Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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EDITORIAL

Adverse drug reactions and ivermectin in COVID-19

In the present issue of Therapies, Campilloa and Faillie, from the clinical pharmacology team at Montpellier Medicine University, France, described adverse drug reactions (ADRs) associated with use of invermectin in patients suffering from coronavirus disease 2019 (COVID-19) [1]. They analyzed ivermectine ADRs recorded in VigiBase®, the World Health Organization's ADR database.

Several results can be highlighted: firstly, a considerable rise in reports with ivermectin with a 2.5-fold increase between 2019 and 2020. Secondly, these ADRs were not clinically insignificant with ''serious'' ADRs involving neurological, gastrointestinal and respiratory systems. Third, harms of these ADRs since ivermectine use was associated with 4 overdoses and 6 deaths [1].

In view of these pharmacovigilance data, the Montpellier authors conclude that great caution should be exercised since ivermectin has not yet demonstrated any clinical efficacy in Covid-19. This has just been confirmed by the TOGETHER clinical trial, a comparative trial versus placebo including more than 3,500 patients, which failed to find any effect of ivermectin on hospital admission due to progression of COVID-19 or of stays in the emergency room of outpatients with an early diagnosis of COVID-19 [2].

Beyond this discussion of the benefits-harms balance of ivermectin in COVID-19, Campilloa and Faillie allow us to remind some basic principles of pharmacovigilance and clinical pharmacology, in addition to those recently published in Therapies by Lechat about COVID-19 [3]:

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- first, importance of fundamental pharmacology (pharmacodynamics and pharmacokinetics) to set up a clinical trial. Pharmacodynamics and pharmacokinetics are the two part of pharmacology. The design of a trial must first be based on a strong foundation of pharmacodynamics with appropriate studies on pre clinical models. However, it is important to consider that data on the sole mechanism of action are not sufficient to justify and start a clinical trial. Contrary to intuitive logic, a sole in vitro effect of a drug on an enzyme, a target, in a Petri dish or other molecular or viral models does not mean that this drug will be effective in sick humans. In addition to pharmacodynamics, pharmacokinetics must also mandatory be taken into account, particularly active concentrations and accessibility of the drug on its target. Unfortunately, several drugs proposed in 2020-21 in COVID-19 were only active at high doses impossible to reach in humans (for the example of hydroxychloroquine [4]). Pharmacological expertise, with its dual valence of pharmacodynamics and pharmacokinetics, is therefore essential before any application to humans can be considered. If this basic rule is not followed, there is a risk of ineffectiveness as well as serious and unknown ADRs in a potentially fatal disease;
- second, importance of clinical pharmacology. Pharmacokinetics, pharmacodynamics and mechanism of action knowledge are important but not sufficient. Pharmacodynamic properties and mechanism of action of ivermectin are well known. Ivermectin immobilizes parasites, inducing muscle paralysis of these parasites. Ivermectin binds to glutamate-activated chlorine channels in nematode nerve or muscle cells, inducing hyperpolarization by increasing intracellular chloride concentration leading to paralysis [5]. This mechanism of action may account for possible in vitro effect on the coronavirus, but this experimental pharmacodynamic action must absolutely be verified in clinical pharmacology by clinical trials: these clinical trials are the only way that allows conclusions to be drawn. It is also important that these clinical trials are well designed and well conducted. Here again, the expertise of the clinical pharmacologist is crucial. Establishing the transferability of these in vitro effects to clinical evaluation is essential: this is the work of clinical pharmacologists. ''Mechanism of drug action cannot take the place of action'';
- importance of an individualized pharmacovigilance for each disease. ADRs do not depend solely on the drug but above all, on the patients' field. As Winifred Castle says, ''Medicines are basically safe, sadly doctors as well as patients can be dangerous''. For example, a drug that does not cause heart rhythm disorders in its original indication can be arrhythmogenic in another disease. This truth was unfortunately verified during the COVID-19 pandemic. This comment about the importance of an individualized pharmacovigilance for each disease illustrates the crucial importance of pharmacovigilance expertise and this kind of pharmacovigilance study as performed by Campilloa and Faillie [1], in order to quantify ADRs in the new indication and according to the terrain.

Finally, respect of these basic and eternal principles of clinical pharmacology should therefore ensure that the unfortunate examples experienced during the COVID-19 epidemic (ivermectin, hydroxychloroquine, etc.) cannot be repeated. It is not reasonable to propose unstudied and therefore potentially dangerous drugs without validated clinical evidence including a sound approach of the benefits-harms balance, even and especially in situations of health crisis or serious or emerging life-threatening diseases.

Disclosure of interest

The author declares that he has no competing interest.

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