(Hydroxy) Chloroquine: Benefits with COVID-19?

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Description

The malaria drugs chloroquine (CQ) and hydroxchloroquine (HCQ) are derivatives of quinine. CQ was first synthesized in 1934 and approved in Switzerland in 1953 (Nivaquine®). Distribution was discontinued in 2019. HCQ received Swiss approval in 1998 and is available as Plaquenil® and as generic HCQ-Zentiva® (1).

Indications

CQ: Prevention and treatment of malaria, lupus erythematosus, rheumatoid arthritis, chronic polyarthritis.

HCQ: chronic polyarthritis, lupus erythematosus, photodermatoses, prevention and treatment of malaria.

Pharmacological effects

CQ accumulates as a weak base in low pH intracellular organelles (2). In the malaria pathogen *Plasmodium falciparum*, CQ inhibits the pH-dependent detoxification of heme, which is produced during the parasitic digestion of haemoglobin (3). In mammalian cells, treatment with CQ has been shown to increase the lysosomal pH (4).

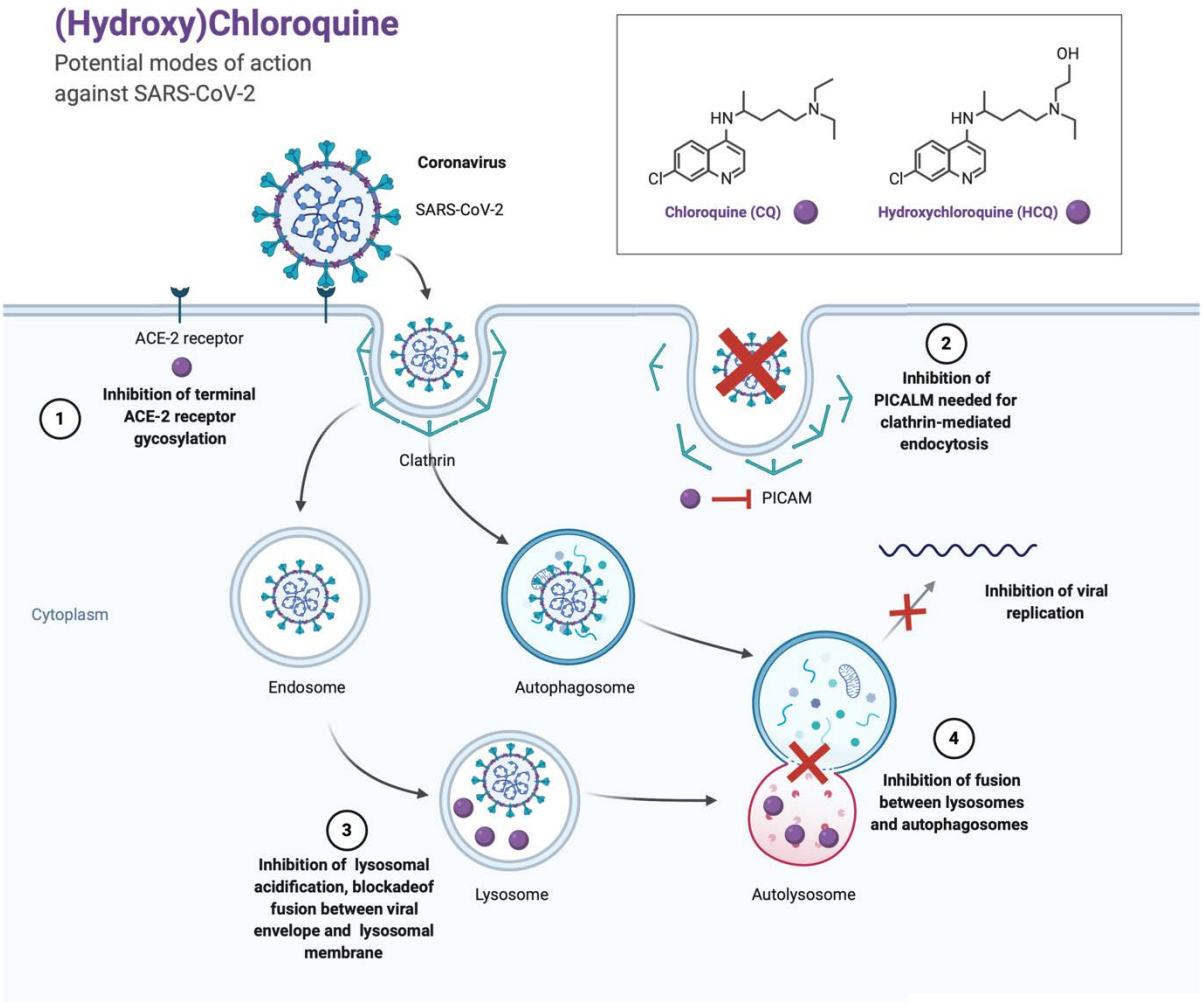
Presumed activity for COVID-19

According to current knowledge, infection with SARS-CoV-2, the COVID-19-causing coronavirus, occurs mainly via respiratory epithelia in the nose and lungs and through interaction with the angiotensinogen converting enzyme 2 (ACE-2) (5). It is suspected that SARS-CoV-2, similar to e.g. the Zika virus, is absorbed into endosomes via a specific endocytosis process (clathrin-mediated endocytosis) (6). To ensure the fusion of the viral and endosomal membrane, the viral spike protein must be cleaved by endosomal enzymes active at low pH (7). If this is not done, the virus remains trapped in the endosomes. Another aspect is the change of the infected host cell to an autophagosomal phenotype (autophagic flux). On the one hand, this mechanism serves to provide energy and nutrients from the cell material (autophagocytosis), on the other hand it serves to defend against viruses or bacteria that have entered the cell (8). However, Zika viruses and also coronaviruses are able to misuse this mechanism for their own replication (9).

It is postulated that CQ acts in several ways on the infection pathway of SARS-CoV-2 (Fig. 1):

1. reduction of viral binding by inhibition of the terminal glycosylation of the ACE-2 receptor (10);

2. inhibition of uptake into the cell by inhibition of PICALM (phosphatidylinositol binding clathrin assembly protein), which is necessary for endocytosis (11);
3. inhibition of lysosomal acidification, blocking the fusion of viral and lysosomal membrane (12);
4. inhibition of autophagy-dependent viral replication, probably by preventing the fusion of lysosomes and autophagosomes (9).



Results of clinical studies (as of April 2020)

The attention of a wider public to the use of CQ/HCQ for the treatment of COVID-19 was triggered by the report of a small study (24 patients) in France (13). This study described positive results in the use of HCQ and the antibiotic azithromycin, which also has an effect on the autophagosomal mechanism. Meanwhile, this study is not considered meaningful due to ethical, technical and scientific errors (14). Another study (80 patients) of the same group (15) has been strongly criticized for the same reasons (16).

A recently published randomized and controlled study of the Shanghai Public Health Clinical Center (China) showed no significant differences between the patients treated with HCQ and the control group (17). Twenty-three clinical trials on the efficacy of CQ

and HCQ that have been applied for and approved (but are not yet active) are currently underway in China (18).

A study (19) with 368 patients at the US Veterans Health Administration Medical Centers, recently submitted for publication, could not show that the use of HQC, alone (97 patients) or in combination with azithromycin (113 patients), reduced the risk of artificial respiration. In contrast, increased mortality was observed in patients treated with HQC alone. A further clinical phase 2b study (81 patients) in Brazil (20), which was to investigate the efficacy of high doses of CQ, had to be discontinued due to increased side effects and mortality (+17%).

The last two studies end with the statement that more, well-founded data are needed to make a statement about the efficacy of treatment with CQ or HCQ. On April 10, a large study (3'000 patients) on the efficacy of HCQ in the treatment and prevention of COVID-19 was initiated in the USA (21). This study called «WHIP COVID-19» will hopefully provide reliable data.

Summary

Even or especially in a crisis situation like the pandemic, science cannot be replaced by wishful thinking or political calculation. Even if indications of the possible efficacy of a drug are discussed, its pharmacological effectiveness and toxicity must be tested in controlled studies and according to strictly scientific criteria. For CQ and HCQ, these are currently not proven for the prevention and treatment of COVID-19. Due to the sometimes severe side effects (retinopathies, severe skin reactions, blood count disorders, central disorders, cramps and cardiac arrhythmia due to prolongation of the QT interval) both active ingredients can only be used under strict clinical control. Furthermore, it must be taken into account that the off-label use of the active ingredients can lead to a bottleneck in the supply of HCQ to patients with recognized applications (lupus, arthritis).

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