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Short Communication

Artemisinin–naphthoquine combination: A directly observed treatment option in malaria

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ABSTRACT

Resistance to standard antimalarials has led to the need for newer options. Artemisinin-based combination therapies (ACTs), which require a tedious three-day treatment schedule, have been introduced for the treatment of drug-resistant malaria. Of late, the new generation artemisinin–naphthoquine (ANQ) combination has been developed, which requires a single dose treatment.

Artemisinin initiates the action through the cleavage of the endoperoxide bridge while naphthoquine maintains the process by getting concentrated in the digestive vacuole of the parasite.

One ANQ tablet contains 50 mg naphthoquine and 125 mg of artemisinin in the ratio of 1:2.5. The optimal dosage in adults is 400 mg of naphthoquine and 1000 mg artemisinin, which amounts to 8 tablets in a single dose. The dosage for children is adjusted based on the body-weight.

The combination has been found to be quite effective with and safe. Studies have demonstrated an adequate clinical and parasitologic response of 98.1–100% in both adults and children. However, further trials are required to confirm its non-inferiority with other ACTs. Adverse reactions with ANQ have been mild. Further studies are needed before safety can be established during pregnancy.

ANQ increases the compliance rates because of single dosage. It may be administered by the peripheral health workers as a directly observed therapy, which would be of special benefit to troops in the North-Eastern Sector.

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Introduction

Resistance to first line drugs against malaria such as chloroquine, sulfadoxine/pyrimethamine and mefloquine has accentuated the research for newer drugs.¹ Among the

newer drugs available for drug resistant malaria, artemisinin based combination therapies (ACTs) hold promise. However, the presently available ACTs require a three-day regimen which adversely affects patient compliance. Of late, the new generation artemisinin–naphthoquine (ANQ) combination has generated special interest.² The novel combination has been

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developed by the Academy of Military Medical Sciences at Beijing, China.

Mode of action

Artemisinin is a trioxane lactone having an endoperoxide bridge which is vital for its action. Although the exact mechanism of action is debatable, artemisinin probably causes cleavage of the bridge through heme mediated action which results in production of carbon-centred free radicals. Thereafter, these free radicals bind to membrane proteins, and alkylation reactions eventually cause elimination of the malarial parasite.³

Naphthoquine belongs to the tetra-aminoquinoline family. It has not yet been used on a large scale for malaria treatment. Naphthoquine acts by getting concentrated in the digestive vacuole of the intraerythrocytic parasite by the process of simple diffusion. It then becomes protonated to cq2+. Since the digestive vacuole has an acidic pH, naphthoquine cannot leave by diffusion. The drug causes heme build up by capping the hemozoin molecules and preventing further biocrystallisation of heme. Naphthoquine then binds to heme to form a highly toxic complex which causes lysis, and finally autodigestion of the malarial parasite cell.

The co-formulation

Both artemisinin and naphthoquine have been found safe and efficacious when administered as monotherapies.⁴ Artemisinin has a quick onset of action, but a shorter half-life. Hence, the drug may fail to clear the parasitemia quickly, thus requiring high dosages over a prolonged period. On the contrary, naphthoquine has a slow onset of action and an extended half-life. The delayed onset of action provides ample time for the malarial parasites present in the blood to move out to the intra-vascular compartment and thus avoid the parasitocidal action of the drug. The aim of combining the two drugs is to circumvent the pitfalls when each is used as monotherapy, thereby providing more quick relief from malaria symptoms by rapid clearance of the parasitemia and having a higher cure rate through synergistic action, which would be difficult to achieve by administering only one of the two drugs in isolation. To sum up, artemisinin initiates the action while naphthoquine completes it.

Besides improving therapeutic efficacy, the co-formulation may also delay the development of drug resistance to the individual drugs. The combination also prevents recrudescence by eliminating the hypnozoites through its extended half life.

Formulation and dosage

ANQ has been manufactured and marketed under the brand name ARCO®. A single tablet contains 50 mg naphthoquine and 125 mg of artemisinin in the ratio 1:2.5.⁴ The co-formulation is meant to be dispensed as a fixed single-dose. The optimal dosage for uncomplicated malaria in adults comprises 400 mg of naphthoquine and 1000 mg artemisinin which amounts to 8 tablets.⁵ The administration of 8 tablets in

Table 1 – Body weight adjusted dosage of ANQ.

Body weight	Dosage (number of tablets)	Naphthoquine content	Artemisinin content
16–20 kg	03	100 mg	375 mg
21–32 kg	04	200 mg	500 mg
33–49 kg	06	300 mg	750 mg
≥50 kg	08	400 mg	1000 mg

a single dose is adequate in treating uncomplicated falciparum malaria infections. The recommended dosage for children is adjusted based on the body-weight which amounts to 20 mg artemisinin and 8 mg naphthoquine per kg body weight. The number of tablets of the co-formulation which needs to be given to children based on the body weight is given in Table 1.

Efficacy

In a randomised, parallel-group study design conducted in Papua New Guinea,⁶ the efficacy of artemether-lumefantrine (AL) was compared with ANQ among children aged 6 months to 5 years infected with *Plasmodium falciparum* and *Plasmodium vivax*. The subjects received either six doses of AL over 3 days or three daily doses of ANQ and were followed for 42 days. Among children with *P. falciparum*, AL had an adequate clinical and parasitologic response (ACPR) of 97.8% while ANQ had a response of 100% ($p = .24$). ACPR among children with *P. vivax* were 30% for AL and 100% for ANQ ($p < .001$).

In another study to test the efficacy of ANQ, a single dose of eight tablets of ANQ was given to patients suffering from falciparum malaria.⁵ The mean fever clearance time (FCT) was 18.2 ± 8.6 h and the mean parasite clearance time (PCT) was 34.6 ± 14.3 h. ACPR was achieved in 98.1% cases. In a three site study carried out in Sudan,⁷ adult patients suffering from uncomplicated *P. falciparum* malaria were subjected to treatment with ANQ, and were followed up for 28 days.⁵ The mean FCT was (12.0 ± 4.8) h, while the mean PCT was (34.8 ± 12.6) h. The overall ACPR was 98.4%.

In a study comparing the efficacy of ANQ and CQ + SP (chloroquine and sulphadoxinepyrimethamine), adult patients with uncomplicated *P. falciparum* in Papua New Guinea were subjected to ANQ and CQ + SP treatment.² After a 28 day follow up period, it was observed that the cure rate for ANQ on day 1, 2, 3, 7, 14, and 28 was 47%, 86%, 92%, 94%, 94% and 94%, respectively, with a recrudescence rate of for 6% which was cleared on day 21. For CQ + SP treated group the cure rates were 24%, 67%, 82%, 82%, 84% and 88%, respectively, with a recrudescence rate of for 6% which was cleared on day 28 except for one patient. The proportion of gametocyte carriers was higher in CQ + SP treated group than ANQ treatment (41% versus 12%). ANQ had a faster anti-malarial action than CQ + SP, with almost 50% of the patients being cleared of parasitemia within the first 24 hours, besides suppressing gametocytogenesis more significantly than the CQ + SP combination.

However, in three small trials from Benin, Côte d'Ivoire, and Papua New Guinea involving 487 subjects, both AL and ANQ had low treatment failure rates after 28 days follow up with no difference in the ACPR.⁸ The study at Papua New Guinea, in

fact, followed 186 subjects till Day 42, with very low treatment failure in both the groups. In a single small trial from Indonesia comprising 144 subjects, ANQ was compared with dihydroartemisinin–piperaquine. It was observed that treatment failure was very low in both groups on Day 42, with no difference in the ACPR.⁸

Adverse effects

The combination has been found to be relatively safe, with adverse events estimated to be low ($\leq 5\%$).⁴ The common adverse events include headache, nausea, vomiting, dizziness, and abdominal pain which are self-limiting. A transient deafness has been reported by some patients. QTc prolongation between baseline and 4 h after the final dose may occur following ANQ treatment.

However, the same has been found to be an adverse effect associated exclusively with naphthoquine. Nevertheless, the drug should not be administered to individuals who are at risk of QTc prolongation, cardiac arrhythmias and in patients with electrolyte imbalance.

Although recent studies in pregnant women have shown the regimen to be well tolerated with no evidence of toxicity to the mother or foetus, further studies are needed before its safety during pregnancy can be established.

Emergence of resistance

Though the malarial parasite is unlikely to become resistant to artemisinin due to its short half life, the resistance to naphthoquine, with a half life of 276 h,⁹ may build up easily if given as single dose which may compromise the efficacy of the coformulation. Hence, the efficacy of ANQ needs cautious monitoring. Resistance may develop on giving substandard doses of ANQ or when the parasite load is high.

Advantages

This ANQ combination has a unique advantage as it can be given less frequently as a single or twice a day dose; without compromising on the cure rates vis-à-vis the other more frequently administered ACTs, though the quality of evidence is low in view of the insufficient data available. Hence, the coformulation definitely increases the compliance rates.

Another advantage of ANQ when compared to its competitor drug AL is that it obviates the need for co-administration with milk, which again improves patient compliance as compared to the relatively complicated AL regimen which has a prolonged six-dose schedule coupled with co-administration of milk.

The public health advantage of ANQ lies in the fact that this combined drug can be administered in the periphery as a directly observed treatment regimen. The same holds immense value in the Indian Armed Forces setup, especially in the North-Eastern Sector, where malaria is rampant and troops are at high risk of acquiring the disease.¹⁰ Frequent movement of troops due to their nature of duty which includes

camping in dense forest canopies and night operations, coupled with space and time constraints may not provide the opportunity for the standard three-day treatment with the conventional ACTs. Here, ANQ may provide the much needed immediate one-time treatment which may be provided by the battlefield medical staff in field conditions.

Conclusion

The ANQ combination may possibly become a potential future generation ACT for malaria treatment of uncomplicated falciparum malaria due to its excellent safety profile and the oral route of administration. It may be more useful in settings where non-compliance to the three-day regimen of ACTs is a major hassle.

However, as the data have been collected from small clinical trials, further research is necessary in a variety of settings to confirm that ANQ is non-inferior to the presently accepted three-day ACT regimens in vogue.⁸

Conflicts of interest

The authors have none to declare.

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