Therapeutic Potential of Chloroquine Added to Zidovudine plus Didanosine for HIV-1 Infected Children

Chulapan Engchanil MD*, Pope Kosalaraksa MD**,
Pagakrong Lumbiganon MD**, Viraphong Lulitanond PhD*,
Piyaporn Pongjunyakul MD***, Ruengsin Thuennadee MD****,
Sasithorn Tungsawad MD****, Olan Suwan-apichon MD*****

This paper was presented as a poster presentation in the 2nd IAS conference on HIV Pathogenesis and Treatment, Paris, France, July 13-16, 2003
** Department of Microbiology, Faculty of Medicine, Khon Kaen University, Khon Kaen*
*** Department of Pediatrics, Faculty of Medicine, Khon Kaen University, Khon Kaen*
**** Northeast Regional Hospital for Infectious Diseases*
***** Region 6 Communicable Disease Control, Khon Kaen*
****** Department of Ophthalmology, Faculty of Medicine, Khon Kaen University, Khon Kaen*

Objective: *To evaluate the efficacy and safety of CHQ in a combination treatment with ZDV/ddI in HIV-1-infected children.*
Material and Method: *Fifty five HIV-infected children were randomly enrolled into 3 treatment groups: (I) ZDV + ddI (n = 25); and (II) ZDV + ddI + CHQ (n = 21); and (III) ZDV + ddI experienced children were non-randomly added CHQ (n = 9). Weight, CD4+ T-lymphocytes and plasma HIV-RNA were measured at weeks 0, 8 and 24.*
Results: *Fifteen, 16 and 8 children from Groups I, II and III were evaluated. No significant improvement in the mean Z-score for weight in groups I and II, but a decrease occurred in group III after 6 months of therapy. In group I, II and III, the respective change in the mean CD4+ T-lymphocyte percentage was +6.7, +4.0 and -0.6. The decrease in the plasma HIV-RNA log was 0.9, 1.1 and 0.7, respectively. There was a trend for more nausea/vomiting in group II/III and more opportunistic infections in group III.*
Conclusion: *1. The addition of chloroquine in ZDV/ddI regimen provided no significant improvement in clinical, immunological and virological parameters.*
2. Chloroquine induced immunosuppression and nausea complicated its use.

Keywords: *Chloroquine, Zidovudine plus Didanosine, HIV 1 infected children*

J Med Assoc Thai 2006; 89 (8): 1229-36
Full text. e-Journal: *http://www.medassocthai.org/journal*

The aim of HIV-treatment in children is to decrease by as much as possible the amount of plasma HIV-1-RNA[1-3]. The most effective treatment available today is the highly active anti-retroviral therapy (HAART), usually comprising two nucleoside reverse transcriptase inhibitors (NRTI) and one protease inhibitor (PI)[4]. HAART is beyond the financial means of rural families in developing countries dependent on income from subsistence agriculture or unskilled labor. Chloroquine (CHQ) and hydroxychloroquine (HCQ) are low-cost and easily-obtained drugs that have anti-HIV-1 activity both *in vitro* and *in vivo*[5-14].

In vitro CHQ interferes with the release of HIV-1 virions from infected cells[5] and that extra-cellular virions, derived from CHQ-treated cells, contain very little gp120[6]. HIV-1 particles from HCQ-treated cells were not infectious, possibly due to the blocking

Correspondence to : Engchani C, Department of Microbiology, Faculty of Medicine, Khon Kaen University, Khon Kaen 40002, Thailand. Phone: 043-363-808, E-mail: cengchanil @yahoo.com

mechanism at the post-transcriptional modification of gp120[7]. The CHQ suppressed interleukin-6 production[8] interfered with enzymatic glycosylation of viral gp120[9] and suppressed HIV-1 replication in both recently- and chronically-infected T-cells[10]. They also inhibited *tat*-gene expression that is necessary for virus replication[11]. Both CHQ and HCQ induced apoptosis in peripheral lymphocytes resulting in increased HIV-1 clearance[12-14].

In an *in vivo* study, one HIV-1-infected adult, who had received HCQ for treatment of inflammatory arthritis, showed a 1-log decrease in HIV-1 RNA and an improved mitogen- and antigen-specific immune response with a large decrease in the IL-6 level[15]. In other studies, 37 HIV-infected patients treated with CHQ demonstrated significant decreases in cutaneous candidiasis and plasma HIV-RNA[16,17]. HIV-infected children or infants born to HIV-infected mothers in Uganda treated with CHQ for documented malaria, exhibited longer survival and slower progression of HIV symptoms[18]. If these observations can be confirmed, CHQ might be a useful addition to a low-cost HIV-treatment protocol such as ZDV/ddI.

Objective

To evaluate the efficacy and safety of CHQ in a combination treatment with ZDV/ddI in HIV-1-infected children.

Material and Method

The present study was conducted at Srinagarind Hospital, Khon Kaen University, Thailand, between March 2000 and August 2002. The study protocol was reviewed and approved by the Ethics Committee of Khon Kaen University. Informed consent and assent was obtained from the parents/caregivers and children, respectively.

Inclusion criteria

1) Symptomatic HIV-infected children;
2) Between 1 and 14 years of age;
3) CDC Clinical Category A, B or C;
4) CDC Immunological Category 2 or 3.

Exclusion criteria

1) Active opportunistic and/or serious bacterial infection;
2) Documented hypersensitivity to CHQ or nucleoside analog;
3) Current diagnosis of malignancy; or,
4) Concurrent therapy with a corticosteroid.

Design

This was a prospective, randomized, open, clinical trial for ARV-na ve children: 25 were randomly assigned to Group I (ZDV+ddI) and 21 to Group II (ZDV+ddI+CHQ). Nine clinically stable, ZDV+ddI-experienced, HIV-infected children were non-randomly selected to have CHQ added to their regimen. The dosages were: ZDV 150 mg/m2 body surface area/dose every 8 hours; ddI 90-100 mg/m2 body surface area/dose every 12 hours; and chloroquine 4 mg/kg/dose daily.

Evaluation

After the pre-entry evaluation, these children were followed-up every 4 to 8 weeks. The parameters assessed included: 1) body weight; and, 2) laboratory tests viz- CBC, serum amylase, alanine aminotransferase [at pre-entry then at weeks 4, 8,16 and 24] and CD4+ T lymphocyte percentage and HIV-RNA counts [at weeks 0, 8 and 24].

The CD4 lymphocyte counts and plasma HIV-RNA measurements were performed at the Department of Microbiology, Faculty of Medicine, Khon Kaen University. The CD4+ T-lymphocyte was measured using flow cytometry and three-color immunofluorescence staining, as per Pattanapanyasat et al[19].

Briefly, all panels of fluorochrome-conjugated monoclonal antibodies were purchased from Becton Dickinson. Stained samples were analyzed using a FacsVantage Flow cytometer (Becton Dickinson, San Jose, CA). The plasma HIV-RNA level was measured using a Cobas Amplicor HIV-1Monitor™ Test version 1.5 (Roche Diagnostics, Branchburg, NJ). The limit of detection was 400 copies/mL.

Drug toxicity

Adverse experiences and toxic effects were assessed every four weeks until six months after discontinuation of the medications under the present study. The measurement of the chloroquine level was performed at the Division of Clinical Pharmacology, Rainbow Babies and Children's Hospital, Cleveland, Ohio, using the high performance liquid chromatographic method of Chaulet et al[20], with modifications for smaller sample volumes, need for greater sensitivity and a shorter time for analysis.

The ophthalmologic complications were checked before and 6 months after therapy.

Statistical analysis

Baseline characteristics were compared among treatment groups using the c^2-test. The change in HIV-

RNA and CD4+ T-lymphocyte percentages are presented as means ± SD. Using an ANOVA for independent group and ANOVA with repeated measurement for the baseline values were compared with the measurements taken at weeks 8 and 24. A p-value of less than 0.05 was considered significant.

Results

HIV-infected children (55) were enrolled in the present study: 25 and 21 ARV-na ve children were randomly assigned to Group I (ZDV/ddI) and Group II (ZDV/ddI + CHQ). Nine ZDV + ddI-experienced, HIV-infected children were selected to have CHQ added to their regimen (*i.e.* Group III = ZDV/ddI add CHQ).

The average age and the number of male/female in group I, II and III were 61, 64 and 73 months and 13/12, 7/14 and 6/3, respectively (Table 1). Twelve patients dropped-out of the study because of fatal bacterial pneumonia after enrollment for one week (1 each from Groups I and III), severe nausea vomiting (3 from ddI, 5 from CHQ), anemia and thrombocytopenia (2 from Group I). Four patients were excluded from the final analysis because of the lack of baseline data on HIV-RNA (3 from Group I and 1 from Group II).

Complete clinical, laboratory and follow-up data were available for 16, 15 and 8 patients in Groups I, II and III, respectively. The baseline characteristics were comparable (Table 1) ($p > 0.05$). All patients were HIV-symptomatic children, clinical categories A-C and immunologic category III.

The mean Z-scores of body weight at weeks 0, 8 and 24 were -1.3, -1.3 and -1.7 and -1.5, -1.4 and -1.8 in Group I, II and III, respectively (Table 2).

In Groups I vs II, the mean increase in the CD4+-percentage from baseline at weeks 8 and 24 was 2.7 vs 3.3 and 6.7 vs 4.0, respectively. However, the mean CD4+ T-lymphocyte in Group III had a minimal increase (0.6%) and decrease (-0.6%) from baseline at weeks 8 and 24, respectively. In Group I, II and III, the mean decrease in plasma HIV-1-RNA at weeks 8 vs 24 was 0.7, 0.9 and 0.1 vs 0.9, 1.1 and 0.7, respectively (Table 3).

During the 24 weeks of treatment, opportunistic infections such as oral thrush, diarrhea and chronic otitis media (Table 4), significantly decreased in Group I and II, but increased in Group III.

Serious complications from ZDV, ddI or CHQ during therapy were not encountered. Two patients in Group I had anemia and thrombocytopenia due to ZDV and dropped-out. Twenty patients had nausea and vomiting complications: 5 from ddI and 15 from CHQ. Ten patients dropped-out due to poor drug compliance (2 from AZT, 3 from ddI, 5 from CHQ). Two patients died during the study from bacterial pneumonia, one in Group I and the other in Group III. Both of them had low $CD4^+$ counts (Table 5).

The plasma chloroquine levels of 13 chloroquine treated children were checked at 2.2 ± 0.6 months and the mean plasma level was 93.2 ± 62.8 ng/ml. However, the authors could not evaluate plasma

Table 1. Baseline characteristic of patients before antiretroviral therapy

RegimenBaseline data	ZVD/ddI	ZVD/ddI + CHQ	ZVD/ddIadd CHQ
Number of patients enrolled	25	21	9
Age (months)			
mean ± SD	61.1 ± 28.2	63.5 ± 34.2	72.8 ± 31.1
Body weight (kg)			
mean Z score ± SD*	-1.5 ± 1.3	-1.4 ± 1.1	-1.2 ± 1.4
Height (cm)			
Mean Z score ± SD*	-2.3 ± 2.1	-1.8 ± 2.2	-2.3 ± 1.3
Male/Female	13/12	7/14	6/3
CD4+ T-lymphocyte (%)			
mean ± SD	8.4 ± 5.9	9.6 ± 4.7	6.0 ± 6.0
< 5.0	14	11	5
5.0-9.9	5	5	3
10.0-14.9	6	5	1
Plasma HIV-RNA (log)			
mean ± SD	5.3 ± 0.1	5.4 ± 0.3	5.0 ± 0.5

* Age- and sex-adjusted with reference to Thai children in the general population

Table 2. Body weight and height in Group I, II and III after 8 and 24 weeks of ARV therapy (n = 39)

Study Group[+] Week[+]	Group I ZDV + ddI (n = 16)	Group II ZDV + ddI + CHQ (n = 15)	Group III ZDV + ddI add CHQ (n = 8)	p-value
Body weight, kg				0.934
Mean Z score ± SD*				
Week 0	-1.5 ± 1.3	-1.4 ± 1.1	-1.2 ± 1.4	
Week 8	-1.3 ± 1.2	-1.3 ± 1.1	-1.7 ± 0.9	
Week 24	-1.5 ± 1.2	-1.4 ± 1.1	-1.8 ± 0.9	
Height, cm				0.79
Mean Z score ± SD*				
Week 0	-2.3 ± 2.1	-1.8 ± 2.2	-2.3 ± 1.3	
Week 8	-2.2 ± 2.0	-1.8 ± 2.2	-2.1 ± 1.1	
Week 24	-2.3 ± 2.0	-2.0 ± 2.2	-2.4 ± 1.1	

* Age- and sex-adjusted with reference to Thai children in the general population
[+] No significant difference between group I and group II and group III
No significant difference between week 0, 8 and 24 weeks

Table 3. T-lymphocyte percentage and plasma HIV-RNA in Group I, II, and III at week 0, 8 and 24 of ARV therapy

Study Group	Group I ZDV + ddI (n = 16)	Group II ZDV + ddI + CHQ (n = 15)	Group III ZDV + ddI add CHQ (n = 8)	p-value
CD4+T-lymphocyte (%)				
Mean ± SD				0.372
Week 0	8.4 ± 5.9	9.6 ± 4.7	6.0 ± 6.0	
Week 8	11.1 ± 10.7	12.9 ± 10.9	6.6 ± 7.6	
Week 24	15.1 ±12.6	13.6 ± 11.4	5.4 ± 8.0	
Plasma HIV-RNA (log)				
Mean ± SD				0.868
Week 0	5.3 ± 0.1	5.3 ± 0.3	5.0 ± 0.2	
Week 8	4.6 ± 0.9	4.5 ± 1.1	5.0 ± 0.8	
Week 24	4.4 ± 1.0	4.2 ± 1.0	4.3 ± 1.3	

Table 4. Number of opportunistic infections before and during the 6-month ARV therapy

Regimen Opportunistic Infections	ZDV + ddI		ZDV + ddI + CHQ		ZDV + ddI add CHQ	
	Before	After	Before	After	Before CHQ	After CHQ
Oral thrush	11	3	10	4	-	3
Diarrhea	8	2	6	2	-	3
Pneumonia (bacterial)	5	-	4	-	-	3
Chronic otitis media	4	1	4	2	-	3
Herpes simplex	-	-	2	2	-	1
TB	3	1	3	1	2	-
PCP	1	-	1	-	-	-
Herpes zoster	1	-	-	-	-	-
Salmonella sepsis	-	-	1	-	-	-
Cryptococcal meningitis	2	-	2	-	-	-

Table 5. Number of adverse drug reactions and dropouts during the first 6 months of study

Regimen Complications	ZDV + ddI n = 2	ZDV + ddI + CHQ n = 21	ZDV + ddIadd CHQ n = 9
Number of dropout from study	9	6	1
- death (bacterial pneumonia)	1	-	1
- severe nausea, vomiting	3	5	-
- no baseline HIV-RNA	3	1	-
- anemia, thrombocytopenia	2	-	-
Adverse drug reaction			
anemia with thrombocytopenia	2 (2)*	-	-
nausea, vomiting	5	10	5
- ddI	5 (3)*	4	-
- CHQ	-	6 (5)*	5
rash	3	2	2

* ( ) Number of dropouts from the study

chloroquine levels in children who stopped chloroquine therapy because of side effects such as nausea or vomiting. There was no ophthalmologic complication in all groups after 6 months follow-up.

During three years of follow-up, the mortality rate in each of these groups of patients was about 50% during dual NRTI therapy. Children dying at home from undiagnosed causes were 8/16, 7/15, 5/8 in Groups I, II and III, respectively. The study lasted 24 weeks for each group because of more opportunistic infections and no immunlogic improvement in the chloroquine groups.

Discussion

In general, HIV-infected children receiving anti-retroviral drugs showed clinical and immunological improvement[1,21,22]; that is, they gained weight and their $CD4^+$ levels increased, except those with drug complications that suppressed the immune system.

In the present study, Group III lost weight at week 24 because of severe nausea and vomiting with resultant anorexia (Tables 2, 5). CHQ was the cause of most adverse effects[23] and some patients dropped-out because of these complications. Therefore, since the side effects of chloroquine and ddI are similar, their simultaneous use may cause greater nausea and vomiting (Table 5). These side effects were found less often in Group I. The plasma chloroquine level in the presented children was 93.2 ± 62.8 ng/mL, which is in the common range for anti-malaria therapy[24]. However, the authors could check chloroquine levels only in children who were able to tolerate chloroquine therapy. Therefore, the authors could not demonstrate any correlation between adverse reactions and plasma chloroquine levels. Moreover, 4 mg/kg might be a high dose to continue daily for 24 weeks. Since chloroquine has a half life of 30 days, some children may have had toxic doses after a couple of months. More frequent pharmacokinetic measures would be needed to determine the correct dose of CHQ in HIV-infected children.

For the immunological outcome, the average in $CD4^+$-percentage increased in Group I, slightly increased in Group II but decreased in Group III, possibly because of the immunosuppressant effect[25,26] or the ability to induce apoptosis of CHQ[13]. However, an ineffective dual-antiretroviral regimen and/or advanced clinical and immunological status might be another explanation of the poor immunological response.

For the virological outcome, all three groups showed decreased plasma HIV-1 RNA. This might result from the AZT and ddI in group I, II. However, in Group III, adding chloroquine for ZDV + ddI-experienced children seemed to reduce plasma HIV-RNA levels, mainly from CHQ. The ability to block the production of HIV-RNA has been reported previously[5-14]. One postulated mechanism is the ability of CHQ or hydroxychloroquine to induce apoptosis[12-14]. The increase in apoptosis might in turn result in a decrease of CD4+ T-lymphocyte, which would explain why there was no clinical or immunological improvement and why there was more opportunistic infections in group III (Tables 2, 3). Moreover, the baseline plasma HIV-RNA was high and CD4+ percentages low in Group III, despite ZDV + ddI, perhaps indicating virological and immunological failure (drug resistance) even before adding CHQ (Table 1). Therefore, the solely anti-retroviral property of CHQ is apparently insufficient to overcome its immunosuppressive-inducing effect in

dual-NRTI-experienced group with virological and immunological failure (Group III).

Because of the small sample size, the authors were not able to demonstrate any differences in the clinical, immunological and virological outcomes between the children in any of the three groups. However, there was also no trend in the authors' evidence to suggest that the addition of chloroquine with AZT + ddI produces more clinical and immunological benefits in severely immunosuppresed ARV-na ve, HIV-infected children. On the contrary, its use as described in this manuscript, may have led to poorer weight gain and poorer immunologic outcomes in some of these children. The outcomes observed in this pilot study do not encourage the addition of chloroquine to dual NRTI treatment.

Acknowledgments

This study was supported by a grant from Health Frontiers. The authors wish to thank the medical staff who cared for the children, Roche Diagnostic Thailand Ltd for partial support of the plasma HIV-RNA measurement, Dr. Carolyn Myers for doing the chloroquine assays, Dr. Karen Olness as a consultant for this paper and Mr. Bryan Roderick Hamman for his assistance with the English-language presentation.

References

1. Englund JA, Baker CJ, Raskino C, McKinney RE, Petrie B, Fowler MG, et al. Zidovudine, didanosine, or both as the initial treatment for symptomatic HIV-infected children. AIDS Clinical Trials Group (ACTG) Study 152 Team. N Engl J Med 1997; 336: 1704-12.
2. McKinney RE Jr, Johnson GM, Stanley K, Yong FH, Keller A, O'Donnell KJ, et al. A randomized study of combined zidovudine-lamivudine versus didanosine monotherapy in children with symptomatic therapy-naive HIV-1 infection. The Pediatric AIDS Clinical Trials Group Protocol 300 Study Team. J Pediatr 1998; 133: 500-8.
3. Mofenson LM, Korelitz J, Meyer WA III, Bethel J, Rich K, Pahwa S, et al. The relationship between serum human immunodeficiency virus type 1 (HIV-1) RNA level, CD4 lymphocyte percent, and long-term mortality risk in HIV-1-infected children. National Institute of Child Health and Human Development Intravenous Immunoglobulin Clinical Trial Study Group. J Infect Dis 1997; 175: 1029-38.
4. Guidelines for the use of antiretroviral agents in pediatric HIV infection. Centers for Disease Control and Prevention. MMWR Recomm Rep 1998; 47: 1-43.
5. Boelaert JR, Sperber K, Piette J. Chloroquine exerts an additive in vitro anti-HIV type 1 effect when associated with didanosine and hydroxyurea. AIDS Res Hum Retroviruses 1999; 15: 1241-7.
6. Chiang G, Sassaroli M, Louie M, Chen H, Stecher VJ, Sperber K. Inhibition of HIV-1 replication by hydroxychloroquine: mechanism of action and comparison with zidovudine. Clin Ther 1996; 18: 1080-92.
7. Gottlieb RA, Nordberg J, Skowronski E, Babior BM. Apoptosis induced in Jurkat cells by several agents is preceded by intracellular acidification. Proc Natl Acad Sci U S A 1996; 93: 654-8.
8. Jiang MC, Lin JK, Chen SS. Inhibition of HIV-1 Tat-mediated transactivation by quinacrine and chloroquine. Biochem Biophys Res Commun 1996; 226: 1-7.
9. Meng XW, Feller JM, Ziegler JB, Pittman SM, Ireland CM. Induction of apoptosis in peripheral blood lymphocytes following treatment in vitro with hydroxychloroquine. Arthritis Rheum 1997; 40: 927-35.
10. Ornstein MH, Sperber K. The antiinflammatory and antiviral effects of hydroxychloroquine in two patients with acquired immunodeficiency syndrome and active inflammatory arthritis. Arthritis Rheum 1996; 39: 157-61.
11. Sperber K, Chiang G, Chen H, Ross W, Chusid E, Gonchar M, et al. Comparison of hydroxychloroquine with zidovudine in asymptomatic patients infected with human immunodeficiency virus type 1. Clin Ther 1997; 19: 913-23.
12. Sperber K, Kalb TH, Stecher VJ, Banerjee R, Mayer L. Inhibition of human immunodeficiency virus type 1 replication by hydroxychloroquine in T cells and monocytes. AIDS Res Hum Retroviruses 1993; 9: 91-8.
13. Tsai WP, Nara PL, Kung HF, Oroszlan S. Inhibition of human immunodeficiency virus infectivity by chloroquine. AIDS Res Hum Retroviruses 1990; 6: 481-9.
14. Wolvetang EJ, Larm JA, Moutsoulas P, Lawen A. Apoptosis induced by inhibitors of the plasma membrane NADH-oxidase involves Bcl-2 and calcineurin. Cell Growth Differ 1996; 7: 1315-25.
15. Sperber K, Quraishi H, Kalb TH, Panja A, Stecher V, Mayer L. Selective regulation of cytokine secretion by hydroxychloroquine: inhibition of interleukin 1 alpha (IL-1-alpha) and IL-6 in human

monocytes and T cells. J Rheumatol 1993; 20: 803-8.
16. Sperber K, Louie M, Kraus T, Proner J, Sapira E, Lin S, et al. Hydroxychloroquine treatment of patients with human immunodeficiency virus type 1. Clin Ther 1995; 17: 622-36.
17. Neely M, Kalyesubula I, Bagenda D, Myers C, Olness K. Effect of chloroquine on human immunodeficiency virus (HIV) vertical transmission. Afr Health Sci 2003; 3: 61-7.
18. Kalyesubula I, Musoke-Mudido P, Marum L, Bagenda D, Aceng E, Ndugwa C, et al. Effects of malaria infection in human immunodeficiency virus type 1-infected Ugandan children. Pediatr Infect Dis J 1997; 16: 876-81.
19. Pattanapanyasat K, Kyle DE, Tongtawe P, Yongvanitchit K, Fucharoen S. Flow cytometric immunophenotyping of lymphocyte subsets in samples that contain a high proportion of non-lymphoid cells. Cytometry 1994; 18: 199-208.
20. Chaulet JF, Robet Y, Prevosto JM, Soares O, Brazier JL. Simultaneous determination of chloroquine and quinine in human biological fluids by high-performance liquid chromatography. J Chromatogr 1993; 613: 303-10.
21. Husson RN, Mueller BU, Farley M, Woods L, Kovacs A, Goldsmith JC, et al . Zidovudine and didanosine combination therapy in children with human immunodeficiency virus infection. Pediatrics 1994; 93: 316-22.
22. de Mendoza C, Ramos JT, Ciria L, Fortuny C, Garcia FJ, de Jose MI, et al. Efficacy and safety of stavudine plus didanosine in asymptomatic HIV-infected children with plasma HIV RNA below 50,000 copies per milliliter. HIV Clin Trials 2002; 3: 9-16.
23. Tracy JW, Webster LT Jr. Drugs used in the chemotherapy of protozoal infections: malaria. In: Hardman JG, Limbird LE, Molinoff PB, Ruddon RW, Gliman AG, editors. Goodman & Gilman's. the pharmacological basis of therapeutics. 9th ed. New York: McGraw-Hill; 1996: 965-86.
24. Walker O, Dawodu AH, Adeyokunnu AA, Salako LA, Alvan G. Plasma chloroquine and desethylchloroquine concentrations in children during and after chloroquine treatment for malaria. Br J Clin Pharmacol 1983; 16: 701-5.
25. Nishimura M, Hidaka N, Akaza T, Tadokoro K, Juji T. Immunosuppressive effects of chloroquine: potential effectiveness for treatment of post-transfusion graft-versus-host disease. Transfus Med 1998; 8: 209-14.
26. Salmeron G, Lipsky PE. Immunosuppressive potential of antimalarials. Am J Med 1983; 75: 19-24.

การใช้คลอโรควินร่วมกับยาไซโดวูดีนและไดดาโนซีนในการรักษาเด็กที่ติดเชื้อเอชไอวี

จุฬาพรรณ อิ้งจะนิล, ภพ โกศลารักษ์, ผกากรอง ลุมพิกานนท์, วีระพงศ์ ลุลิตานนท์, ปิยะพร พงศ์จรรยากุล, เรืองศิลป์ เถื่อนนาดี, ศศิธร ตั้งสวัสดิ์, โอฬาร สุวรรณอภิชน

วัตถุประสงค์: *เพื่อประเมินประสิทธิผลและความปลอดภัยของคลอโรควิน (CHQ) เมื่อใช้ร่วมกับไซโดวูดีน (ZDV) และไดดาโนซีน (ddI) ในการรักษาเด็กที่ติดเชื้อเอชไอวี*

วัสดุและวิธีการ: *เด็กติดเชื้อเอชไอวี จำนวน 25 และ 21 ราย ถูกสุ่มให้อยู่ในกลุ่มการรักษาด้วย (I) ZDV + ddI และ (II) ZDV + ddI + CHQ นอกจากนี้เด็กที่กำลังได้รับการรักษาด้วย ZDV และ ddI จำนวน 9 รายได้รับ CHQ เพิ่มเข้าไปในสูตรการรักษาโดยไม่มีการสุ่ม (III) มีการประเมินผลการรักษาจากการเปลี่ยนแปลงของน้ำหนัก ระดับภูมิคุ้มกัน (CD4+ T-lymphocyte) และระดับไวรัส (HIV-RNA) ในเลือดในสัปดาห์ที่ 0, 8 และ 24 ของการรักษา*

ผลการศึกษา: *การติดตามประเมินผลเด็กจำนวน 15, 16 และ 8 รายในกลุ่มที่ I, II และ III ตามลำดับ ไม่พบว่ามีความแตกต่างของน้ำหนักเฉลี่ยที่เพิ่มขึ้น (mean Z-score) อย่างมีนัยสำคัญระหว่างเด็กกลุ่มที่ I และ II แต่มีการลดลงของน้ำหนักเฉลี่ยในเด็กกลุ่มที่ III เมื่อ 6 เดือน หลังการรักษา พบการเปลี่ยนแปลงของภูมิคุ้มกัน (CD4+ T-lymphocyte percentage) คือเพิ่มขึ้นร้อยละ 6.7, 4.0 และ -0.6 และมีระดับไวรัส (HIV-RNA) ในเลือดลดลง 0.9, 1.1, 0.7 log ในเด็กกลุ่มที่ I, II และ III ตามลำดับ ในกลุ่มที่ได้รับคลอโรควิน (กลุ่ม II, III) พบมีอาการคลื่นไส้อาเจียนมากกว่า และพบมีการติดเชื้อฉวยโอกาสมากขึ้นในเด็กกลุ่มที่ III*

สรุป: *การเพิ่มคลอโรควินเข้าไปสูตรการรักษาด้วย ZDV + ddI ผลการรักษาไม่ดีขึ้นมื่อเปรียบเทียบตัวชี้วัดทางคลินิก ภูมิคุ้มกันและปริมาณไวรัสในเลือด นอกจากนี้คลอโรควินมีฤทธิ์กดภูมิคุ้มกันและมีผลข้างเคียงทำให้อาเจียน จึงไม่เหมาะที่จะนำมาใช้ร่วมในการรักษาเด็กที่ติดเชื้อเอชไอวี*