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The result of artesunate and mefloquine treatment in pregnant women with quinine resistance Plasmodium falciparum infection.

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ABSTRACT

Objective To study the result of artesunate and mefloquine treatment in pregnant women with quinine resistance Plasmodium falciparum (P.falciparum) infection.

Method The cases were P. falciparum infected pregnant women who had been treated with quinine for 7 days and still had the parasites in the blood smear during 1 June 1993 to 31 May 1995. The exclusion criteria were cerebral malaria and the patients who did not cooperated. The cases were treated with artesunate 2 mg./kg. loading dose and maintenance with 1 mg./kg. every 12 hours intravenously for 5 days and on the sixth day with mefloquine 15 mg./kg. loading dose and following by 10 mg./kg. 6 hours orally. The cases were studied until they had delivered and the babies had been 12 months old.

Result There were 56 pregnancies with P. falciparum infection, 2 maternal deaths, 15 abortions before 28 weeks, 36 cases were treated with quinine successfully and 3 cases had full-filled inclusion criteria. They were infected with malaria at 10, 27 and 33 weeks. The third case of the study had acute renal failure. All cases developed shock and hypoglycemia. The parasites disappeared from the blood circulation 3 days after treatment and could not be found on the twenty-eighth day of treatment. The intrauterine growth rates were normal. The fetal biparietal diameter and abdominal circumference were also normal. The babies were born at 39,36,39 weeks vaginally and Apgar scores were 9 at 1 minute,10 at 5 minutes in all cases. No congenital anomalies were detected. Three babies had normal growth and development after they had been followed up for 12 months.

Conclusion The artesunate and mefloquine are useful in treatment of pregnant women who are infected with quinine resistance P. falciparum and they seem to have no harmful effects to the fetus.

Key words: artesunate, mefloquine, pregnancy

In the malarial endemic area, the pregnant women have the high risk to be infected with P. falciparum. The quinine resistance rate of P. falciparum are increasing now. The malarial infection in pregnant women will jeopardizes both mother and child by increasing abortion, premature and low birth-weight rate.[1,2] The

longer time malaria infects, the more obstetrical and medical complications the mother has. The effective treatment and prevention of complication are the good method to help the mother and child to be healthy.[2] The intravenous quinine is used to treat severe P. falciparum infection. But we treat the patient with quinine resistance P. falciparum by artesimin drug group intravenously and mefloquine orally.[3] The artesimin drug group is the herbal extraction from artemisia annnal.(qinghoa) There are three derivatives of artemisinin now, artesunate, artemeter and arte-ether. These derivatives can get rid of the malarial parasite from blood circulation faster than artemisinin and the patient can recover rapidly. However there is often the parasite relapsing because the drugs have the short half life.[4-6] For solving this problem, mefloquine which has the long action is used with the artesimin to prevent the parasite relapsing.[7-9] The artesimin and its derivatives kill non-sex form parasite by inhibition of parasite cell-division and red blood cell attachment of parasite.[10] But they can not kill sex and intra-tissue parasite form.[11] The artesunate dose for quinine resistance P. falciparum is 2 mg./kg. loading dose and maintenance with 1 mg./kg. every 12 hours intravenously for 5 days and on the 6th day mefloquine 15 mg./kg. loading dose and following with 10 mg./kg. 6 hours orally.[12,13] The qinghaousu derivatives have adverse embryo effects in animal whose dosages are 20 mg/Kg in mice and rat, 11 mg/Kg in rabbit but no available human data.[4,6] This research is the preliminary report that study the result of artesunate and mefloquine treatment in pregnant women with quinine resistance P. falciparum infection .

Material and Method

To study the result of artesunate and mefloquine in pregnant women who were infected with quinine resistance P. falciparum. The studied cases were P. falciparum infected pregnant women who had been treated with quinine for 7 days and they still had the parasites in their blood smears. The study-period was during 1 June 1993 to 31 May 1995. The exclusion criteria were cerebral malaria and the mother who did not cooperated. They were counseled about risks and benefit of the drug treatment and they gave their informed consented. Then they were treated with artesunate 2 mg./kg. loading dose and maintenance with 1 mg./kg. every 12 hours intravenously for 5 days and on the 6th day mefloquine 15 mg./kg. loading dose and following with 10 mg./kg. 6 hours orally.[12] The cases were examined and followed up until they delivered and the babies were 12 months old. The babies were tested the development by using Denver developmental screening test[15] in personal-social, fine motor-adaptive, language, gross motor at two, six and twelve months old.

Results

During 1 June 1993 to 31 May 1995 there were 56 pregnant women who were infected with P. falciparum, there were 2 maternal deaths, 15 abortions and 36 cases were treated with quinine successfully, 3 cases matched the criteria for study. Their ages were between 16 to 22 years old. Their parity were third, first and second. They were infected with the malaria at 10, 27 and 33 weeks. The duration before admission were 3-5 days. The third case had acute renal failure and pulmonary edema at the beginning of artesunate treatment. All had shock and hypoglycemia before we treated them with artesunate. The duration of fever after artesunate treatment were 2-3 days. The parasites disappeared 1-2 days after the treatment. Hematocrit values were 22-28 percents. Two to four units of packed red cell were infused to all cases. The thick and thin film blood smears were negative on the 28th day after the treatment. The creatinine clearance of the first and second cases was normal but in the third case it decreased to 23.5 ml/min. before artesunate treatment but it recovered to 80 ml/min on the 7th day and 90 ml/min on the 10th day. The first and second cases received artesunate 2 mg/kg. loading dose and maintenance with 1 mg/kg /day for 5 days but the third patient had 0.5 mg/kg. loading dose and maintenance with 0.25 mg/kg/day for 5 day. The doses of mefloquine were 15 mg/kg on the 6th day and following by 10 mg/kg 6 hour after that in all patient as the figure1-3. The maternal weight gains were 8-12 kilograms. Biparietal diameter(BPD) and abdominal circumference (AC) of the three fetuses were within normal limit as the figure 4-5. The non-stress tests were performed at 34 weeks were

normal in all cases. The babies were born at 39,36 and 39 weeks spontaneously by vaginal route and without oxytocin use. The Apgar scores were 9 at 1 minute and 10 at 5 minutes in all cases. The fetal birth weights were 3000, 2600 and 3000 grams. Their length were 52,48 and 50 cm. The three babies had no congenital anomaly.

At 2, 6 and 12 months old three babies had normal development. The Denver developmental tests (self-care and social, small muscle group, large muscle group, language and hearing test) were within normal limit. The growth curves were normal for 12 months follow-up as the figure 6.

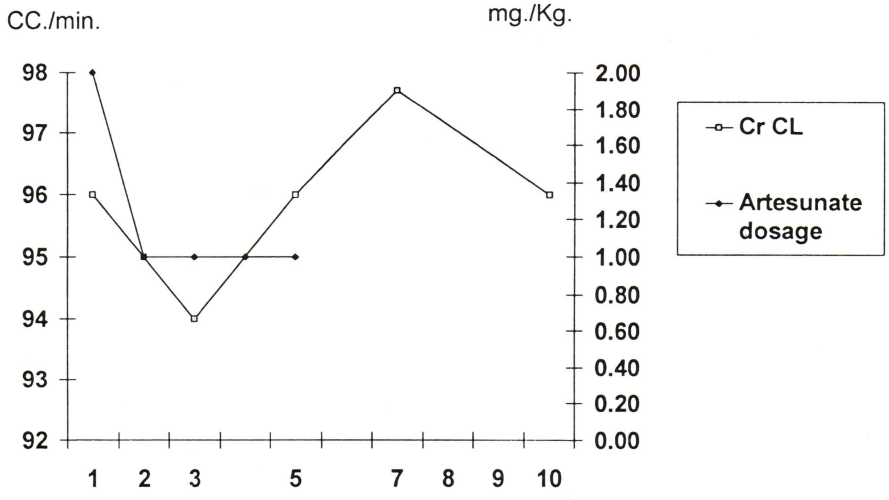

Figure 1. Artesunate dosage & Creatinine clearance (Cr CL) CASE I

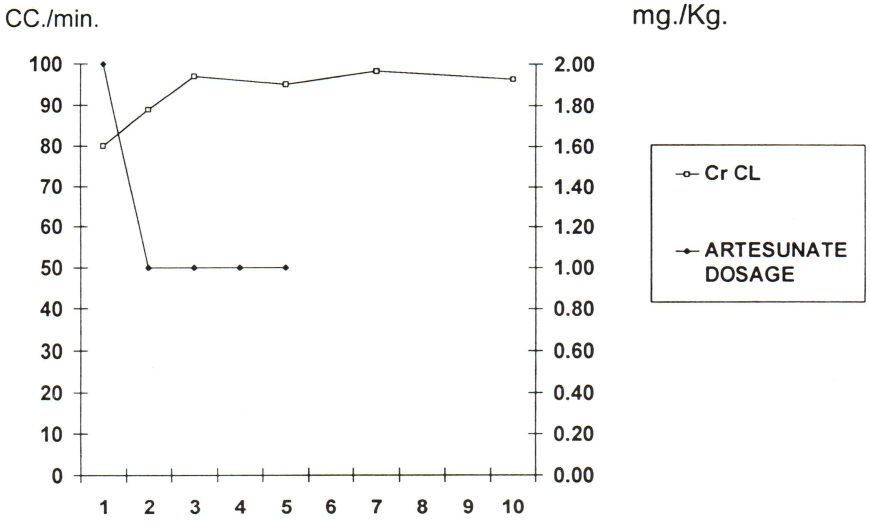

Figure 2. Artesunate dosage & Creatinine clearance (Cr CL) CASE II

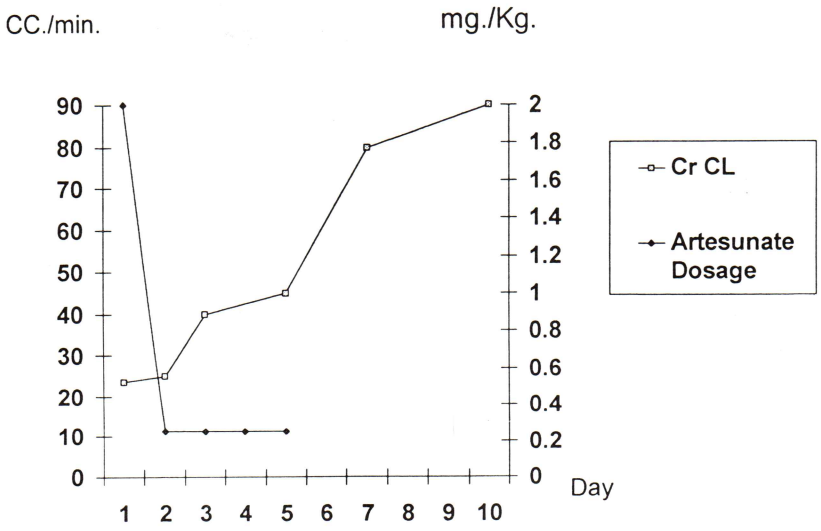

Figure 3. Artesunate dosage & Creatinine clearance (Cr CL) CASE III

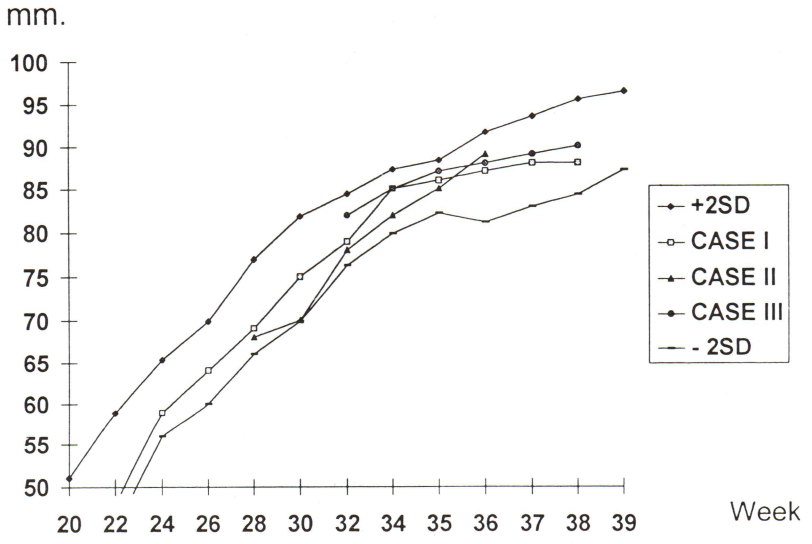

Figure 4. Biparietal Diameter (BPD) CASE I, II, III

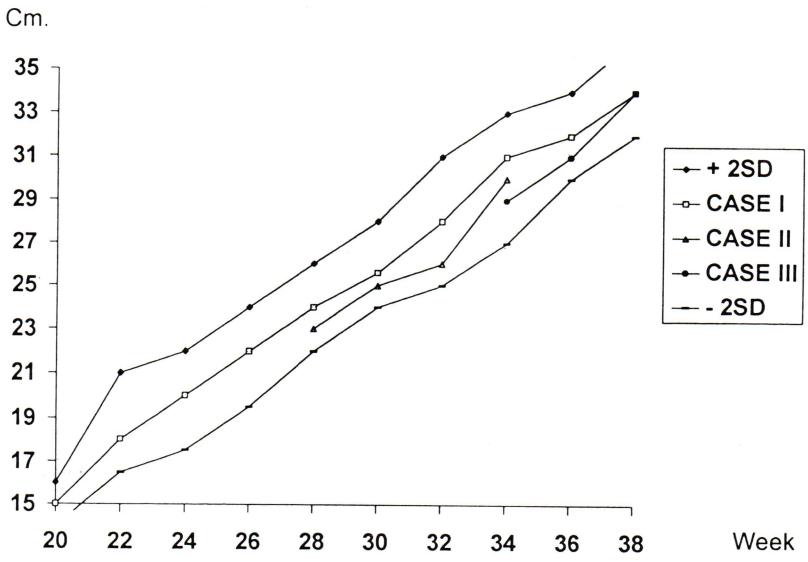

Figure 5. Abdominal Circumference (AC) CASE I, II, III

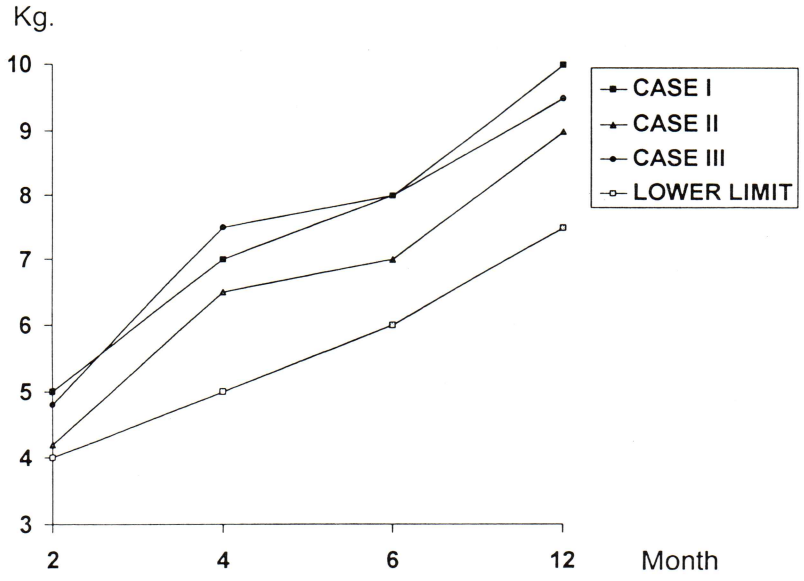

Figure 6. Growth Curve CASE I, II, III

Table 1. The maternal data.

The patients	No 1	No 2	No 3
1. Maternal age (Year)	20	16	22
2. Parity	3	1	2
3. Gestational age (week)	10	27	33
4. Previous malarial infection	YES	NO	NO
5. Duration before treatment (day)	3	3	5
6. Malarial complication			
-Acute renal failure	NO	NO	YES
-Pulmonary edema	NO	NO	YES
-Shock	YES	YES	YES
-Hypoglycemia	YES	YES	YES
7. Blood pressure (mm.Hg)	90/60	80/40	70/50
8. Central venous pressure (Cm.H_2O)	9	16	20
9. Body temperature (°C)	42	39.8	39.3
10. Dopamine use	NO	YES	YES
11. Duration of fever that > 38 °C. after treatment (Day)	2	3	2
12. Duration of parasite presentation in blood smear after artesunate treatment. (Day)	1 22	2 28	2 24
13. Hematocrit (%)	4	1	2
14. Blood transfusion (Unit)	NO	NO	NO
15. Parasite presentation in blood smear on 28^{th} day.			

Table 2. The pregnancy results.

The patients	No 1	No 2	No 3
1. Maternal weight gain (Kg.)	10	8	12
2. New-born baby condition			
Apgar score at 1 minute	9	9	9
Apgar score at 5 minutes	10	10	10
3. Baby birth weight(gm.)	3000	2600	3000
4. Fetal length (cm.)	52	48	50
5. Gestational age at delivery	39	36	39
6. External anomaly	NO	NO	NO
7. Mode of delivery	Vaginal	Vaginal	Vaginal
8. Non stress test at 34 weeks	Reactive	Reactive	Reactive

Discussion

The Quinine-resistance P. falciparum malarial infection will prolong the duration of infection and treatment. The patient in this group will have more complications than Quinine-sensitive group. The pregnant women will be infected with malarial easier than non pregnant women because they have lower immunity and they will die rapidly in case of P. falciparum infection. Therefore early diagnosis and treatment are important.[14] Not only the strain of malarial and maternal condition are considered but also the drug safety to the fetuses are. The malarial infection incidence in the pregnant women who are not in the endemic area but have been to the endemic area is about 0.01-0.1 percents. But in the endemic area as Maehongson province the incidence increases to 4 percents.[2] The prevention of infection can be the a Lamda-Cyhalothrin bednet or drug prophylactic. Chloroquine is useful in pregnant women who are necessary to go to the endemic area temporarily.[16,17] But for a long time, we prefer to the net or Lamda-Cyhalothrin net because they do not have drug-resisted problem. The patients who have ever infected, will have more chance to re-infect than ones who have never, because their environment is suitable for malarial infection. However they have often less severity and complication because they have the malarial immunity.[2] The pregnant women who are infected with malaria, should be diagnosed and prevented its complication by input-output fluid controls early. The correction of imbalance hemodynamic and dose adjustment of malarial drug are also important in management of these patients. Because the patient often have acute renal failure. In the severe cases (algid malaria) the antibiotic together with anti-malarial drug against Gram-negative may be necessary.[3] But all these three cases recovered well after artesunate treatment so we did not use antibiotic. Generally, the treatment of P. falciparum infection in pregnancy is Quinine. However in the case of quinine resisted P. falciparum, artesunate and mefloquine can be used effectively.[3,19,20] Although there is little data of artesunate using in pregnancy and it may affect to animal embryo. (20-27 mg/kg. in rats and 11 mg/kg. in rabbits) but there is no teratogenic effects.[4,6] For mefloquine safety there is a report that no abnormal development in child who his mother have ever gotten it after 12 years follow-up.[21] The first case of study had gotten artesunate since 10 week pregnancy. The development of neural groove, neural tube and neural fold grow to be primary brain vesicle at this period and the musculo-skeleton system at the late 12th week.[22] Artesunate and its metabolite usually effect the neurological tissues. If they were toxic to human embryo, it could have detected the neurological defect in this baby.[23] But the development and growth of this baby are normal after 1 year follow-up. However they should be follow-up further more than this. The non-stress tests were normal in all three cases. This provides that the physiology of cardio vascular, neurological system (autonomous nervous system)[24] are normal. Although the second-case the baby delivered at 36 gestational weeks but its birth weight were 2600 grams. The cause of pre-term delivery in this case might be the severe malarial infection or the anti-malarial drug effect or others cause, it was uncertain. However the baby looked normal. The explanation for this may be the time for follow-up is so short that it can not detect the abnormal, otherwise the artesunate dose is too low (lesser the animal embryonic toxic 10 folds).[4,6] The pregnant woman has the plasma fluid and tissue binding more than the non-pregnant. So blood level of artesunate is relatively lower in pregnancy.[25] The artesunate has the endoperoxide effect that can clear the ring form from blood stream rapidly so the patient can recover fast and has less complications.[26,27] If it were really safe to the fetus, it would be the best anti-malarial drug for the pregnancy. However the vector control and prevent the target from the mosquitoes, bed-net, are the cheaper and safer measurement for pregnant women than chemo-prophylactic or anti-malarial drug. And it is important that the pregnant women should not go to or stay in the malarial endemic area.

Conclusion

The quinine resisted P. falciparum in pregnant women can be treated with artesunate 2 mg./kg.

loading dose and maintenance with 1 mg./kg. every 12 hours intravenously for 5 days and on the sixth day with mefloquine 15 mg./kg. loading dose and following by 10 mg./kg. 6 hours orally for mother life saving. This study could not find the drug adverse effects to the babies after follow-up them for 12 months. But we can not conclude absolutely that artesunate has no effect to the fetus because of few cases. We can only comment that there is a usefulness of artesunate and mefloquine in treatment of quinine resistance P. falciparum in pregnant women and they are rather safe to fetus.

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