Revista de Ciências Farmacêuticas Básica e Aplicada
Journal of Basic and Applied Pharmaceutical Sciences

Rev Ciênc Farm Básica Apl, 2019;40:e651
ISSN 1808-4532

Extemporaneous compounding for the drugs that may be used in COVID-19 treatment

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To the editor,

Some drugs have been proposed for the treatment of the new coronavirus (SARS-CoV-2 or COVID-19), such as chloroquine, hydroxychloroquine or ivermectin (Caly et al., 2020; Colson et al., 2020). Yet, the efficacy, safety or posology of these drug on the infected population it will be yet to be demonstrated by clinical trials occurring worldwide. Additionally, a study in Wuhan, one of the first places to live the pandemic showed the approximately 3.2% of the patients with COVID-19 required intubation and invasive ventilation during disease course (Meng et al., 2020). Thus, a extemporaneously compounded drug may be necessary in these cases due the lack of liquid pharmaceutical forms of chloroquine, hydroxychloroquine and ivermectin in many countries including Brazil.

Consequently, if the patient's condition demand the extemporaneous compounding for the drugs administration, the healthy team must be aware of the risks of doing this off-label procedure (Logrippo et al., 2017). The pharmacokinetic and pharmacodynamic parameters between the extemporaneous preparation and the original pharmaceutical form may not always be the same and may lead to differences in drug efficacy and/or safety, and can be a risk to patient safety (Donnelly et al., 2009; Batchelor & Marriott, 2015). To provide an extemporaneous technique to ensure drug stability and thus contribute to patient safety culture, a search was performed in the databases ScieELO and Pubmed using the following descriptor: chloroquine or hydroxychloroquine or ivermectin and pharmaceutical preparations or drug stability or extemporaneous compounding.

This search showed that for chloroquine and hydroxychloroquine, the extemporaneous compounding techniques are based on the tablet (or the active pharmaceutical ingredient for chloroquine) comminution followed by the re-suspension with suspending agents, with posterior stability analysis (Table 1). However, it was not found studies showing ivermectin extemporaneous compounding techniques.

Additionally, the use of these drugs to treat COVID-19 may also be seem as an off-label, since none of them followed pre-commercial studies for this use. Thus, the extemporaneous compounding necessary to treat patients with this need may act as an confounding factor for the possible inefficacy or for the adverse drug event.

To date, little is known about the relationship between the extemporaneous preparations and the incidence of adverse drug events although this procedure is quite common in hospitals (Benzi & Mastroianni, 2016). Therefore, if this procedure is necessary to treat COVID-19 infected patients in intubation or invasive ventilation, close clinical care should be provided by the healthy team in order to prevent safety related problems to the extemporaneous compounding of the drugs used.

Table 1 – Extemporaneous compounding techniques for chloroquine and hydroxychloroquine.

Drug	Previous pharmaceutical form	Extemporaneous compounding technique	Storage and stability	Reference
chloroquine	Tablets or active pharmaceutical ingredient (API)	Tablets or API placed in a mortar. Comminution to a fine powder. Addition of suspending agents*[1] in geometric portions, mixing in each addition. Transfer the content to a calibrated bottle and adjust the final volume.	60-90 days under room temperature (20-25 °C) or refrigerated (5 °C). Extemporaneous formulation stored in low-actinic bottles or clear polyethylene terephthalate (PET) with low-density polyethylene foam cap linings.	Allen & Erickson (1998). Ferreira et al. (2016).
hydroxychloroquine	Tablets	Tablets placed in a mortar. Comminution to a fine powder. Re-suspending the powder with suspending agents*[2].	91 days under room temperature (24 ± 2 °C) or refrigerated (4 °C). Extemporaneous formulation stored in amber PET bottles.	McHenry, et al. (2017).

*[1] – Suspending agents used: Ora-Sweet®, Ora-Plus®, Ora-Sweet SF® (Paddock Laboratories), SyrSpend® SF PH4 (Fagron Laboratories) or cherry syrup.
*[2] – Suspending agents used: Oral Mix and Oral Mix SF (Medisca Laboratories). Alternatives suspending formulations can be found in Ferreira (2010).

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Received on April 9th 2020
Accepted on April 13th 2020