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An effective parasitic agent---oxamniquine

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ABSTRACT: *Oxamniquine, with the brand name Vansil, is a medication used to treat schistosomiasis, the worldwide parasitic disease. This report includes the history, the structure, the synthesis and development, the side effects and the contribution of oxamniquine.*

KEYWORDS: *Oxamniquine, Schistosoma mansoni infection, schistosomes, schistosomal enzyme, epileptiform convulsions.*

1. Introduction

Schistosomiasis is a worldwide endemic disease and is also one of the most serious parasitic disease after malaria, it affects a lot of different countries and regions. Around 200 million people was affected by Schistosomiasis, and this disease should take responsible for approximately 500000 deaths per year. Oxamniquine is one of the most clinically important drug in the treatment of schistosomiasis which is a 2-aminomethyltetrahydroquinoline derivative. It was widely used after it was put on the market in 1975, it is still used today in some countries such as Brazil. [1][2]

2. History and synthesis

2.1---- The history of oxamniquine.

Initially, the only drugs used in the treatment of schistosomiasis were tricyclic structure lucanthone and stibocaptate, but both of them would produce toxic side effects on human bodies, such as nausea, vomiting and even affects central nervous system. In terms of the practicality of drugs, they are not effective enough to against all the pathogenic strains [1][3]. Therefore, in 1964, in order to discover a non-toxic orally active agent which was effective on against all three pathogenic strains, Pfizer initiated a project and this research led to the discovery of oxamniquine. Although oxamniquine does not meet all the goals set by Pfizer at Sandwich, it is effective against all stages of Schistosoma mansoni infection. The discovery of the drug made an outstanding contribution both on the treatment to Schistosoma mansoni patients

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and the tropical medicine, therefore it earned Pfizer the Queen's Award for Technological Achievement in 1979. The oxamniquine has been put on the market 11 years after the start of the project in 1975. [1]

2.2----The synthesis of oxamniquine

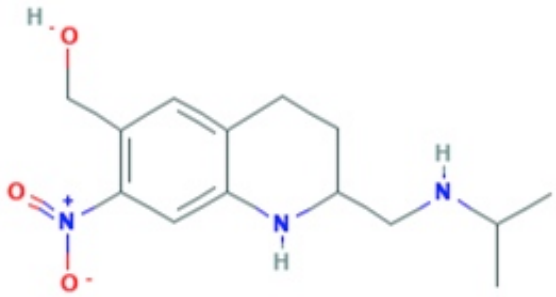

Figure 1

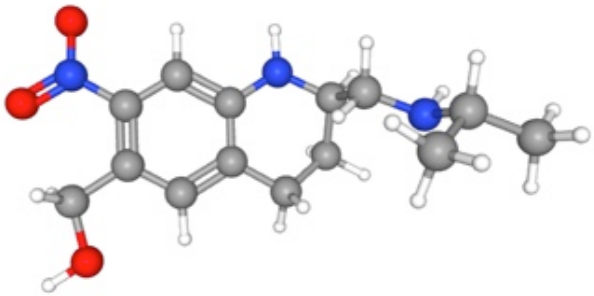

Figure 2

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As shown in figure 1 and figure 2, this is the structure of oxamniquine, with the IUPAC name [7-nitro-2-[(propan-2-ylamino)methyl]-1,2,3,4-tetrahydroquinolin-6-yl]methanol. [4]

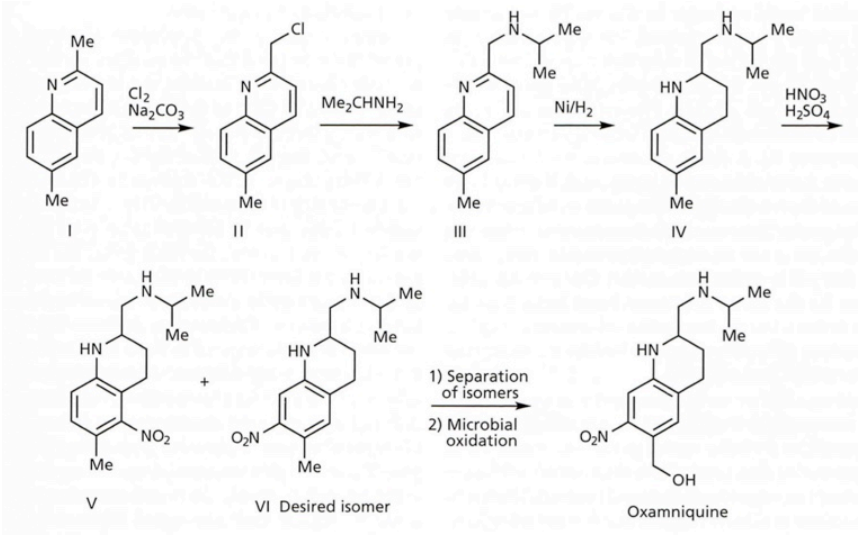

Figure 3

As shown in figure 3,[1] the most common method of synthesizing oxamniquine is starting from the quinoline structure, which is compound I. One of the methyl substituent on the heterocyclic ring is chlorinated and forms compound II, alkyl chloride(II). After undergoing a nucleophilic substitution with 2-aminopropane, compound III has formed, then it reacts with hydrogen gas and use nickel as a catalyst, reduction reaction occurs and forms tetrahydroquinoline, which is the compound IV. Tetrahydroquinoline is nitrated with oxidizing agent, sulfuric acid and nitric acid to form a mixture of isomers, compound V and compound VI. After separating the desired isomer from the mixtures, hydroxylate the isomer with fungus Aspergillus sclerotiorum and catalyze by microbial enzymes, after the oxidation reaction has occurred, the desired product oxamniquine forms. [1]

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3. The reason why the scientists developed oxamniquine and the function of oxamniquine.

3.1---- The reason to explain why the scientists developed oxamniquine.

As mentioned above, schistosomiasis is a disease caused by parasites, small flatworms (schistosomes) in the larval form can penetrate human body when they are swimming or wading in the infected water, larvae can develop rapidly to the adult stage since they are in human's blood supply. The female flatworms can release eggs and trap in different organs and tissues cause inflammations. The influence of these inflammations could lead to bladder cancer, liver damage or even be fatal, because there are three pathogenic species: Schistosoma mansoni, S.haematobium and S.japonicum. Oxamniquine is well absorbed after oral administration, there was a study related to the effects of oral oxamniquine syrup or capsule in controlling endemic Schistosomia mansoni in Castro Alves, northeast Brazil. The report included the data for 11 years before and after oxamniquine treatment, the data showed that before treatment (1974 to 1977), the incidence of liver and splenomegaly is high due to severe population infection. In the next 8 years, over 80% of the people in that studies received further treatments for the control of schistosomiasis. After the treatments, the prevalence of splenomegaly decreased from 10% to 2% and the regression rate of splenomegaly rose from 43% to 91%. The decline in morbidity has been accompanied by a significant decline in the prevalence and intensity of Schistosoma mansoni infections. Although oxamniquine is not effective on against all those three pathogenic species, it is effective as an anthelmintic with schistosomicidal activity against Schistosoma mansoni.[1][5]

3.2---- The mechanism of action of oxamniquine.

Oxamniquine can mediate by ATP-dependent generation of an intermediate that alkylates essential macromolecules, including DNA, it can cause adult worms to become paralyzed. Lead to disorganization of the suckers with which the worms attach to blood vessels and lose attachment, shift the schistosomes from mesenteric veins to the liver and the female worms return to the mesentery and can no longer release eggs. Oxamniquine can inhibit nucleic acid synthesis in schistosomal cells, the mechanism is thought that the sulfotransferase enzyme in parasitic cells can involve prior activation.[1][5]

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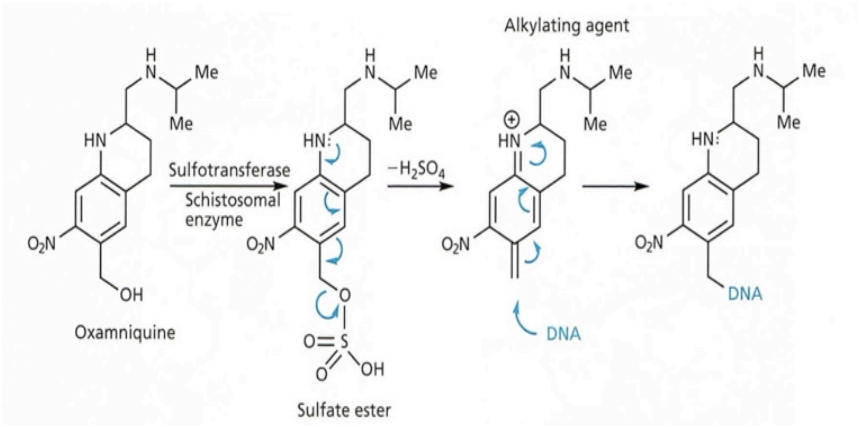

Figure 4

As shown in figure 4, the oxamniquine is bound to the active site on the schistosomal enzyme, the hydroxyl group on oxamniquine is converted to a sulfate ester, which is a good leaving group, so the molecule dissociates. The structure which is formed is an alkylating agent and can prevent DNA replication and is also selectively toxic for the parasite rather than mammalian cells. Therefore, oxamniquine is a good prodrug, and the target binding site in the parasitic sulfotransferase enzyme's active site.[1]

3.3----The side effects of oxamniquine.

The side effects of oxamniquine is relatively mild compared to other drugs such as lucanthone, the most frequent side effects are dizziness, headache and drowsiness and will last for 4 to 6 hours only, states of excitement and hallucinations are rare, there were no consistent statistics on abdominal discomfort, vomiting or diarrhea. Urine may show a harmless orange-red discoloration, but it is temporary. In general, oxamniquine is pretty tolerated, and are virtually no contraindications, but there are types of patients that need to be closely monitored. Because there have been a few epileptiform convulsions and systemic seizures following medication, all patients with a history of epilepsy should be supervised for 48 hours after they have taken oxamniquine orally. Any patient engaged in the care of heavy machinery or employed in the transport industry, such as pilot, truck driver, dockworker and crane driver should cease to work 48 hours after treatment. Studies on the safety of the drug during pregnancy have been lacking, so as a preventive measure, oxamniquine should not be used in the first four months of pregnancy. [5][6]

4. Conclusion

Oxamniquine is a highly useful antiparasitic agents for treating various forms of

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S. mansoni infection, including many advanced and complicated syndromes. It is often the preferred and a more convenient treatment, because it is given by mouth and used as a single dose. Although it can cause some mild side effects on human body and the patients who have a history of seizures should take this medicine cautiously, we cannot deny that the discovery of oxamniquine is a milestone in tropical medicine and it saves millions of people in the world.

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