






Position paper of Scientific Committees of the Polish Academy of Sciences (Committee on Therapy and Drug Research, Committee on Physiology and Pharmacology) and Polish scientific societies (Polish Society of Pharmacology, Polish Society of Clinical Pharmacology and Therapy, Polish Society of Arterial Hypertension, Working Group on Cardiovascular Pharmacotherapy of the Polish Cardiac Society) on chloroquine in the treatment of COVID-19 patients infected with SARS-CoV-2 and some other aspects of using chloroquine in concomitant diseases

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Artykuł jest tłumaczeniem pracy: Mirowska-Guzel D, et al. Stanowisko Komitetu Terapii i Nauk o Leku PAN (KTiNoL PAN), Komitetu Nauk Fizjologicznych i Farmakologicznych PAN (KNFiF), Polskiego Towarzystwa Farmakologicznego (PTF), Polskiego Towarzystwa Farmakologii Klinicznej i Terapii (PTFKiT), Polskiego Towarzystwa Nadciśnienia Tętniczego (PTNT) oraz Sekcji Farmakoterapii Sercowo-Naczyniowej Polskiego Towarzystwa Kardiologicznego (SFSN PTK) dotyczące chlorochiny w leczeniu zakażenia SARS-CoV-2 powodującego COVID-19 i wybranych aspektów terapii tym lekiem w schorzeniach współistniejących. Folia Cardiol. 2020; 15(2): 114–117. DOI: 10.5603/FC.a2020.0015. Należy cytować wersję pierwotną

Introduction

On March 13, 2020, the Director General of the Office for Registration of Medicinal Products, Medical Devices and Biocidal Products issued a decision regarding an amendment to the marketing authorization for the medicinal

product containing chloroquine phosphate (250 mg tablets). The amendment involved adding a new therapeutic indication, supportive treatment of betacoronavirus infections, such as severe acute respiratory syndrome-related coronavirus (SARS-CoV), Middle East respiratory syndrome-related coronavirus (MERS-CoV), and severe

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acute respiratory syndrome-related coronavirus 2 (SARS-CoV-2), and adding a new dosing schedule for this medicinal product [1]. This decision has been related to the rapid spread of coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2 and the March 11, 2020, declaration of a pandemic state by the World Health Organization. Efforts are underway to develop an effective therapy of COVID-19. Based on the available information, it is supposed that chloroquine may be beneficial as a supportive therapy [2–4].

Chloroquine was first licensed by the U.S. Food and Drug Administration (FDA) in 1949 for the treatment of malaria and intestinal amoebiasis [5]. One chloroquine preparation, 250 mg tablets, is manufactured and available in Poland. In response to the reports of the drug's efficacy and an urgent need to use it, a new indication has been added to the summary of product characteristics (SmPC) [6] and the medication package insert [7]. In SARS-CoV, MERS-CoV and SARS-CoV-2 infection, the recommended dose is 250 mg twice daily for 7–10 days or, if deemed required, 500 mg twice daily for 7–10 days. Regardless of the dose used, the duration of therapy should not exceed 10 days.

Apart from this, chloroquine is licensed in Poland for the following indications:

- prevention and treatment of acute episodes and maintenance treatment of malaria due to *Plasmodium vivax*, *Plasmodium malariae*, *Plasmodium ovale* and chloroquine-susceptible strains of *Plasmodium falciparum* (in practice, the resistance to chloroquine increased largely over the years and currently there are few endemic areas where the drug can be effectively used; of note, it should not be used for the treatment of patients in whom chloroquine prophylaxis was ineffective);
- hepatic amoebiasis and liver abscess due to *Entamoeba histolytica*, usually in combination with drugs active against amoebas in the intestine (chloroquine is used as a second-line drug if metronidazole is ineffective or not available);
- various forms of lupus, including systemic lupus erythematosus, chronic lupus and discoid lupus erythematosus;
- rheumatoid arthritis.

Chloroquine is a 4-aminocholine derivative. Despite years of use, its mechanism of action remains unclear. The drug inhibits intracellular pH-dependent fusion of some viruses (retroviruses and coronaviruses) with the host cell membrane, which determines viral entry to the cell and host infection. Chloroquine inhibits glycosylation of cellular SARS-CoV receptors [8]. It also affects the immune system by inhibiting the synthesis and release of some inflammatory mediators including tumour necrosis factor alpha (TNF- α), interleukin 1, and interleukin 6. Experimental data indicate that chloroquine inhibits lymphocyte proliferation and may directly affect phospholipase A₂, antigen presentation to the immune system cells, release of some

enzymes from cellular lysosome, and release of toxic reactive oxygen species from macrophages [9]. Experimental studies and anecdotal clinical observations indicate that chloroquine reduces the progression of lung interstitial inflammation and fibrosis [10, 11].

Precautions, adverse effects and interactions

Precautions usually relate to the situations when a drug is used long-term, *i.e.*, in this instance more than 3 months. Of note, the recommended duration of SARS-CoV-2 infection therapy with chloroquine is limited to 10 days. Even in these settings, however, the dose should be adjusted in severe renal failure, and the drug should be used with caution in patients with liver failure, including those with alcohol liver disease.

The drug may exacerbate porphyria, psoriasis, and myasthenia. It reduces the seizure threshold and thus should be used with caution in patients with a history of seizures or treated for a seizure disorder. It was shown that chloroquine may induce severe hypoglycaemia, potentially leading to a loss of consciousness, which may be life-threatening. Patients treated with chloroquine should be informed about the risk of hypoglycaemia and related clinical symptoms. If symptoms and signs suggestive of hypoglycaemia (such as tremor, excessive sweating, palpitations, impaired concentration, anxiety, somnolence, nausea, and vomiting) develop during chloroquine treatment, blood glucose level should be measured and the treatment should be adjusted accordingly if required.

A very severe adverse effect of chloroquine is macular retinopathy but this effect is related to the cumulative and not the single dose. However, drug safety in this regard has been shown during pregnancy, even with a long-term treatment (on average 7.2 months with the daily dose of 332 mg) [12]. When prescribing chloroquine, other adverse effects of the drug should also be considered (*e.g.*, vision impairment, complete blood count parameter changes, electrocardiogram [ECG] changes, paraesthesias, hearing impairment and others), which have been reported mostly during long-term therapy and are described in detail in the SmPC [6].

Interactions of chloroquine with other drugs should also be considered, in particular:

- interactions with some anticonvulsant drugs, such as carbamazepine and valproate, leading to attenuation of their effect due to a reduced blood level;
- interactions with potentially proarrhythmic drugs (*e.g.*, amiodarone) which are associated with an increased risk of cardiac arrhythmia, including bradycardia, ventricular arrhythmia and cardiac conduction disturbances; although concomitant use of chloroquine and amiodarone is generally contraindicated, patients receiving

amiodarone should not be excluded from this treatment option, taking into account the lack of effective COVID-19 therapies and a large population of patients treated with amiodarone; ECG monitoring for arrhythmia and QT interval seems a sufficient precautionary measure;

- elevation of blood ciclosporin and possibly digoxin level by chloroquine.

Special patient populations

The drug may be used in the elderly (without dose adjustment) and in children above 14 years of age. In countries where parenteral chloroquine preparations are available, the drug is used in children above 5 years of age. The maximum dose administered parenterally in children is 5 mg/kg of body weight and does not exceed the maximum dose in adults.

Special patient populations include pregnant and lactating women. Mice studies using labelled chloroquine showed that the drug crosses the placenta, with accumulation mostly in the foetal eye tissue. Chloroquine was detected in the foetal eye tissue as late as 5 months after drug discontinuation [6]. The SmPC states that chloroquine should not be used during pregnancy unless in a physician's opinion the potential benefit outweighs the risk for the foetus. When the drug is used short-term for the prevention of malaria, it is believed that the risk associated with contracting malaria outweighs the risk associated with drug administration, which may also be theoretically extrapolated to the SARS-CoV-2 infection, although the foetal sequelae of such an infection have not been determined yet. As a reminder, the dose used for the prevention of malaria is 500 mg weekly during the week preceding a trip to an endemic malaria region, throughout the stay in the region, and for 4 weeks after the return. Taking into account the dosing schedule for SARS-CoV-2 infection, foetal exposure for chloroquine is higher compared to that during the drug use for the prevention of malaria.

When treating rheumatological disease, experts believe that antimalarial drugs may be continued during pregnancy but hydroxychloroquine is preferred [13, 14]. Of note, chloroquine dosing for this indication is similar to that used for the treatment of SARS-CoV-2 infection, but in the latter situation, the treatment duration is limited to 10 days.

Chloroquine penetrates to breast milk. When it is used for the prevention of malaria, its amounts are too small to harm the child but also insufficient for the effective prevention of an infection. Thus, separate prevention measures are needed in a breastfed child. According to the SmPC, patients with rheumatological disease should not breastfeed during long-term use of chloroquine [6]. In the expert recommendations cited above, it was noted that the drug level in breast milk was found to be low (0.6%)

to moderate (14%) compared to the maternal blood level and chloroquine use by breastfeeding mothers was considered acceptable [14].

Additional remarks and information

Recent reports of an effective SARS-CoV-2 viral load reduction with a combined hydroxychloroquine and azithromycin treatment, albeit in very small patient groups [15], may prompt some infectious disease experts to combine chloroquine and azithromycin, particularly in view of transient hydroxychloroquine shortages in Poland. Also in this case, despite contraindications for combined chloroquine and azithromycin treatment (due to a risk of QT interval prolongation on ECG and torsade de pointes arrhythmia), it seems reasonable to consider this a relative contraindication in the settings of 10-day therapy with ECG monitoring.

In general, COVID-19 patients with concomitant cardiovascular disease and/or hypertension in whom chloroquine treatment is initiated do not require modification of antihypertensive drug therapy (withdrawal or substitution of the renin-angiotensin system inhibitors). In addition, the reports of harm associated with the use of some non-steroidal anti-inflammatory drugs (ibuprofen) in this patient group have not been confirmed yet.

Summary

In the current system of medicinal product licensing, the drug information included in the SmPC should be based on properly conducted clinical studies, optimally performed in large patient groups. The safety and efficacy data pertain to a specific licensed preparation, with a specific name, formulation and dosing schedule.

In case of the new indication for chloroquine phosphate, supportive treatment of coronavirus infection, appropriate studies as required by the evidence-based medicine (EBM) could not be performed for obvious reasons. In addition, these data and indications should not be generally extrapolated automatically to hydroxychloroquine although the available literature indicates that the effects of both drugs are similar.

However, our long experience with chloroquine, its well-established safety and efficacy profile during long-term use for other indications in the real-life clinical practice settings, and the lack of alternative COVID-9 therapies, with no prospects of their rapid introduction in the future, coupled with the reports of the drug's efficacy in SARS-CoV-2 infections warrant using chloroquine for the treatment of the latter, with appropriate precautions. In contrast, there have been no sufficiently documented reports of the effectiveness of chloroquine for the prevention of SARS-CoV-2 infection. In view of known adverse effects of the drug during its long-term administration, such prophylactic use is currently

unjustified and potentially hazardous. Prophylactic administration of chloroquine in the healthcare personnel exposed to patients infected with SARS-CoV-2 is only a research hypothesis that will be tested in the future.

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