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COMPARISON OF ANTIMALARIA DRUGS IN LIBYAN ESSENTIAL DRUG LIST WITH THE NEW ANTIMALARIA DRUGS (ARTIMISININ AND ITS DERIVATIVES) WARRANTS THEIR ADDITION TO THE LIST

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ABSTRACT

Malaria is the most serious protozoa disease, although it is not endemic in north Africa especially in Libya .Travellers to malarias areas risk infection, the risk can be greatly reduced by taking chemo-prophylactic drugs, however drug resistant plasmodium falciparum is an increasing problem in many parts of the world especially African and some Asian countries. Travellers to endemic countries are at risk to be infected. In African countries with the increasing levels of chloroquine resistance coupled with fears of toxicity and decreased efficacy for sulfadoxine/pyrimithamine (those drugs are included in the Libyan essential drug list); there is an urgent need for an effective and safe alternative to above named drugs. Artemisinin and its derivatives presently showed no cross-resistance with the known anti malarials and as such are important for treating severe infested malaria areas with multidrug resistance also can be administered in combination with other antimalarial drugs. In case of treatment, the Antimalarial activities of Artemisinin and its derivatives are extremely rapid; most patients show clinical improvement within 1-3 days after treatment the recrudescence rate is high even when these drugs are used as monotherepy. In conclusion: This study demonstrates the advantage of artemisinin and its derivatives as anti malarial drugs and the importance there selection and addition to the Libyan Essential drug list.

KEYWORDS:Malaria,Travellers,Artemisinin,Antimalarialdrugs,Sulfadoxine/pyrimithamine,Libyan Essential drug list

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INTRODUCTION

Malaria disease: of the many insect-borne diseases, malaria causes the greatest mortality worldwide; it is one of the most serious and complex health problems facing humanity in the 20th century. Approximately 300 million of the world's people are infected by the disease and year; it kills more people than any other communicable disease except tuberculosis. This is usually the result of a person, infected with malaria in other country, being bitten by local mosquitoes. Malaria is caused by protozoan parasites of the genus plasmodium. Four species of plasmodium can produce the disease in its various forms.

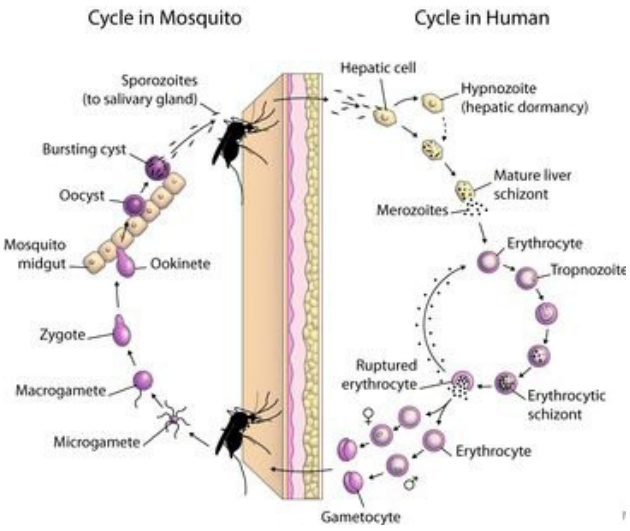
- Plasmodium falciparum.
- Plasmodium vivax.
- Plasmodium ovale.
- Plasmodium malaria.

Prelevance

The worldwide distribution of malaria is illustrated by the map years, but control is becoming more difficult and gains are being eroded. Increased risk of the disease is linked with changes in land use linked to activities like road building, mining, logging and agricultural and irrigating projects, other causes of its spread include global climatic, disintegration of health services, armed conflicts and mass movement of refugees. The emergence of multi-drug resistant strains of parasite is also exacerbating the situation.via the explosion of easy international travel; imported cases of malaria are now more frequently registered in developed countries. Malaria is re-emerging in areas where it was previously under control or eradicated. Malaria is endemic in a total of 101countries and territories:45countries in who's African region,21 in who's Americas region,4 in who's European region,14 in who's eastern Mediterranean region,8 in who's south-Asia region, and 9 in who's western pacific region. P.falciparum is the most widespread and dangerous of the four: untreated it can lead to fatal cerebral malaria.

SYMPTOMS OF MALARIA

Symptoms of malaria include fever, shivering, pain in the joints, headache, repeated vomiting, generalized convulsions and coma. Severe anaemia is often the attributable cause of death in areas with intense malaria transmission.



MALARIA TREATMENT

Malaria can be treated, but over one million people die from disease each year, mostly children under 5 years. One problem in treating malaria is that some malaria drugs are no longer effective against the malaria parasite. This may be due to the parasite becoming resistance. Drug resistance to malaria varies within countries and also between countries. For this reason it is not possible to give specific information about which drug to use for particular patient. In

Libyan pharmaceutical list there are four products have been used:

- Chloroquine phosphate (250mg tab).
- Dapsone (100mg tab).
- Mafloquine (250mg tab).
- Pyrimethamine (25mg+sulfadoxine 500mg tab).

1-uncomplicated malaria where patients can take oral therapy can be treated with one of
Three regimens

- Quinine: is an alkaloid found in the bark of the Cinchona tree and it is the only drug which has strongly effective for treating the disease over a long period of time . It is now only used for treating severe Falciparum malaria partly because of undesirable side effects.
- Malarone: This drug is a combination of proguanil and atovaquone. So there is synergistic effect but some caution should be exercised when using this drug as a prophylactic. It is a very expensive drug.

2-Severe malaria

Where patient have coma, jaundice, renal failure, hypoglycaemia, acidosis, severe anaemia, high parasite count, hyperpyrexia is ideally treated in an intensive care or high dependency unit where patient can be monitored closely both clinically and biochemically. Intravenous quinine is the treatment of choice but rapid injection can lead to hypotension, dysrhythmias and death. The second type of parasite is P.vivax, which is still sensitive to chloroquine, so adult treatment based on chloroquine. Tablets, primaquine and malarone.the third and fourth type of parasite are called P.malaria, P.ovle.treatment for the eradication of these two strains of malaria is the same as that for P.vivax except it is not necessary to give primaquine to those patients with P.malaria.

Choice of region is based on

1-local cost and availability of antimalarial drugs.
2-Area of malaria acquisition i.e. drug resistant pattern of P.falciperum.
3-prior chemophylaxis.
4-known allergies.
5-Concomitant illness other than malaria.
6-Age and pregnancy.
7-likely patient compliance.
8-Risk of re-exposure to malaria after treatment.

METHODS

Comparison of antimalarial drugs in Libyan essential list with new antimalarial drugs artemisinin and its derivatives

1-Chloroquine (250mg tab): Very effective for treatment and prophylaxis. In the past it was effective in curing all forms of malaria, with few side effects when taken in the dose prescribed for malaria and it was low in cost. Unfortunately most strains of falciparum malaria are now resistant to chloroquine and more recently chloroquine resistant vivax malaria has been reported.

2-Dapsone (100mg tab): Is pyrimethamine. resistance to this drug is now widespread so due to this cause no longer recommended.

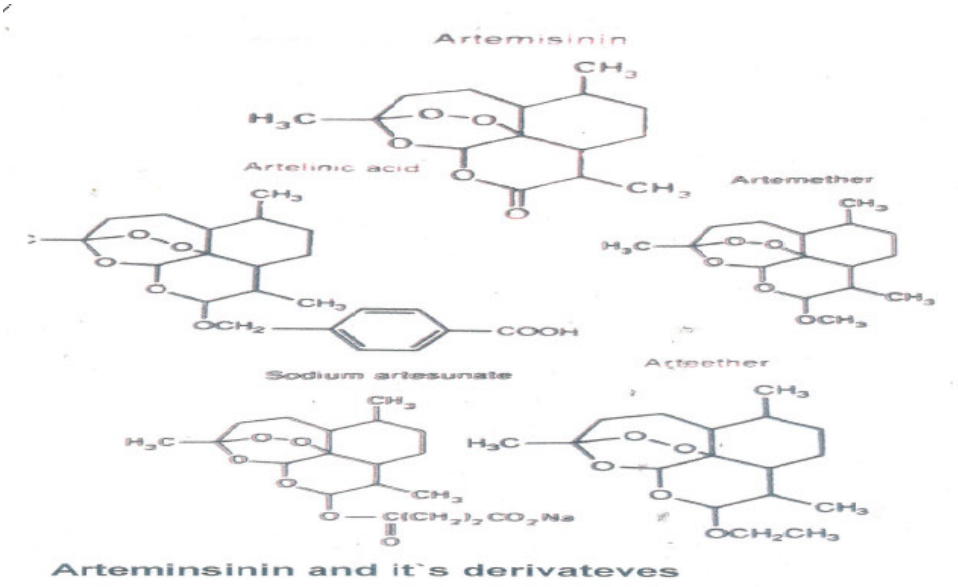
3-Mefloquine (250mg tab): This drug related structurally to quinine. The compound was effective against malaria, resistant to other forms of the treatment when first widespread resistance has now developed and this together with undesirable side effects has resulted in a decline in its use.

***4-fansidar*:**This drug, containing sulphadoxine 500mg.and pyrimethamine 25mg.The mechanism of action of this combination is interfering with folate metabolism. Resistance to fansidar is now widespread and serious side effects have been reported. It is no longer recommended.

ARTEMISININ (QINGHAOSU)

Artemisinin is one of the newest anti malarial compounds purified from an ancient Chinese herbal tea qinghaou (sweet worm wood) that have been used traditionally to treat malaria in china. This new drug going to revolutionaries how we treat malaria and replace chloroquine, however, a radical cure with an entirely different mode of action from the quinine family is urgently needed. So artemisinin extracted from Artemisia annua (compsitae), which is an aromatic annual herb that occurs naturally as part of steppe vegetation in the

northern parts of Chahar and suiyuan province in china. It is widespread, being found in Europe, North and South America. The secondary metabolite is an end peroxide sesquiterpene lactones efficient against multidrug resistant strains of plasmodium. The malaria parasite. These antimalarial properties are linked with the peroxide function of this sesquiterpine lactone.artemisinin has poor solubility in water or oil and can thus only be administered orally. In-patient with severe malaria, oral treatment is often impossible and a parenteral formulation of the drug is required. Therefore water-soluble artesunate, the hemi-succinate of dihydroartemisinin and the oil soluble artemether have been developed by Chinese scientists for intravenous and intramuscular administration, respectively. The antimalarial efficacy of oral artesunate in un-complicated malaria appears to be a function of the duration of therapy. Recrudescence rates are unacceptably high in patients given less than five days of treatment. Combined treatment with mefloquine improves efficacy and allows shorter course of artesunate to be given. Since 1994, a combination regimen of mefloquine 25mg/kg plus a three-day course of artesunate 12mg/kg has become the treatment of choice for uncomplicated falciparum malaria. The recrudescence rate by day 63 with this treatment is less than 10%, but patients whose infections do recur are symptomatic and their management poses a difficult problem.re-treatment with mefloquine again increases the risk of severe neuropsychiatry reactions.artemether has rapid action against chloroquine-resistant P.falciparum malaria, and is currently being used in china as injection formulations.arteether has similar activity. Artemether and arteether are both extensively decomposed in acidic conditions, but are stable in alkali. The ester artesunic acid is also used in china, as an injection or in tablet form, but is rather unstable in alkaline solution; hydrolysing todihydroartemisinin.the ether artelinic acid is considerably more stable. These two compounds have a rapid action and particular application in the treatment of potentially fatal cerebral malaria.dihydroartemisinin is a more active antimalarial than artemisinin and appears to be the main metabolite of these drugs in the body. The artemisinin derivatives were all as well tolerated and had no significant side effects.artemisinin and it is derivatives are potent blood schizontocides.they are also gametocytocidal.



Arteminsinin and it`s derivateves

SOME IMPORTANT ARTEMISININ DERIVATIVES

1-Artemether:- Artemether, a methyl ether derivative of artemisinin was found to be more active than artemisinin.it is effective in cerebral malaria by intramuscular injection (vikas dhingra, et al., 1999), (nosten, et al., 1998).

2-Arteether:- Arteether is the B-annoyer of the ethyl ether of dihydroartemisinin.it was synthesized originally in china by(lid et al.,1981).the drug has been formulated as a solution in sesame oil for intramuscular use;arteether is a potent antimalarial and is very effective against drug sensitive strains of P.falciperum in vitro as well as in vivo in the mouse malaria model, and monkey malaria model.presently,artemether has been registered in 27 countries intheworld,includingfrance,Thailand,Pakistan,sudan,niger,etc...(Vikas dhingra et al., 1999), (nosten, el al., 1998).

3-Artesunate:- Artesunate is a water-soluble hemisuccenate derivative of artemisinin.its only analogue that can be given intravenously.However, since it is unstable in water, it should be contiguously reconstituted with 5% sodium bicarbonate solution prior to injection (vikas dhingra et al., 1999), (nosten et al., 1998).

Adverse effects and toxicity

It is very different from experiences with most other antimalarials.no neurological abnormalities in patients have been seeing until now. It's unknown if cumulative neurotoxicity is of concern but sub clinical injury could occur with each treatment course for separate episodes of malaria.

RESULTS

Situation in Which They should or should not be used.

Reduction of mortality from malaria depends on accurate early diagnosis and promotes effective drug treatment. Selection of an antimalarial sensitivity profile of plasmodium falcipererum isolates in an area. Even when a drug effective, it's appropriateness for a given patient may depend on whether it is available in a form appropriate for clinical situation. For example, a malarial child with persistent vomiting might not be able to enough oral mefloquine to prevent progression of the disease to a severe form even if the parasites were sensitive to mefloquine. Hence mefloquine, because of its non availability in inject able form. So drug selection is determined by suitability for use in particular setting. For example, the standard treatment for cerebral malaria is quinine given by slow intravenous infusion (WHO, 1990). In the most malaria endemic countries, that kind of drug administration is possible only in tertiary health care facilities found mainly in the major cities. The Artemisinin drugs are suitable in the initial treatment of vivax malaria, followed by primaquine for elimination of the liver stage form. Artemisinin. Artesunate appeared to be the most rapidly acting of available drugs, but it was less stable than artemether, and parental use needed to be made up in 5% sodium bicarbonate before injection. Artemisinin suppositories. Were clearly effective and could well represent a major advance, especially in rural areas where injections could not be given. But they were not generally available and in some areas. There could be cultural difficulties with their acceptance. For seven falciparum malaria, intravenous route od administration is preferred , this kind of I.v formulations are not optimal . Clearly intramuscular administration of artemether has proven effective for severe disease, also much easier to use, especially in isolated regions: and it is more economical, because it avoids the need for an i.v .moreover, the Risk of accidental over dosage is certainly less with an Im.thanI.v. from. Major advantage of artemether is that it is given i.m.Thus can be used at peripheral facilities where treatment withi.v., infusions of quinine would not be possible also its good way because its half life is longer than that of other artemisinin derivatives. Tolerance to the single dose of artemisinin was good. No adverse effects were detected.

CONCLUSION

Increasing resistance to chloroquine and sulfadoxine/pyrimethamine will probably lead to an increase of malaria and mortality, particularly in children, and urgent action is needed to replace antimalarial drugs, which have become, or are rapidly becoming ineffective.Artemisinin and its derivatives are the only compounds that have come top of the list in term of efficacy, low toxicity,resistance,cost,rapidly acting and first order pharmacokinatics.the high frequency of recrudescence's necessitates protected

treatment in immunotherapy (five to seven days)or preferably combination with some other longer acting agent such as mefloqine or benflumetol.the artemisinin derivatives should be reserve for those situations where problems of resistance or unwanted side effects of the available antimalarial drugs are to be expected. All the artenisinin drugs act faster than any other antimalarial drugs. And that they are well tolerated and without evident toxicity.artemisinin compounds appear to be well absorbed, rapidly hydrolysed to the biologically active metabolite and rapidly eliminated. Based on available safety and efficacy data, the following therapeutic options are available now and have potential for deployment (in prioritized order) if costs were not an issue:

i.Artemether-lumefantrine (coartem).

iiArtesunate (3days) plus amodiaquine.

iii.Artesunate (3days) plus sp in areas efficacy remains high.

The rule of intra muscular artemether /arteether as an alternative to intravenous quinine because of simplicity of administration and less frequent dosing schedule in the management of severe malaria in complex emergency situations is re-emphasized.

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