Sulfadoxine-Pyrimethamine Information Paper

A licensed antimalarial drug developed by DoD & its partners

UNITED STATES ARMY MEDICAL RESEARCH AND MATERIEL COMMAND

Product name: Sulfadoxine-Pyrimethamine
Commercial name: Fansidar
Application: Antimalarial drug for treatment
Company of manufacture: Hoffman-LaRoche
Date of U.S. licensure: 1983
Type of product: folic acid inhibitors

Reasons for development:
Beginning in 1959, chloroquine-resistant malaria was noted in Columbia (and eventually Thailand and Vietnam). During the U.S. involvement in Vietnam, approximately 81,000 cases of malaria were associated with 1.4 million malarial sick days and 133 deaths. P. falciparum parasites resistant to the available antimalarial drugs such as chloroquine-primaquine were encountered. At the same time, use of the residual insecticide DDT was discontinued because of insecticide-resistant mosquitoes and adverse environmental effects.

Division of Experimental Therapeutics at the Walter Reed Army Institute of Research (WRAIR) in Silver Spring, Maryland is developing new prophylactic and therapeutic anti-malarial drugs for military use.

Role of DoD: Faced with waning usefulness of existing drugs to treat falciparum malaria during the Vietnam War era, the U.S. Army gradually established an malaria research and development program beginning in 1961 to develop new prophylactic and therapeutic drugs for military use. This research was coordinated through the Division of Medicinal Chemistry (later renamed as the Division of Experimental Therapeutics) at the Walter Reed Army Institute of Research (WRAIR) now located in Silver Spring, Maryland. Scientists of the United States Army Antimalarial Drug Development Program explored the effect of combinations of drugs that block folic acid on malaria parasite growth. The antimalarial activity of sulfa drugs has been recognized since the 1940's, and dapsone was a sulfone used for chloroquine-resistant malaria in Vietnam. Use of dapsone was limited

During the U.S. involvement in Vietnam, an estimated 1.4 million sick-days involving 81,000 infections and 133 fatalities were attributed to malaria.

by adverse effects afflicting skin, blood, liver and nerves. Folic acid is vital to the synthesis of nucleic acids which are prerequisites for cell multiplication. Compounds that have an anti-folic acid effect inhibit the replication of malaria parasites. Sulfadoxine and pyrimethamine interfere with folic acid synthesis at two different steps in parasite replication, so the combination treatment results in a higher degree of anti-folic acid activity compared to when only one of the drugs is given. Pyrimethamine was first created by Burroughs Wellcome in 1950 during a research effort to develop anticancer agents, and was licensed as an antimalarial drug in Britain in 1951. Pyrimethamine was widely used with chloroquine in the WHO control programs of the 1960's. The Walter Reed Institute Army Institute of Research (WRAIR) was involved in clinical trials and FDA approval for the sulfadoxine-pyrimethamine combination (known by the commercial name of Fansidar) to be used to prevent malaria. However, the drug was licensed in other countries prior to U.S licensure.

Current status:
Fansidar is still licensed in the United States. Although effective both as prophylaxis and treatment, the use of Fansidar (particularly as a prophylactic agent) is limited because of infrequent but serious adverse allergic reactions involving skin, liver and blood. However, the drug is still used as treatment in some countries where chloroquine resistance is widespread and where other drugs remain unobtainable for financial reasons. Also, the emergence of resistance to the drugs has somewhat limited the usefulness of Fansidar. Although types of antimalarial drugs other than antifolates have been discovered and invented, the mechanism of action of these other drugs is often less clear.

Sulfadoxine-Pyrimethamine References:

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Maier J, Riley E. Inhibition of antimalarial action of sulfonamides by p-aminobenzoic acid. Proc Soc Exp Biol Med 1942;50:152-154.