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Treatment of Neglected Diseases with Prodrugs

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Abstract

The World Health Organization (WHO) and Médecins Sans Frontières (MSF) recently proposed a classification of diseases into three categories: global, neglected, and very neglected. The majority of pharmaceutical companies' R&D efforts are focused on global ailments such as cancer, cardiovascular disease, and mental (CNS) diseases. Millions of individuals around the world are affected by neglected diseases, but current pharmacological therapy is limited and sometimes ineffective. Furthermore, persons living in deplorable conditions with only the minimal essentials for survival are affected by extremely neglected diseases. The majority of these disorders are not included in the goals of pharmaceutical R&D projects, and hence fall outside the pharmaceutical market. Infectious diseases kill over 14 million people each year, mostly in developing nations. Only 1% of new medications licenced between 1975 and 1999 were for the treatment of neglected diseases. These figures have remained constant, indicating that new medication design and synthesis are urgently needed in those countries, and the prodrug method is a promising area in this regard. It improves the marketability of present and novel medications by enhancing activity and reducing toxicity, among other things. It's worth mentioning that saving time and money is critical in drug development, and prodrug techniques are of particular relevance in this regard.

Keywords: Prodrug design • American trypanosomisasis • African trypanosomiasis • Malaria

Introduction

Each year, billions of dollars are spent on medicine research and development for illnesses that affect wealthy individuals, such as obesity, baldness, and ageing. The world's impoverished, on the other hand, are utterly ignored. Neglected tropical infectious diseases include protozoan infections, helminth infections, and other disorders such as sickle cell disease [1]. The World Health Organization and Medicins San Frontieres recently designated these diseases as neglected and/or very neglected diseases. They have an impact on places of extreme poverty and promote poverty itself. As a result, they do not draw the attention of drug developers, who do not see this category of disorders as a profitable target [2]. Market logic dictates that if there is no profit, there will be no investment. Only 10% of global health research is focused on diseases that account for 90% of global disease burden and require new treatments urgently. Only 16 (1%) of the 1,393 novel medications introduced to the market between 1975 and 1999 were for the treatment of tropical diseases [3]. The etiologic agents that produce certain diseases have progressed in biology, molecular biology, and genetics. This knowledge, however, has not been applied to medication development, which is unacceptable.

Combinations of current medications, new indications for existing drugs, improvements to established pharmaceuticals and compound classes, and focused sample collections were some of the core approaches to drug development for tropical disorders.

Chagas disease

Carlos Chagas discovered American trypanosomiasis, also known as Chagas' disease, a parasitic infection caused by Trypanosoma cruzi, in 1909. The disease is predominantly seen in Latin America, where it affects 21 countries [4]. The parasite is thought to infect 16 to 18 million individuals, with 50,000 people dying each year as a result of the disease. Chagas disease is still considered to be incurable. Due to a lack of commercial incentives, the pharmaceutical industry has shown little interest in creating novel antichagasic medications. The medications available to treat this parasitosis are benznidazole and nifurtimox. Both medications, however, are hazardous nitroheterocyclic derivatives that are almost exclusively effective during the acute phase of the disease. They've been utilised for a long time as a treatment. Natural resistance of T. cruzi to nitro derivatives has been proposed as an important factor to explain the low rates of cure detected in chagasic patients, and natural resistance of T. cruzi to nitro derivatives has been suggested as an important factor to explain the low rates of cure detected in chagasic patients [5]. As a result, finding new medications to combat T. cruzi is critical and must be prioritised.

Sleeping sickness

Infection with parasitic protozoa of the Trypanosoma brucei (T. brucei) subspecies, which are introduced to the human circulation by bites of infected tsetse flies in the inter-tropical regions of Africa, causes human African trypanosomiasis (HAT), also known as sleeping sickness. In West and Central Africa, Trypanosoma brucei gambiense causes a chronic form of the disease [6]. Sleeping sickness affects more than 60 million individuals in 36 countries, with an estimated number of victims ranging from 300,000 to 500,000.

African trypanosomiasis chemotherapy is still reliant on ancient medications, some of which have deadly side effects. Before the emergence of central nervous system symptoms, suramin and pentamidine are the medications of choice for the Rhodesian and Gambian variants of the disease, respectively. Melarsoprol, a melaminophenyl arsenical medication, is used to treat late-stage illness. Eflornithine (DFMO) is also utilised in the treatment of T. b. gambiense illness. For human African trypanosomiasis, new medications are desperately needed, and drug resistance is expected to be a problem that must be addressed.

Malaria

Malaria is a life-threatening parasitic infection caused by Plasmodium falciparum, Plasmodium vivax, Plasmodium ovale, and Plasmodium malariae parasites, with P. falciparum being the only one capable of causing fatal consequences. Malaria affects about three billion people, and it is estimated that 300 to 500 million new cases of malaria are diagnosed each year, resulting in approximately two million fatalities. The poorest countries account for the majority of these cases [7]. Malaria continues to be a global epidemic due to the lack of a viable vaccine and the widespread emergence of multidrug resistance. For the majority of antimalarial medicines now in clinical use, resistant forms of malaria have been found [8]. For malaria chemotherapy, a variety of medications have been employed, including chloroquine, primaquine, mefloquine, halofantrine, artemisinin, and atovaquone. Drug or multidrug resistance, on the other hand, has been a problem for chemotherapy effectiveness. The urgent need for medications to combat tecidual forms, as well as the emergence and spread of resistance to chloroquine and other main antimalarial drugs, has prompted the development of a new generation of safe and effective antimalarial pharmaceuticals.

Schistosomiasis

Schistosoma mansoni, Schistosoma japonicum, Schistosoma haematobium, Schistosoma intercalatun, and Schistosoma mekong are the five principal Schistosoma species that infect people. Two billion people are thought to be chronically infected with soil-transmitted helminths and schistosomes, with many of them suffering from severe morbidity. According to the World Health Organization, 200 million people are affected, 600 million more are at risk of infection, and more than 200,000 people die each year from schistosomiasis. When it comes to the size of endemic areas and the number of individuals infected, it's only second to malaria. It is sold in 52 countries in South America, the Caribbean, Africa, and the East Mediterranean [9]. The parasite's intermediate host is a snail that lives in fresh water, and infection is disseminated through skin contact with the water. Schistosomiasis poses both a public health and a socioeconomic issue.

Chemotherapy has proven to be the most effective treatment for endemic disease, with therapeutic medicines such as metrifonate, oxamniquine, and praziquantel available. Only oxamniquine and praziquantel are used in some countries. The latter has been the preferred treatment since it is effective against all forms of human schistosomiasis. The development of resistance, on the other hand, is a major source of concern. Because of its negative effects, particularly those related to the central nervous system (CNS), oxyamniquine is used as a backup medicine. Because vaccine research is still years away from becoming a reality, new schitosomicide medications are urgently needed.

Tuberculosis

Similar to tropical endemic illnesses, tuberculosis (TB) looks to be a major problem for global health organisations and allied research groups. Tuberculosis (TB) is the world's most dangerous infectious lung disease and the main cause of death caused by a single infectious organism. It is found all across the world, although it is most prevalent in Africa. It is projected that two billion people are infected, and that between 2005 and 2020, one billion people will become infected, over 125 million will become sick, and 30 million will die from tuberculosis if control is not increased. Because HIV inhibits cell-mediated immunogenicity, the percentage of patients infected with M. tuberculosis who acquire active TB over a shorter period of time climbs to 50%. This, along with the advent of drug-resistant Mycobacterium tuberculosis strains, has posed enormous hurdles and necessitated the rapid development of new and better treatments.

Sickle cell disease

Sickle Cell Disease (SCD) is an inherited abnormality of haemoglobin production caused by a single point mutation in the -globin subunit that replaces valine with glutamic acid. It causes red blood cell distortion, which can lead to vaso-occlusive events, ischaemia, tissue and organ damage, and even death. This disorder is typically found in tropical areas and is most common in Africa [10]. This disease has harmed millions of individuals over the world, primarily in Sub-Saharan Africa, Latin America, the United States, Saudi Arabia, India, and Mediterranean countries such as Turkey, Greece, and Italy. The sickle gene, on the other hand, offers a genetic advantage: it protects heterozygous carriers from Plasmodium falciparum malaria infection in endemic areas. Hydroxyurea is the only medicine licenced by the US Food and Drug Administration (FDA) for the treatment of SCD. Butyric acids, aldehydes, decitabine, clotrimazole, L-arginine, and zileuton are some of the chemicals that have been explored for sickle cell treatment. The use of molecular modification methods to improve the pharmacological, pharmacokinetic, or even pharmacodinamic profile of existing medications is a recommended choice for most neglected diseases. Prodrug design is one of the most promising of these strategies. In this work, we summarise the key findings of 20 years of study into prodrug design for a number of neglected diseases.

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