Quinacrine – The Winding Road from the Most Important Antimalarial of Its Time to an Indispensable Antiparasitic (Orphan) Drug of our Days

Andreas Neumayr*abc and Esther Kuenzliab

Abstract: Quinacrine, the main antimalarial drug during World War II, has had a chequered history that included the successful repurposing as an intrapleural sclerosant for the treatment of malignant pleural effusions, a non-surgical method of female sterilisation, and the use as an immunomodulatory drug in lupus erythematosus. While no longer used for these former indications, quinacrine (re)emerged as an indispensable second-line drug for the treatment of nitroimidazole-refractory Giardia duodenalis infections, and thus depicts an indispensable ‘orphan drug’.

Keywords: Atabrin · Giardiasis · Mepacrine · Orphan drug · Quinacrine

1. The Rise and Fall of Quinacrine as an Antimalarial

When asked about the first available effective antimicrobial drugs (‘antibiotics’), Paul Ehrlich’s Salvarsan (1910), Gerhard Domagk’s sulfonamides (1936) or Alexander Fleming’s penicillin (1940s) are usually named as the pioneer substances. It is often forgotten that the quinine-containing bark of the Cinchona tree was the first true antimicrobial drug, effectively used to treat malaria already since at least the early 17th century. In addition, it is remarkable that, following the isolation of its active ingredient quinine in 1820, the drug remained the mainstay of malaria treatment until the 1920s.[2] After the massive problems caused by malaria during World War I among all war parties, extensive research efforts were made in the 1920s to develop synthetic antimalarial drugs to gain independence of the Cinchona-tree-dependent quinine production. The most important of these synthetic antimalarials was quinacrine (syn. Atabrin, Atebrin, Mepacrine, Chinacrin, Erion, Acricrine, Acрине, Palacrin, Metoquin, Halchin; Fig. 1), which was introduced in 1930/31 and was extensively used by the Allied forces in North Africa and the Pacific during World War II (Fig. 2).

When the office of the Surgeon General of the United States of America declared quinacrine the official drug for the treatment of malaria in 1943,[3] production increased from the prewar levels of 1,200 pounds per year to 1 ton per day. Impressive follow-up studies by US armed forces physicians generated considerable amounts of data, ranking it among the best studied drugs ever introduced: 3 million soldiers took the drug in a ‘controlled’ setting for up to 4 years.[4] The success of quinacrine was only to be halted by chloroquine, which finally proved more efficacious and less toxic, becoming the most widely used antimalarial in the 1950s and 1960s. Although the era of quinacrine as an antimalarial ended with the introduction of chloroquine, the drug was rediscovered and repurposed for several other indications over the years.

2. Quinacrine as Agent for Pleurodesis

In the late 1950s and the early 1960s, quinacrine was studied as a potential candidate compound for the treatment of malignant tumors following in vitro studies suggesting a cytotoxic effect on tumour cells in tissue culture.[5] Especially malignant lung tumours were considered a potential target for quinacrine.[6] Although the hoped-for cytotoxic effect on tumour cells did not materialise, quinacrine showed a marked inflammation-induced scarring effect when instilled into the pleural cavity and thus proved to be
a highly effective agent for pleurodesis. Quinacrine pleurodesis became a widely used method in the context of palliative management of malignant pleural effusions and the drug was used and studied for this indication until the 1990s. However, with the advent of improved alternative methods, the use of quinacrine slowly faded and the drug finally also disappeared for this indication.

In recent years, however, there has been a resurgence of interest in quinacrine sterilisation due to its ease of use and its proven efficacy. Chloroquine largely replaced quinacrine for giardiasis treatment in the 1960s due to its favourable safety profile and equal efficacy. Consequently, metronidazole and the subsequently introduced other 5-nitroimidazole compounds (e.g. tinidazole, ornidazole and secnidazole) became the first-line drugs for the treatment of giardiasis. Although the effectiveness of the 5-nitroimidazoles remained high over decades, an increase of nitroimidazole-refractory cases, very likely attributable to emerging resistance, has been reported in recent years. At the Hospital for Tropical Diseases in London, for instance, the rate of nitroimidazole-refractory giardiasis cases increased from 15% in 2008 to 40% in 2013.

For these treatment refractory cases, quinacrine (re)emerged as the most effective second-line drug in recent years. After several small retrospective studies had suggested a high efficacy of quinacrine as second-line treatment for refractory giardiasis, two prospective studies confirmed the excellent efficacy of quinacrine for this indication. With no other effective drugs currently available and no new drugs for giardiasis in sight, quinacrine is likely to remain the only drug available to treat refractory giardiasis for the foreseeable future.

6. Conclusions

The story of quinacrine is an illustrative example of drug repurposing and highlights the critical role that orphan drugs play in today’s clinical routine. Especially in the context of treatment of refractory giardiasis, quinacrine currently remains the best available option, which is not likely to change in the foreseeable future. The problem, as with all orphan drugs, is that a once widely available and cheap drug is becoming increasingly difficult to obtain. Additionally, companies still producing these drugs have misused their monopoly to increase the prices, leading to exorbitant costs for previously cheap drugs. Besides the obstacles of obtaining quinacrine, clinicians are faced with legal issues linked to the off-label use of quinacrine (quinacrine is not licensed for the treatment of giardiasis in any country we know of) and patients may have to cover the costs themselves, as health insurance companies may not reimburse non-licensed drugs. It is to be hoped that the demand for quinacrine will continue to be sufficient to keep its production profitable and that potential new indications for its use will emerge and secure its survival. That the quest for the reuse of quinacrine is not yet over is evident from the number of studies on quinacrine that have been and are being published across diverse medical fields, from Crohn’s disease to ulcerative colitis and COVID-19.

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