Clinical Pharmacology and Therapeutic Potential of Artemisinin and its Derivatives in the Treatment of Malaria

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Summary

Artemisinin and its derivatives are renowned for their potent antimalarial activity. They have found their way into clinical use in many areas where malaria is endemic. The in vitro concentration at which artemisinin can inhibit 50% of the growth of Plasmodium falciparum ranges from 3 to 30 μg/L. The fat-soluble derivatives artemether and arteether are approximately twice as active. The water-soluble dihydro-artemisinin and artesunate are 4 to 5 times more active in vitro. Artemisinin is available only for oral and rectal administration. Absorption is incomplete and elimination is fast, with an elimination half-life of 2 to 5 hours. Plasma concentrations after a single 500mg oral dose most often exceed 200 μg/L. Artesunate and arteether can be considered as prodrugs. Biotransformation into the active metabolite dihydro-artemisinin occurs rapidly – almost immediately for artesunate. The reported elimination half-life of artesunate is less than 1 hour,
Artemisinin is an extraction product from the herb *Artemisia annua* L. This plant was used in traditional Chinese medicine for the treatment of febrile diseases. Artemisinin was isolated and its structure resolved by Chinese researchers in the early 1970s. Initially, researchers thought that the herb qinghao (green herb), mentioned in Chinese traditional medical literature, referred to *Artemisia annua*. Later, botanical studies showed that qinghao probably referred to another *Artemisia* species. Therefore, the name artemisinin seems more appropriate than qinghaosu and is used throughout this article. Artemisinin appeared to be a very potent antimalarial compound. Chinese researchers recognised the impact of this finding and set out on a series of investigations, resulting in the development of a new group of antimalarial drugs.

### 1. Chemistry

Artemisinin is a so-called sesquiterpene (fig. 1) with a molecular weight of 282. Terpenes are compounds built up from isoprene units (C₅H₈). These are grouped according to the number of double isoprene units. A sesqui- (i.e. one-and-a-half) terpene thus contains 15 C-atoms. It is a tetracyclic structure with a trioxane ring and a lactone ring. The trioxane ring contains a peroxide bridge, the active moiety of the molecule.

Artemisinin, dissolved in aprotic solvents, is stable up to a temperature of 150°C. It is not very soluble in either water or oil. This and its short elimination half-life (t₁/₂) led to the search for derivatives that had improved pharmacological properties as well as better antimalarial activity. Reduction of the lactone to a lactol yielded dihydroartemisinin, which is a potent antimalarial compound.

With dihydro-artemisinin as an intermediate, other active derivatives were synthesised. To date artemisinin, dihydro-artemisinin, the water-soluble artesunate (the sodium hemisuccinate salt, molecular weight 384) and the lipophilic alkylether arteether (the methyl ether, molecular weight 298) are being used for treatment of malaria. Arteether (the ethyl ether, molecular weight 312) is being used in phase III trials. This article reviews the currently available drugs of this group.

### 2. Current Status

Some of the artemisinin compounds are being used on a large scale, especially in Asia.