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Administration of chloroquine or hydroxychloroquine through feeding tubes: new challenges in times of coronavirus pandemic

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ABSTRACT

The use of chloroquine and hydroxychloroquine as off-label treatments for COVID-19 is a resort for critical care patients under enteral nutrition (EN). However, the use of solid pharmaceutical forms of these drugs through feeding tubes can pose a challenge to the health care team. Therefore, we performed a review of literature regarding administration of chloroquine and hydroxychloroquine through feeding tubes. For this end, a search was performed on PubMed and Lilacs database using key-words and free terms referring to drug administration via feeding tubes, and, specifically chloroquine and hydroxychloroquine. Also, a search on Micromedex® database and on the Handbook of Drug Administration via Enteral Feeding Tubes were performed. A total of 1.784 articles were retrieved. However, 4 articles fitted in the inclusion criteria. Two articles exploring the administration of chloroquine via feeding tubes on children with malaria found no difference on clinical results or tolerability when comparing it with oral or intramuscular administration. Other article showed full dispersion of hydroxychloroquine on water after crushing with mortar and pestle. A review found no information regarding the administration of hydroxychloroquine via postpyloric feeding tubes. No information was found on Micromedex® or the consulted Handbook; however, they pointed out the interaction between chloroquine and multivalent ions if coadministered.

Keywords: Enteral Nutrition. Chloroquine. Hydroxychloroquine.

The administration of enteral nutrition (EN) through feeding tubes is the preferred method of nutrition support in the presence of a functional gastrointestinal in critical care patients (Pash, 2018). And the in the midst of a coronavirus pandemic, the number of people demanding critical care and, consequently, EN is growing rapidly (World Health Organization, 2020). In parallel, the use of chloroquine and hydroxychloroquine as off-label treatments for COVID-19 is a resort for critical patients, and also EN users (Colson et al., 2020; Cortegiani et al., 2020; Touret & Lamballerie, 2020), being indicated on current Brazilian documents for hospitalized patients with severe forms of COVID-19 and critical care patients (Brasil, 2020). However, the use of solid pharmaceutical forms of these drugs through feeding tubes can pose a challenge to the health care team.

Therefore, we performed a review of literature regarding administration of chloroquine and hydroxychloroquine through feeding tubes. For this end, a search was performed on PubMed (Medline Library) and Lilacs database (*Literatura Latino-Americana e do Caribe em Ciências da Saúde*). The following search strategies with key-words and free terms were used:

- ("drug" OR "pharmaceutical preparations") AND ("enteral nutrition" OR "nasogastric tube" OR "gastric tube" OR "enteral tube" OR "enteral feed" OR "orogastric tube" OR "nasogastric tube" OR "nasogastric feeding" OR "gastric feeding" OR "enteral feed" OR "nasoenteric tube" OR "oroenteric tube" OR "feed tube" OR "enteric feeding" OR "intubation, gastrointestinal")
- ("chloroquine" OR "hydroxychloroquine") AND ("enteral nutrition" OR "nasogastric tube" OR "gastric tube" OR "enteral tube" OR "enteral feed" OR "orogastric tube" OR "nasogastric tube" OR "nasogastric feeding" OR "gastric feeding" OR "enteral feed" OR "nasoenteric tube" OR "oroenteric tube" OR "feed tube" OR "enteric feeding" OR "intubation, gastrointestinal")

A language limit was used and only articles in English, Portuguese and Spanish were retrieved. The selection of

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articles was composed of three stages: initially by the title of the work; then by analyzing the summary and, finally, by reading the entire text. The articles were selected by two independent researchers and, in case of disagreement between them, the inclusion of the article for full analysis was defined by a third researcher.

The following inclusion criteria were adopted, and only articles that included at least one of the information described below regarding chloroquine or hydroxychloroquine were analyzed in the present study: most appropriate preparation and administration techniques for the medication; the possibility of drug-enteral nutrition interaction occurring; other relevant recommendations related to the administration of the drug via a tube. Studies carried out on animals were excluded during the selection process.

In addition, information on the listed drugs was sought from a tertiary source Handbook of Drug-Nutrient Interactions (Boullata & Armenti, 2010), and from the Drug-Reax® database of Micromedex® (IBM Micromedex, 2020), which has specificity and sensitivity for identifying interactions for the purposes of scientific investigation and use in clinical practice.

A total of 1.784 articles were retrieved. However, 4 articles fitted in the inclusion criteria (Beserra et al., 2017; McIntyre & Monk, 2014; Neequaye et al., 1991; White et al., 1988). A pharmacokinetics study in children with severe malaria found no difference in effectiveness or tolerability between oral administration or administration by nasogastric tube of chloroquine, even in comatose children (White et al., 1988). The initial dose tested was 10 mg/Kg followed by 5 mg/Kg every 6, 24 and 48 hours later (White et al., 1988). A similar comparison was performed in children with cerebral malaria by Neequaye et al. (1991). They compared the intramuscular administration of chloroquine with the administration via nasogastric tube and found no difference in outcomes (cure or mortality) (Neequaye et al., 1991).

Beserra et al. (2017) tested the dispersion of tablets crushed in a mortar and pestle of various drugs and found that the use of this technique for hydroxychloroquine was successful. A review performed by McIntyre & Monk (2014) retrieved no information regarding the administration of hydroxychloroquine though postpyloric feeding tubes.

No specific information regarding interaction with EN were found on the Micromedex® or on the Handbook of Drug-Nutrient Interactions. However, there were recommendations to distance the oral administration of chloroquine from antacid or kaolin by 4 hours (IBM Micromedex, 2020), since there is an indication that multivalent cations could cause adsorption interaction and possible treatment failure with increased risk of resistance (Boullata & Armenti, 2010). For hydroxychloroquine, the Micromedex® brought the recommendation to administer with food or milk (IBM Micromedex, 2020); in the consulted Handbook, however, the interaction between magnesium and hydroxychloroquine was pointed out as a factor for potential reduction on drug absorption or activity (Boullata & Armenti, 2010).

The present review shows the lack of information regarding the administration of chloroquine and hydroxychloroquine via feeding tubes. This probably is due to the fact that those medications are mostly used to treat malaria, a neglected disease known to be frequent only in low- and middle-income countries (Guerra et al., 2010). A small number of articles of interest were retrieved by the research and two of them involved the use of chloroquine in children, which, so far, is known to be the population that is less probable to develop severe cases of COVID-19 and demand the use of medications though feeding tubes (Kelvin & Halperin, 2020).

On the other hand, the in vitro tests made by Beserra et al. (2017) point out an important factor to be taken in consideration: the solubility of hydroxychloroquine after trituration. In Brazil five pharmaceutical specialties are currently registered on Anvisa (Brazilian regulatory agency – *Agência Nacional de Vigilância Sanitária*) and all of them are immediate release coated tablets with very similar qualitative composition that are, in theory, of rapid disintegration and dissolution (Agência Nacional de Vigilância Sanitária, 2020). The same is expected for chloroquine, which is also known to be highly soluble in water and, in Brazil, also has the form of immediate release coated tablets (only one pharmaceutical specialty is currently registered on Anvisa) (Agência Nacional de Vigilância Sanitária, 2020; The International Pharmacopoeia, 2019). Therefore, the trituration, solubilization and administration of hydroxychloroquine or chloroquine most probably will not be a challenge, even though pharmacokinetic studies on adult population were not performed so far.

However, is important to point out that chloroquine is photosensitive and, therefore, should be prepared right before administration (The International Pharmacopoeia, 2019). Also, the lack of studies about the most adequate timing between the administration of chloroquine or hydroxychloroquine and enteral nutrition, and the evidence of potential interaction with polyvalent cations (Boullata & Armenti, 2010) show that is probably more adequate to hold the administration of enteral nutrition before and after drug administration. The development of other studies regarding the administration of those drugs via feeding tubes should be encouraged, especially during the pandemic, since their use is already focus of current multiple randomized controlled trials (Cortegiani et al., 2020).

RESUMO

Administração de cloroquina e hidroxicloroquina via sonda enteral: novos desafios em tempos de pandemia do coronavírus

O uso de cloroquina e hidroxicloroquina como tratamentos *off-label* para o COVID-19 em tempos de pandemia por coronavírus é um recurso para pacientes de cuidados intensivos em nutrição enteral. No entanto, o uso de formas farmacêuticas sólidas desses medicamentos através de sondas enterais pode representar um desafio para a equipe de saúde. Portanto, realizamos uma revisão da literatura

sobre a administração de cloroquina e hidroxicloroquina via sondas enterais. Para tal, foi realizada uma busca no PubMed e Lilacs, utilizando palavras-chave e termos livres referentes à administração de medicamentos por sonda enteral, e, especificamente, cloroquina e hidroxicloroquina. Também foi realizada uma pesquisa no banco de dados Micromedex® e no *Handbook of Drug Administration via Enteral Feeding Tubes*. Um total de 1.784 artigos foram recuperados. No entanto, 4 artigos se enquadravam nos critérios de inclusão. Dois artigos que exploraram a administração de cloroquina via sondas enterais em crianças com malária não encontraram diferença nos resultados clínicos ou na tolerabilidade quando compararam com a via oral ou intramuscular. Outro artigo mostrou dispersão total de hidroxicloroquina em água após a trituração em almofariz. Uma revisão não encontrou informações sobre a administração de hidroxicloroquina através de sondas de posicionamento pós-pilórico. Nenhuma informação foi encontrada no Micromedex® ou no *Handbook* consultado, apesar de ambos apontarem a interação entre cloroquina e íons multivalentes se coadministrados.

Palavras-chave: Nutrição Enteral. Cloroquina. Hidroxicloroquina.

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