1. **Purpose**

This SOP describes the dosing of chloroquine and hydroxychloroquine in the COPCOV study.

2. **Procedure**

2.1. **Tablets & Dose**

- Both drugs are dosed by BASE equivalents
  - Chloroquine phosphate – 250 mg of chloroquine phosphate contains 155 mg of chloroquine BASE
  - Hydroxychloroquine sulphate – 200 mg of hydroxychloroquine sulphate contains 155 mg hydroxychloroquine BASE

The loading dose is 10 mg/kg of BASE on the first day. Thereafter, one tablet of either drug will be given daily.

- The loading dose is given to achieve high plasma concentrations so concentrations in the tissues, including the lung, will also be high.
- The daily dose will maintain high concentrations over time.
- Patients will take the trial medications for 90 days from the blisters they are given by the research team.

2.2. **Loading Dose**

- Weight based dosing uses the actual body weight.
- Well-built muscular individuals with little subcutaneous fat and obese subjects will be dosed by their actual weight but the dose is capped at 5 tablets.

<table>
<thead>
<tr>
<th>Weight kg</th>
<th>Number of tablets</th>
<th>Dose (base) received mg</th>
<th>Dose (base) in mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>40 – &lt;55</td>
<td>3</td>
<td>465</td>
<td>8.61 – 11.63</td>
</tr>
<tr>
<td>55 – &lt;70</td>
<td>4</td>
<td>620</td>
<td>8.99 – 11.27</td>
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<tr>
<td>≥ 70</td>
<td>5</td>
<td>775</td>
<td>≤ 11.07</td>
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</tbody>
</table>

2.3. **How to Give the Loading Dose**

- Give the loading dose with food or a snack to reduce upper gastrointestinal symptoms like anorexia, nausea and epigastric discomfort.
2.4. SIDE EFFECTS

- Both drugs are usually well tolerated and side effects tend to be mild and resolve without the need for treatment. Side effects that subjects may experience on short term use include:
  - abdominal discomfort
  - anorexia
  - nausea
  - vomiting
  - blurred vision/difficulty focusing
  - dizziness
  - headache
  - itching (tends to be more common in individuals of African descent)
  - rashes

2.5. MANAGEMENT OF SUBJECTS WHO HAVE EARLY VOMITING (≤ 30 MINUTES) OF THE LOADING DOSE

- For convenience, we only redose after the first dose (the initial tablets if the loading dose is split).
- If vomiting occurs within 30 minutes of the first dose, the dose should be repeated.
- The subject will need to let the research team know so the repeat dose can be given.
- The repeat dose should be taken when the subject feels better and when he/she takes his/her next meal.
- If vomiting recurs, the subject will be withdrawn from the study because of drug induced vomiting.
- Vomiting any doses after the first dose does not require redosing.

2.6. MISSED DOSES

- To improve adherence the study drug should be taken at a similar time each morning.
  - For those working regular night shifts then taking the study medication in the evening is encouraged.
  - If a participant works a variable shift patterns then the participant should take the medication a similar time each day and not switch mornings/evenings.
If a participant remembers that they have not taken the study medication at their usual time they can take the study medication up until an hour before the next dose would have been scheduled, otherwise the dose is considered missed.
  o A double dose must not be taken.

3. RELATED DOCUMENTATION

  • None

4. SOP VERSION HISTORY

<table>
<thead>
<tr>
<th>Version number/date</th>
<th>Major revisions</th>
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<tbody>
<tr>
<td>1 / 08 Apr 2020</td>
<td>Initial version</td>
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<tr>
<td>2 / 09 Apr 2020</td>
<td>The section “Management of subjects who have early vomiting (≤ 30 minutes) of the loading dose” was shorten and add information that vomiting after 30 minutes does not require redosing).</td>
</tr>
<tr>
<td>3 / 28 Apr 2020</td>
<td>Vomiting issue was updated from “If early vomiting occurs within 30 minutes, the dose should be repeated” to “If early vomiting occurs within 30 minutes of the first dose, the dose should be repeated”.</td>
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</table>
| 4 / 24 Feb 2021     | 1. Vomiting issue was updated from “Vomiting after this time (30 minutes of the first dose) does not require redosing” to “Vomiting any doses after the first dose does not require redosing. ”
  2. The section “2.6” was added. |

5. SOP SIGNOFF

<table>
<thead>
<tr>
<th>Authored by:</th>
<th>Signature:</th>
<th>Date: 09/03/2021</th>
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<tbody>
<tr>
<td>James Callery</td>
<td></td>
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<tr>
<td>Approved by:</td>
<td>Signature:</td>
<td>Date: 09/03/2021</td>
</tr>
<tr>
<td>Will Schilling</td>
<td></td>
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