Drug Update

NEWER ANTIMALARIAL DRUG
Fixed Dose Combination Of Arterolane with Piperaquine

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Abstract:

A fixed dose combination of arterolane with piperaquine **(Synriam)** developed as simplified once a day therapy for three days for the treatment of acute uncomplicated P. falciparum malaria in adults. It is fully synthetic, effective and well tolerated. It has been approved in 2011 by Drug Controller General of India.

KEYWORD: Synriam

Introduction:

Malaria is a major public health problem in India, accounting for sizable morbidity, mortality and economic losses. Around 1.5 million confirmed cases of malaria are reported annually by National Vector Borne Disease Control Programme of which about 50% are due to P. falciparum.[1] Malaria is curable if proper treatment is started early. P. falciparum had shown 100% resistance to cloroquine in India.[2,3]

As per World Health Organisation's guidelines, new antimalarial adopted as policy should have an ACPR (28 days follow-up) of at least 95%. Currently only two ACTs (Artemisinin Combination Therapy) have shown ACPR more than 95% i.e. Artemether+Lumefantrine(97.4%) and Artesunate+Mefloquine (96.9%). Issues with these ACTs are high cost, food dependent absorption and supply limitation (plant source).

Synriam is a fixed dose combination of arterolane with piperaquine developed as simplified once a day therapy for three days for the treatment of acute uncomplicated P. falciparum malaria in adults, approved in 2011 by Drug Controller General of India.

Synriam is developed in line with WHO (World Health Organization) recommendations of using fixed dose combination formulation of a rapid/short acting artimalarial drug (arterolane) with long acting anti malarial partner drug (piperaquine) with complimentary effects.

Arterolane is the first fully synthetic non-artemisinin, oral antimalarial compound having rapid parasiticidal activity. Piperaquine is a bisquinoline compound and has antimalarial activity against both P. vivax and P. falciparum including strains of chloroquine resistant P. falciparum.

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Mechanism of Action :

Both components (arterolane and Piperquine) are blood schizontocides.

Arterolane, a synthetic peroxide anti-malarial, is a rapidly acting blood schizonti- cide against all blood stages of P. falciparum without effect on liver stages.

Arterolane is an active moiety which gets accumulated either in cytosol or food vacuole of the parasite. It acts by inhibition of PfATP6, a sarcoplasmic endoplasmic reticulum calcium ATPase encoded by P. falciparum. In the food vacuole of parasite reductive cleavage of peroxide bond of arterolane by ferrous iron (Fenton reaction) occurs. This irreversible redox reaction produces free radicals that alkylate the membrane associated parasite proteins. The reactive species inhibits an ATP dependent Ca2+ pump located on the endoplasmic reticulum, PfATP6. The reactive C radicals subsequently reacts with different protein targets as well as with ferriproto-porporphyrin IX thus preventing heme detoxification and inhibiting a multitude of enzymes .

Piperaquine is a bisquinoline antimalarial drug having good activity against plasmodium strains. It inhibits the heme digestion pathway in the parasite food vacuole. In chloroquine resistant strains of Plasm. Falciparum it acts by inhibiting the transporters that efflux chloroquine from the parasite food vacuole.

Rational of combination : Arterolane kills the malarial parasite in the blood providing fast relief from symptoms of malaria like fever and chills. Piperaquine on the other hand has a longer lasting effect than arterolance and kills residual parasites, preventing the recurrence of malaria.

Formulation : Synriam is a fixed dose combination of arterolane and piperaquine. Each tablet contains : Arterolane 150 mg and Piperaquine 750 mg.

Pharmacokinetics

Synriam tablet is well absorbed orally irrespective of the presence of food in stomach. T ½ of Arterolance is 2 to 4

hrs. T ½ of piperaquine phosphate ranged from 11 to 18 days. Both the drugs are metabolized by liver.

Indication

Treatment of acute, uncomplicated malaria infection due to Plasmodium falciparum in adults.

Limitations of use

Synriam tablets are not indicated for patients with severe or complicated P.falciparum malaria. Synriam tablets are not indicated for prevention of malaria. Presently not indicated for use in children below 12 yrs of age.

Dose and method of administration :

A 3 day treatment schedule with a total of 3 doses is recommended.

Tablet 1 : to be consumed immediately on diagnosis of uncomplicated P. falciparum malaria

Tablet 2 : to be consumed between 24 ± 4 hours of tablet 1.

Tablet 3 : to be consumed between 24 ± 4 hours of tablet 2.

Tablets may be taken with or without food.

Use in special Population:

1) Pregnancy : Categrory C drug i.e. it should not be used in pregnancy unless the benefit to the mother out weighs the potential risk to the fetus.

2) Lactation : safety of synriam in lactating mothers has not been established.

3) Pediatrics : the safety and efficacy of synriam tablets has not been established in pediatric patients aged less than 12 years .

4) Geriatrics : Clinical studies of synriam tablets in uncomplicated P. falciparum malaria did not include patients aged above 65 years.

5) Hepatic or renal impairment: No specific pharmaco-kinetic studies have been performed in patients with hepatic of renal impairment. Caution should be exercised when administering synriam tablets in patients with moderate to severe hepatic or renal impairment.

Contraindications : Patients hypersensitive to any of the active ingredients of product (Synriam).

Warnings & Precautions :

1) Hepatic & Renal impairement

2) QT Prolongation (Congenital QT prolongation, Drugs prolonging QT e.g. quinidine, Amiodarone, macrolide antibiotics , triazole antifungal agents)

3) Halofantrine & Synriam tablets should not be administered within three months of each other due to long elimination half life of piperaquine phosphate and potential additive effects on QT interval.

Drug interaction :- ARTs (Protease inhibitor & non-nucleoside reverse transcriptase inhibitor , causing inducation or competition for CYP3A4, may result either in increased concentration of piperaquine Phosphase leading to QT prolongation or a derease concentration of ARTs resulting in loss of efficacy or decrease in concentrations of arterolane and/or piperaquine concentrations resulting in loss of antimalarial efficacy .

Advantages:

Cheap, fully synthetic, low transmission risk (100% gametocyte clearance at Day42) so no need to administer primaquine, good tolerability, once daily dosing for 3 days only and food independent absorption.

Side effects :(Clinical adverse events)

Frequently reported adverse effects (>1%): anemia, headache, vomiting, cough, abdominal pain, pyrexia, Diarrhoea, anorexia, nausea, dizziness .

CAE <1% :- Splenomegaly, sinus bradycardia, vertigo, dyspepsia, fatigue, pain, myalgia, Pruritus, nasal congestion, rash and urticaria.

Trials :

Phase III Double blind randomized, multicentre (carried out in India and South East Asia) clinical trial found that Synriam was non- inferior to Coartem (Artemether+Lumefantrine). FCT (Fever Clearance Time) with Synrium was 18 hrs as compared to 24 hrs with Coartem. PCT (Parasite Clearance Time) with Synriam was 36 hrs as compared to 34 hrs with Coartem. ACPR on Day28 (PCR corrected) with Synriam was 97.9% as compared to 98.9% with Coartem. No deaths had occurred in this trial and no serious adverse event reported with Synriam as compared to 2.8% with Coartem. Another Phase III clinical trial in P.vivax has been successfully completed in India, results of which has been submitted to DCGI (Drug Controller General of India). Other ongoing trials are Phase III multicentre clinical trial in P.falciparum malaria patients in Africa and Phase II multicentre clinical trial in P.falciparum malaria pediatric patients in Africa and India.

Conclusion:

Synriam is an effective, well tolerated simplified once a day therapy for three days for treatment of acute uncomplicated P.falciparum malaria in adults.

References:

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