., those who were infected a few years (<10) earlier, who, for purposes of treatment, behave as acute-phase patients). In practice, all children with positive serological reactions are treated. For individually selected cases, and as a research tool, patients with the indeterminate form, slight cardiac form and digestive form may be treated as well. For those cases with megaeosophagus, symptomatic treatment of the dysphagia is recommended prior to treatment, in order to assure the free passage of the drug and hence, its absorption. In terms of Public Health programmes, treatment is not encouraged because it is not clear whether etiological intervention will stop the progression of the disease for chronic phase patients. As the majority of patients are in this chronic phase, operational problems are envisaged, because treatment demands follow up because of the adverse effects of the drugs, which may be important on some occasions (see below).

Accidental infection. This may occur in health professionals, mainly those working in laboratories. Any confirmed or suspected contamination should be treated immediately. A serum sample should be collected before starting treatment, in order to compare with samples taken on the follow-up (benznidazole® 7-10 mg kg⁻¹ for ten days is the recommended schedule for these cases). It is also recommended that serological tests for American trypanosomiasis be carried out for any laboratory worker at risk, and that these tests be repeated periodically. An individual who has received blood from a chagasic donor should be treated in the same manner as referred for a laboratory accident.

Organ Transplantation and Specific Treatment for Chagas Disease

It is necessary to know if either the donor or the recipient is chagasic. The transplantation of an organ of a chagasic individual (as a donor) may transmit the parasite to the recipient. Equally, a chagasic recipient of any transplantation may experience reactivation of Chagas disease because of the use of immunosuppression. Clinical manifestations of the reactivation usually differ from those of the acute phase. For this reason, adequate monitoring of the chagasic infection should be performed in both situations: (donor or chagasic recipient of any organ). Treatment should be performed with benznidazole® 5 mg kg⁻¹ per day for 60 days.

Treatment during Chagas Disease Reactivation

Reactivation of Chagas disease may occur in immunodepression by several circumstances. Because of the high prevalence of the acquired immunodeficiency syndrome (AIDS), it is necessary to verify (by serological tests) if HIV-infected individuals may have concomitant Chagas disease before any reactivation occurs. This may be confirmed by epidemiological data. If parasitological reactivation is detected, treatment with benznidazole® should be provided for a period long enough to control any possible infection. Chemoprophylaxis has been suggested for these patients, but there is still a lack of data.

Drugs and Doses

Benznidazole®: adults, 5 mg kg⁻¹ per day, for 60 days; children 5-10 mg kg⁻¹ per day, for 60 days. Total dose per day

Box 1. Participants at the Workshop and Co-authors of this Technical Report

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should be divided into two (given every 12 h) or three (given every 8 h) doses. Nifurtimox® (not available in Brazil): adults, 8–10 mg kg⁻¹ per day, for 60–90 days; children, 15 mg kg⁻¹ per day, for 60–90 days. Total dose per day should be divided into three, and given every 8 h.

Both drugs cause some adverse effects; while these are comparable, benznidazole® exhibits fewer and less severe side effects, and is more readily available, and so is the drug of choice.

Adverse side effects. Toxicity reactions and adverse effects due to benznidazole and nifurtimox are similar. Manifestations related to the digestive system, as epigastralgia, hyporexis, nausea, vomiting and weight loss, are more frequent with nifurtimox®, while skin reactions are more frequent with benznidazole®. The main side effects observed with both drugs are the following:

(1) Haematologic alterations by hypersensitivity: leucopenia and low platelet count may be observed from the use of these drugs and are sometimes associated with purpura and agranulocytosis. Severe bone marrow depletion is seldom observed. Fever is usually observed together with these haematologic alterations; if this is the case, drug treatment should be discontinued.

(2) Dermatologic alterations: dermatomy by hypersensitivity, of variable intensity, from slight to severe, may occur in up to 30% of treated patients, mainly those on benznidazole® (it may also occur with nifurtimox®). If severe, the drug should be discontinued. These alterations occur frequently by the ninth day after the onset of the drug. Lymph node enlargement may be present along with the skin reactions.

(3) Neurological alterations: polymyelopathy is dose related and observed mainly in those schedules with higher doses. At a daily dose of 5 mg kg⁻¹ of benznidazole®, 10–30% of patients are expected to experience neurological alterations, generally observed at the end of the 60 day treatment.

Interestingly, children and patients treated during the acute phase have a much better tolerance for both drugs.

Precautions. Neither benznidazole nor nifurtimox should be prescribed to patients with other severe illnesses associated with Chagas disease, or to pregnant women (because of the potential risk to the baby, the possible adverse side effects of treatment and the fact that this non-emergency treatment may be carried out after the pregnancy is completed).

Assessment of Cure

This is a controversial issue and it is still under research evaluation.

For the acute phase and the recent chronic infection, follow-up should be performed through haemoculture and/or xenodiagnosis plus serological tests. Sustained negative results for parasite detection and for antibodies are currently recognized as indicative of cure of the infection.

In relation to the chronic phase (excluding recent chronic phase in children), there is no consensus. A situation often observed is the absence of parasites, with persistent antibodies detected by several conventional methods. Some authors emphasize the importance of the disappearance of lytic antibodies (complement mediated lysis) as indicative of cure.

As a whole, treatment is possible using either of the drugs, and, if performed, it should be recorded properly in order to increase expertise and accumulate experience for the scientific community. Proper follow-up is strongly recommended. Treatment may be performed only when the diagnosis has been established, based on the demonstration of the parasite or on positive serological reactions through at least two different serological techniques (any combination of: enzyme-linked immunosorbent assay, indirect haemagglutination or indirect immunofluorescence).

Who performs the treatment? Both benznidazole and nifurtimox (available drugs) are classified as 'high complexity' drugs, which means they should be prescribed by physicians who are familiar with the drugs' characteristics, as well as with the disease itself. The acute phase is considered an emergency and requires treatment to be given quickly and efficiently, because it may be severe, and because a high proportion of cases may be cured. In this case, a non-experienced physician should consult an experienced colleague or institution before commencing treatment.

Where is treatment carried out? Acute-phase patients are better treated in a hospital, as 'in patients'. Chronic phase patients may be treated as 'out patients', under the control of an experienced physician.

Available Drugs

It is hoped that the Ministry of Health will grant the supply of benznidazole® to professionals and institutions that are able to perform treatment. Furthermore, this drug should be sold only after the presentation of a proper prescription by a physician.

The main problems with the use of available drugs are: (1) the long-term schedule needed for treatment; (2) several adverse side effects; and (3) the efficacy, which is partial in most cases. Reactional forms in chagasic immunosuppressed patients are becoming more frequent due to HIV infection and the possible development of AIDS. New drugs are needed. It is hoped that universities and other institutions will undertake their development.

Acknowledgements

This technical report for the meeting on 'Etiological Treatment for Chagas Disease' held at the Chagas Disease Technical Division, National Health Foundation, Ministry of Health, Brazil, 5–6 February 1996, has been written by the 13 participants (see Box 1). Antonio Carlos da Silveira, Lúcio Flávio Castro Nasser and Marcio Costa Vinhaes (as representatives from the Ministry) were also present. A small handbook (16 pp) has been published in Portuguese (Etiologico Tratamento para o Doenca de Chagas, ed. by Abilio Augusto Fraga Filho et al., Fundacao Nacional de Saude) and is currently being distributed throughout Brazil to Health Centres and Hospitals.

Reference


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Headlines from Honduras

Central American Countries now recognize the importance of Chagas Disease and the feasibility of controlling it by eliminating the main insect vectors in accordance with the methods applied by the Southern Cone Programme (see pp. 141–144, this issue). The Director General of WHO has committed the organization to helping Honduras to eliminate its Chagas disease problem, offering an initial donation of $400 000 to get the Programme started. The Honduran Programme has three stated objectives: (1) elimination of Rhodius prolatus; (2) reduction of other vectors, especially Triatoma dimidiata; and (2) elimination of transfusional transmission through screening of Trypanosoma cruzi infected blood in bloodbanks.