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DOSE RESPONSE RELATIONSHIP OF HYDROXYCHLOROQUINE SULPHATE IN THE TREATMENT OF RHEUMATOID ARTHRITIS: A RANDOMISED CONTROL STUDY

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ABSTRACT: Background: RA is an autoimmune disease triggered by faulty immune system and affects various joints of body including wrist and finger. Nowadays slow acting or DMARDs (Disease modifying anti-rheumatoid drugs) are mainstay of treatment in RA. HCQs belong to this group. They are slow acting so they take weeks to months to become effective. HCQ is less effective when compared to gold or penicillamine but its tolerance is better than other DMARDs. **Objective:** 1. To observe a dose-response relationship for hydroxychloroquine (HCQ), in terms of the proportion of patients achieving the Paulus 20% criteria for improvement in patients with rheumatoid arthritis (RA) receiving a 24 week loading regimen of 400, 800, or 1,200 mg HCQ daily. 2. To investigate possible relationships between increased dosage of HCQ and measures of efficacy and toxicity. **Methods:** 422 Patients with RA began a 24-week study comparing 3 different doses of HCQ at 400, 800, or 1,200 mg/day, followed by 18 weeks of open-label HCQ treatment at 400 mg/day. Patients were evaluated at 0, 6 and 18 week to measure the efficacy and adverse reaction of the drug. **Results:** There was a positive correlation between the Paulus 20% improvement criteria response and increased dose of HCQs during weeks 1-6 ($P < 0.001$). Adverse gastrointestinal events were associated with higher HCQ levels ($P \leq 0.001$) during 0-3 weeks. **Conclusion:** There is a weak, but predictable, relationship between increase HCQs dosage and efficacy of treatment with HCQ.

INTRODUCTION: Hydroxychloroquine is generally regarded as a safe and reasonably effective treatment for patients with rheumatoid arthritis, with a recommended daily dose of approximately 400 mg per day. Approximately 70% of patients receiving HCQ have clinical improvement in their disease course.^{1,2}

The onset of action after ingestion of HCQs is gradual. It takes around 4-6 months for maximum efficacy³. Loading dose is quite helpful to achieve higher concentration of drug in blood level and attaining maximal efficacy of the drug⁴.

To evaluate the feasibility of a loading regimen, a 24-week study was conducted with either 400, 800, or 1,200 mg/day of HCQ being given during the first 6 weeks, followed by 18 weeks of open-label treatment with 400 mg HCQ daily⁵. The concentration of HCQ in blood gradually increase and it becomes evident at around 6 week of therapy, which suggest the dose response relationship of hydroxychloroquine sulphate in rheumatoid arthritis.

The most feared complication of HCQ treatment is retinopathy^{6,7} however it is reversible at low doses whereas gastrointestinal (GI) side effects are the most frequent problem reported by patients taking HCQ. This latter complication limits the use of HCQ in some individuals but it mostly occurs at higher doses. The purpose of this study was to investigate efficacy and toxicity of HCQ with increasing dosage.

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MATERIAL AND METHODS: It is a randomized experimental study of 422 people suffering from RA with increased dosage of HCQ (400,800,1200mg) daily. This is a randomized prospective study done at Civil Hospital, Ahmedabad between January 2014 to January 2016.

Inclusion Criteria:

- Patients with known case of RA disease.
- Age ≥18 years
- No concurrent use of DMARDs
- Washout of any previous DMARDs, and minimal (if any) previous use of HCQ;

Exclusion Criteria:

- Pregnancy
- Age >75 years
- Children
- Active inflammatory GI disease

- Significant malignancy within the previous 5 years
- Previous failure to respond to naproxen therapy

Procedure: 422 patients who were ≥18 years of age and who met the Paulus 20% improvement criteria for RA⁸ were included in our study. 422 patients were randomly distributed in 3 groups receiving 400mg, 800mg and 1200mg dose/day.

Paulus criteria includes 20% improvement in 4 out of 6 following measures:

1. Joint tenderness score
2. Joint swelling score
3. ESR(Erythrocyte Sedimentation Rate)
4. Morning stiffness
5. Physician global assessment score
6. Patients global assessment score

Observation and Analysis: Association between increased dosage and improvement in terms of 20% Paulus criteria was found during week 1 and 6.

TABLE 1: ASSOCIATION BETWEEN INCREASED DOSAGE AND IMPROVEMENT

Week 6			
Dose of HCQ per day(mg)	paulus 20% achieved	paulus 20% not achieved	Row Totals
400	84 (97.59) [1.89]	92 (78.41) [2.36]	176
800	78 (74.30) [0.18]	56 (59.70) [0.23]	134
1200	72 (62.10) [1.58]	40 (49.90) [1.96]	112
Column Totals	234	188	422 (Grand Total)

The chi-square statistic is 8.2017. The p-value is .016559. The result is significant at $p < .05$

Adverse events data showed that adverse gastrointestinal events were associated with higher HCQ levels ($P \leq 0.001$) during 0-3 weeks.

TABLE 2: ASSOCIATION BETWEEN INCREASED DOSAGE AND IMPROVEMENT (WEEK 3)

Week 3			
Dose of HCQ per day(mg)	Adverse GI Events+	Adverse GI Events -	Row Totals
400	13 (56.72) [33.70]	163 (119.28) [16.03]	176
800	55 (43.18) [3.23]	79 (90.82) [1.54]	134
1200	68 (36.09) [28.20]	44 (75.91) [13.41]	112
Column Totals	136	286	422 (Grand Total)

The chi-square statistic is 96.1074. The p-value is < 0.00001. The result is significant at $p < .05$.

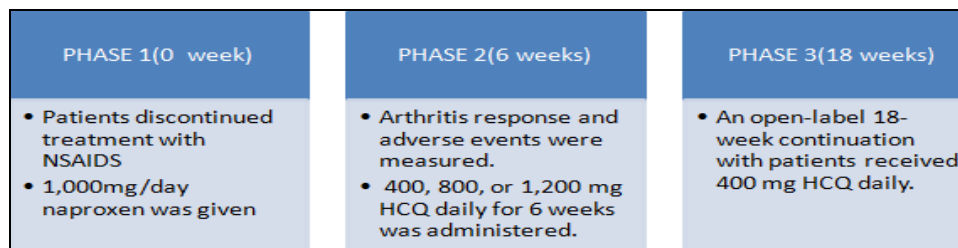


FIG. 1: MEASUREMENT OF BLOOD HCQS LEVEL AT PHASE 1,2,3 OF EVERY PATIENTS AND TREATMENT IS CHANGED ACCORDING TO THAT

DISCUSSION: The main aim of this randomized study is to know the efficacy of increasing dosage of HCQ in treatment of RA and adverse effect with increasing dosage of RA. The proportion of patients in our study achieving the modified Paulus 20% improvement criteria at week 6 was 47%, 58%, and 64% of the patients receiving 400, 800, and 1,200 mg HCQ daily. By comparison, the proportion of patients achieving the Paulus 20% improvement criteria at week 6 was 48%, 58%, and 64% for patients receiving 400, 800, and 1,200 mg HCQ daily, respectively⁹. As indicated in the original report, other response measures (i.e., tender joint count, swollen joint count, ESR, morning stiffness, patient and physician global evaluations) were not dose-dependent at week 6.

There was little evidence of an HCQ dose–adverse event relationship. However, it was found that during weeks 0–3 week, there was a greater incidence of nausea, vomiting, and abdominal pain in the 800 mg and 1,200 mg dose groups as compared with the 400 mg dose group.

In our study, the ability to discern a relationship between effect and dosage of HCQ was enhanced by including larger number of patients in our study.

According to Tino Munster study, the proportion of patients in the subset achieving the modified Paulus 20% improvement criteria at week 6 was 48% (n = 42), 60% (n = 40), and 64% (n= 36) of the patients receiving 400, 800, and 1,200 mg HCQ daily, respectively. There was a positive correlation between the Paulus 20% improvement criteria response and blood DHCQ concentrations during weeks 1–6 (P < 0.001). A potential relationship between ocular adverse events and BDCQ levels was found (P = 0.036). Logistic regression analysis of adverse events data showed that adverse gastrointestinal events were associated with higher

HCQ levels (P = 0.001–0.021) during weeks 1, 2, and 3.¹⁰

CONCLUSION: There is a weak, but predictable, relationship between dose of HCQ and efficacy of treatment with HCQ. There is a positive correlation between gastrointestinal adverse events and elevated blood HCQ concentrations during 0-3 week.

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