Proceedings of the 2nd International Conference on Biological Engineering and Medical Science (ICBioMed 2022), Part I
DOI: 10.54254/2753-8818/3/20220315

Fexinidazole, A Promising Oral Treatment against Human African Trypanosomiasis, Clinical Research, and Potential

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Abstract. HAT, a parasitic disease that has significant impact on human nervous system, has caused several epidemic in sub-Sahara area. Between 1960-1990, approximately 5 HAT epidemic broke out in these areas. HAT can be aggressively communicable and vital without any treatment with a death rate of 95%. In addition, only little symptoms showed after infection so many patients who are not conscious about it may cause even more severe epidemic. In recent years, roughly 300 patients still die for it yearly. To cope with the disease, several medical companies make efforts to seek for treatments effectively against HAT. These research on treatment can prevent the wide spread of HAT and help patients to come back to their normal lives. The life expectancy and quality will also improve with treatment for HAT. Therefore, in this review, we collect information and data about HAT and relevant treatment. Among treatments, we focus on a recent drug named Fexinidazole, which can be effective to treat all phases of HAT. Furthermore, it also has potential to guide a new approach in finding new drugs by research on its mechanism.

Keyword: HAT, HAT treatment, fexinidazole, Human African Trypanosomiasis.

1. Introduction

Human African Trypanosomiasis (HAT), or so−called Sleeping sickness is a disease caused by genus Trypanosoma parasites, which are spread by tsetse flies. Those flies are commonly found in 36 countries to the south of Sahara in Africa. If patient was not treated properly, this disease can be developed into fatal stages. Patients who were infected by tsetse flies are commonly residences in countryside and majorly working in fishing, agriculture, stock farming and hunting, etc. [1]. Two types of HATs were found and are consequences of infection of different subspecies respectively. There are about 95% of clinical reports are results of infection of Trypanosoma brucei. Due to gradually improved treatment procedure and technology against this disease, total number of cases shows an incline of falling each year. In 2009, the total cases of infection dropped below 10,000 which is for the first time over the past 50 years. In addition, 992 cases and 663 cases were reported in 2019 and 2020 respectively.

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This sickness requires medical workers to be specially trained for treatment and care taking procedures due to its difficulty and complexity. However, the development of the new drug, Fexinidazole, may possibly be the game changer. Fexinidazole, Fxn or FEX, is a 2-substituted 5-nitroimidazole and function as a sort of DNA synthesis inhibitor. The molecular formula for Fexinidazole is C12H13N3O3S and molecular weight is about 279.3 [2].

Clinical studies show that patients who have received Fexinidazole therapy for 18 Months, Fexinidazole was successful in treating 185 out of 189 patients (98%) with stage 1 HAT caused by Trypanosoma brucei gambiense (g-HAT) and 40 out of 41 patients (98%) with early stage 2 g-HAT [3]. This result shows Fexinidazole to be a promising clinical drug for treating HAT due to its high cure rate percentage (98%) is way higher that it was expected (91%). There is also just one significant unfavorable incident (SAE; psychotic disorder) and two SAEs in 230 patients, which indicated that Fexinidazole can be effectively used against Human African Trypanosomiasis by Trypanosome brucei gambiense with little undesirable results. Therefore, fexinidazole can target the toxicity towards the parasites and eliminate them with efficacy.

However, Fexinidazole is not a permanent solution to HAT. Reports shows that if the parasites undergo mutations that give them resistance of Nifurtimox, the parasites will be even more resisted to Fexinidazole than its resistance to Nifurtimox.

In this review, we are focused on clinical case studies of Fexinidazole, its application and possible studies in the future.

2. Types and phases of HAT

HAT, Human African Trypanosomiasis, which is also called sleeping sickness, is a sort of parasitic disease caused by Trypanosoma brucei. There are two types of Trypanosoma brucei: the Trypanosoma brucei gambiense and the Trypanosoma brucei rhodesiense. However, in 98% of cases of Human African Trypanosomiasis, Trypanosoma brucei gambiense infection was blamed. ([4] Wikipedia)

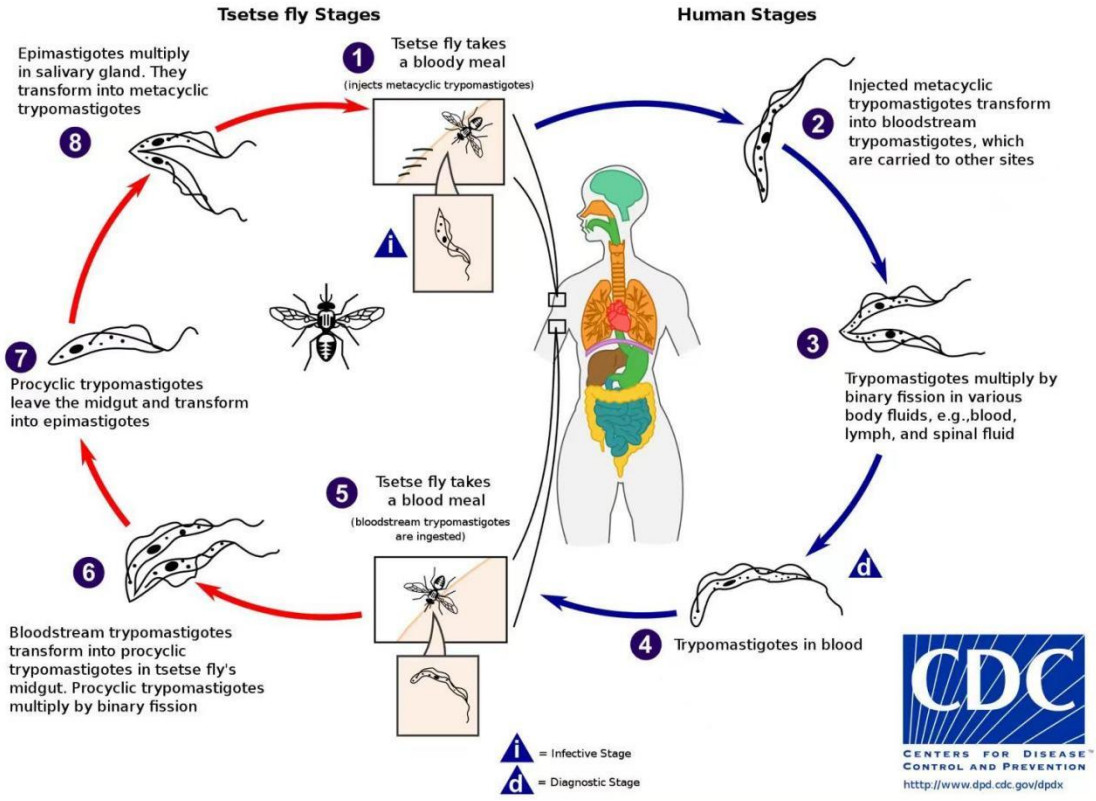


Figure 1. By Pixelsquid - This file was derived from:AfrTryp LifeCycle.png by Jованв62005 Surface Anatomy of the Heart [5].

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As figure shows, the parasites can be transmitted by tsetse flies (1 in Fig 1), which and caused pandemic in 36 sub-Saharan African countries. Most patients were bitten by tsetse flies in rural areas when they were fishing, hunting, etc. There are two phases of the Human African Trypanosomiasis which are hemolymphatic stage, the incubation of Trypanosoma (2 in Fig 1), and the neurological phase in which the parasites have invaded the patient's central nervous system through the hemato-encephalic barrier (After 3 and 4 in Fig 1). In the hemolymphatic stage, the patients may suffer from non-specific, generalized symptoms including intermittent fever, severe headaches, joints pain, itching, weakness, malaise,f atigue, weight loss, lymphadenopathy, hepatosplenomegaly and other features which can present on the skin or in organs. Patients in this stage probably do not notice that they may be infected by Trypanosoma and just consider the symptoms as nothing. Even sometimes the patients ask the staffs of health care for help, they may still not diagnose that as infection of Trypanosoma unless checking clinical signs -- swollen cervical lymph nodes or serological tests (only for Trypanosoma brucei gambiense) are done,which is the most confidential way to diagnose Human African Trypanosoma. After an estimated 21-60 days in case of Trypanosoma brucei rhodesiense infection or 300-500 days in case of Trypanosoma brucei gambiense infection, the neurological phase,also called the meningoencephalic stage ,begins. There are multiple symptoms in this phase comprising sleep disorders,neurocognitive symptoms and psychiatric symptoms. For neurocognitive symptoms, the patients may suffer from tremor, muscle weakness, hemiparesis, and paralysis of a limb. Furthermore, the patients probably become aggressive, confused,anxious and show emotional lability and psychotic reactions to psychiatric symptoms. In this phase, the parasite has caused irreversible damage to patients' brain. Even though the patients can still be treated and survive, the damages in the brains cannot be healed and will leave sequalae. In the late second phase of Trypanosomiasis, the patients suffer from coma, systemic organ failure and finally, death. In this duration, the parasites keep living in patients' blood vessels and when patients are bitten by tsetse flies, the parasites are taken with blood stream by tsetse flies. The parasites taken will grow and multiply being ready for next infection. (5-8 in Fig 1) Trypanosomiasis is considered to be invariably fatal without any treatment and is extremely epidemic. In the history, the epidemic broke out between 1896 and 1906,1920 and between 1970 to 1990s in several African countries. It was recorded that almost 40,000 cases in 1998 but estimated that 300,000 cases were not reported and treated. In 2009, with continued control efforts by WHO [6], the number of cases dropped below 10,000 and the decline in number continued during the later years.

3. The history of fexinidazole

The fexinidazole was firstly discovered by scientists in Hoechst AG, which was a German chemical then life-sciences company that became Aventis Deutschland after its merger with France's Rhône-Poulenc S.A. (from Wikipedia), in 1977. However, in 1980, any research for Fexinidazole as a medication was stopped for unknown reasons. In 2005, after the Drug for neglected Diseases initiative, DNDi was established,scientists in DNDi together with scientists of Sanofi S. A., which is a French multinational pharmaceutical and health care company, restarted the research for Human African Trypanosomiasis. They screened a large number of chemicals that could be effectively against Trypanosoma brucei, and this led to the identification of Fexinidazole. The research on Fexinidazole started in 2009 and 2012 all showed positive feedback as DNDi declared in 2017([6] from DNDi website). Soon,the DNDi received a positive endorsement from the European Medicines Agency in 2018. It was then approved for the treatment of Tryoanosoma brucei gambiense Human African Trypanosomiasis (HAT) in the Democratic Republic of the Congo (DRC) in late 2018.In 2020, Fexinidazole was included in the 'role og honor' in Préscrire magazine's prize list. In July 2021, Fexinidazole was approved in markets of the United States.

4. Mechanism of fexinidazole

Fexinidazole is a yellow colored crystalline, which is non-hygroscopic powder that particularly insoluble in water, sparingly soluble in acetone and actonitrile, slightly soluble in ethanol and methanol. It's achiral and does not show optical activity. Fexinidazole has two main metabolites, sulfoxide, and

DOI: 10.54254/2753-8818/3/20220315

sulfone metabolite. Fexinidazole and its two primary metabolites have in vitro activity in the 0.2-0.9 g/mL range against all types of HATs [2]. Future research demonstrated its tolerable toxicity on both animal and human beings and in vivo efficacy in HAT animal models. Importantly, it was established that Fexinidazole was non-inferior to the current NECT treatment in late-stage g-HAT infection. The precise mechanism and fundamentals of Fexinidazole are still unknown. However, it's suggested that Fexinidazole and its metabolites will be activated by the bacterial-like nitroreductates encoded by the parasites through reductions to synthesize a reactive intermediate that capable of damaging the DNA and proteins of the parasites. A whole-body autoradiography of 14C-labeled Fexinidazole in rats reveals widespread distribution across all tissues, with a concentration in the brain to blood of 0.4–0.6 g/mL that is within the functional range [2]. This ensures that Fexinidazole is effective against HATs in both the early and late stages of infection because it can directly be harmful to the parasites across the entire body and brain.

5. Case study and analysis

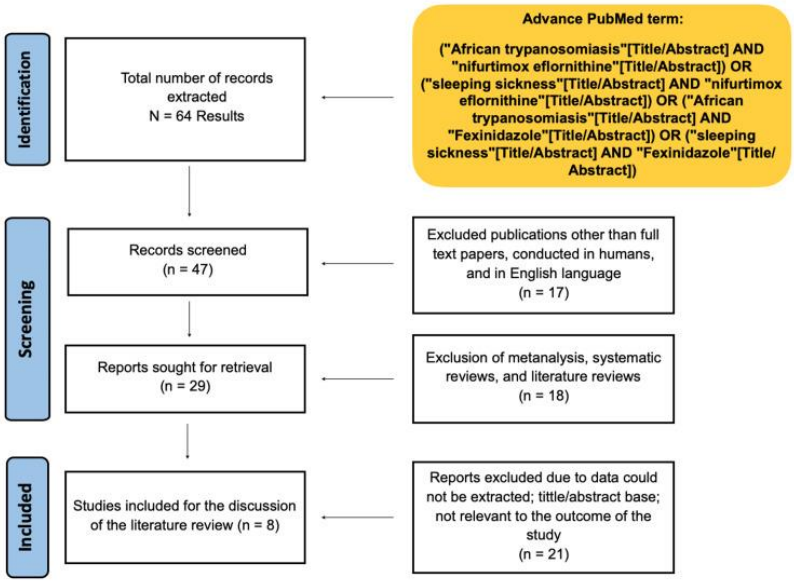


Figure 2. The results of the study using the PRISMA flow chart.

6. Limitations and future development

The European Parliament for Tropical Medicine and International Health published the report on the final clinical trial of Fexinidazole on July 17, 2017. Fexinidazole cured 91% of patients with severe sleeping sickness and 99% of patients in the early stages of the disease and is expected to eliminate African human trypanosomiasis (sleeping sickness) within a decade, the trial showed. The approval of Fexinidazole's phase I and phase II HAT in adults and children over 6 who weigh more than 20 kg by the European Medicines Agency (EMA) on January 16, 2018, encouraged Fexinidazole's application for marketing authorization of Azole 2019 in endemic countries. Fexinidazole was given a marketing license for the treatment of sleeping sickness (HAT) in the Democratic Republic of the Congo on January 30, 2010. (DRC). For the first time, human African trypanosomiasis can be cured with drugs alone.

Fexinidazole can produce active amines that are indirectly toxic and mutagenic to trypanosoma. In vitro, the sulfoxide (M1) and sulfoxide (M2) metabolites showed similar activity against Trypanosoma gonbiae and many other trypanosoma subspecies, including Trypanosoma Rhodesia and Trypanosoma Brucei. Fexinidazole showed therapeutic ability in mouse models including acute trypanosoma sembiense, Trypanosoma rhodesiensis infection, and chronic Trypanosoma brucei infection. Additionally, fexinidazole proved effective against chronic rather than acute trypanosoma cruzi

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infection in comparable in vivo models of the disease generated by different Trypanosoma cruzi species. Fexinidazole is effective against Trypanosoma lewi in vitro and Leishmania duri in a mouse model of visceral leishmaniasis, among other parasites. No interactions between Fexinidazole and its sulfoxide metabolites and sulfoxide metabolites, or between these compounds and other prescription medications such eflurniacin, valamidine, and melarsoprol, were seen during in vitro trypanosoma activity. Fexinidazole enhanced the efficacy of melarsoprol in mice with chronic trypanosoma infection when used in combination with a drug gel preparation. Oral Fexinidazole can be used to treat acute and chronic HAT infection models in mice. Preclinical studies of absorption, distribution, metabolism, and elimination have shown that the drug is well absorbed and easily distributed throughout the body, including the brain. Although Fexinidazole, like many nitro heterocyclic compounds, has mutagenic effects in Ames tests, it is not genotoxic to mammalian cells in vitro or in vivo. Unlike other HAT therapies, Fexinidazole has almost no nonspecific cytotoxicity.

Fexinidazole does have certain adverse effects, including black, tarry stools, chills, confusion, coughing up blood, fever, lower back or side pain, mood swings, and more [7].

7. Conclusion

Fexinidazole is promising in treating HATs due to its high cure rate and acceptable side-effects. Its appearance symbolized another step forward in treating difficult miscellaneous diseases and minimize the pain and suffer. However, we still need to find a solution to conquer other situations that might affect the Fexinidazole therapy.

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