Published in final edited form as:

Trans R Soc Trop Med Hyg. 2009 December ; 103(12): 1199–1201. doi:10.1016/j.trstmh.2009.06.007.

Mode of action and choice of antimalarial drugs for intermittent preventive treatment in infants

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Abstract

Intermittent preventive treatment in infants (IPTi) is an effective and safe malaria control strategy. However, it remains unclear what antimalarials should be used to replace sulfadoxine-pyrimethamine (SP) when and where SP is no longer an effective drug for IPTi. Work recently conducted in Tanzania, combined with the findings of previous studies, indicates that IPTi is essentially intermittent chemoprophylaxis; consequently, long-acting antimalarials that provide a long period of post-treatment prophylaxis will be the most effective alternative to SP. However, because of concerns about development of drug resistance, new combinations of long-acting drugs are urgently needed.

Intermittent preventive treatment in infants (IPTi) has been evaluated as an addition to the currently available strategies to control malaria. There is now evidence that IPTi with three courses of sulfadoxine-pyrimethamine (SP) has a protective efficacy of 20-30% against clinical malaria in infancy ¹. However, it remains unclear how IPTi with SP will be affected by the high levels of antifolate resistance now found in many parts of sub-Saharan Africa, and what drugs should be used to replace SP where it is no longer an effective drug for IPTi. Rational choice of alternative regimens depends upon the acquisition of a better understanding of the mode of action of IPTi, in particular the relative importance of clearing existing infections at the time of treatment versus post-treatment prophylaxis ².

Two studies of the duration of protection given by SP IPTi in areas of moderate SP resistance found detectable protection for a period of 4-6 weeks after each dose of IPTi ³⁴, consistent with a previous prediction of how long SP would remain at protective levels post-treatment ⁵. This finding suggests that protection from IPTi is limited to the direct action of drugs and not through some indirect effect on immunity as has been suggested ⁶⁷. At the high concentrations found immediately after treatment, sulfadoxine and pyrimethamine act

Author contributions

DC and BG designed the Kilimanjaro IPTi study and analysed the data. RG implemented the trial protocol, directed the study and analysed the data. SG and JM carried out clinical assessments and data collection. MC performed the statistical analysis described here, presented the findings at the Society meeting and drafted the manuscript. All authors contributed to interpretation of the data, revised the draft manuscript and approved the final version. MC is the guarantor of the paper.

Conflicts of interest

None declared.

Ethical approval

The Kilimanjaro IPTi Drug Options Trial was registered as a randomised clinical trial (<http://www.clinicaltrials.gov>: NCT00158574), and was approved by the ethics committees of the National Institute for Medical Research, Dar es Salaam, Tanzania and the London School of Hygiene and Tropical Medicine, London, UK.

in synergy and are able to suppress the replication of even highly resistant parasites. However, highly resistant infections may survive this period without being completely eliminated and recrudescence⁸. Additionally, resistant strains may be able to successfully reinfect an individual sooner after treatment than a sensitive strain, leading to a shorter period of post-treatment prophylaxis⁹.

Work at the London School of Hygiene and Tropical Medicine, in collaboration with Tanzanian colleagues from the National Institute of Medical Research and Kilimanjaro Christian Medical College has investigated the efficacy and duration of protection given by SP and two alternative regimens, mefloquine (MQ) and chlorproguanil-dapsone (CD) in an area of high antifolate resistance. These results will be reported in full elsewhere. In brief, SP and CD were no more effective than placebo, while MQ provided substantial protection [Gosling et al. 2009, in press]. However, some evidence for protection was seen during the period immediately after the administration of SP but, as previously hypothesised²⁹, this was shorter than the duration of protection seen in areas with lower SP resistance. Furthermore, some malaria episodes may simply be delayed rather than prevented by administration of SP due to the drug suppressing but failing to eliminate resistant infections [Cairns et al. 2009, submitted].

Mefloquine remains in the circulation of children for a long time after administration⁸. The high efficacy of MQ in this study can be attributed to a substantial period of highly protective post-treatment prophylaxis after each dose of IPTi. Conversely, chlorproguanil-dapsone is rapidly eliminated¹⁰, provides no post-treatment prophylaxis and CD-IPTi gave no protection against malaria in infancy. These findings indicate that prophylaxis is vital to the efficacy of IPTi, and therefore strongly support the use of long-acting antimalarials as alternatives to SP for IPTi.

However, the use of long-acting antimalarials poses new challenges. Long-acting antimalarials may be particularly vulnerable to development of drug resistance when used as monotherapies because they remain present at sub-parasiticidal levels for a long period of time¹¹. Because IPTi is given at scheduled vaccine contacts rather than with respect to malaria transmission intensity, some children given IPTi with a long acting drug will have drug concentrations that are ideal for the selection of resistant parasites at the time they are most likely to be infected. One possible means to address this problem is to use combinations of long-acting antimalarials, since two or more drugs which are eliminated at a similar rate could protect each other from development of resistance during the terminal elimination phase¹².

Two current options for this role are SP-amodiaquine and SP-piperaquine. Both have been used successfully in trials of intermittent preventive treatment in children in Senegal¹³ and [Cisse et al., 2009, submitted] and in The Gambia [Bojang et al., 2009 in preparation]. However, neither combination is currently ideal because the partner drugs to SP require administration over three days, making directly observed therapy of the full course impractical. The ideal regimen for IPTi and IPT in older children would be a fixed formulation of two long-acting antimalarials with similar pharmacokinetic profiles that could be given as a single dose. Additionally, an excellent safety profile is paramount for drugs for IPT given that many children who receive IPT will be healthy at the time of treatment. More research is therefore urgently needed to identify and develop such combinations for IPT in infants and in older children.

Acknowledgments

The authors gratefully acknowledge the support of the IPTi Consortium and its members.

Funding

MC is funded by the United Kingdom Medical Research Council. The Kilimanjaro IPTi Drug Options Trial was funded by the IPTi Consortium and by the Gates Malaria Partnership, both of which are supported by the Bill and Melinda Gates Foundation, Seattle, WA, USA.

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