

Prescribing Tip for Information

Hydroxychloroquine, chloroquine: increased risk of cardiovascular events when used with macrolide antibiotics ; reminder of psychiatric reactions

An [observational retrospective study](#) published in August 2020 compared the **frequency of adverse events** seen in patients initiated on **hydroxychloroquine alone** to those initiated on **sulfasalazine alone** for rheumatoid arthritis. The study also **compared severe adverse events** associated with use of **hydroxychloroquine plus azithromycin with those associated with use of hydroxychloroquine plus amoxicillin**.

Study findings were

- With **short-term use** there was **no excess risk of severe adverse events** seen in patients treated with hydroxychloroquine alone (compared with sulfasalazine), **but longer-term use past 30 days was associated with increased cardiovascular mortality**.
- **Up to 30 days** after the first use of hydroxychloroquine treatment in combination with azithromycin **there was an increased risk of angina or chest pain, heart failure, and cardiovascular mortality compared with the combination of hydroxychloroquine and amoxicillin**.

It is proposed that events could be caused by the **cumulative effects of hydroxychloroquine and azithromycin on the QT interval**, potentiating arrhythmias and cardiac death, or through other additive cardiotoxic effects. Existing evidence suggests both hydroxychloroquine and chloroquine can prolong the QT interval, especially in overdose or when used in combination with other medicines with the potential to induce cardiac arrhythmias. Warnings exist for azithromycin, clarithromycin, and erythromycin to use with caution in patients with a history of QT interval prolongation or when used concurrently in patients receiving other medicine known to cause QT prolongation.

[A recent review](#) of safety data has recommended that product information is amended for hydroxychloroquine and systemic azithromycin medicines to reflect these risks. As other macrolide antibiotics possess similar safety profiles, the risks are considered to apply to concurrent use of hydroxychloroquine and other systemic macrolide antibiotics (clarithromycin or erythromycin) and to use of chloroquine with systemic macrolide antibiotics. It is recommended that similar warnings should also be added to the product information for chloroquine and for systemic clarithromycin or erythromycin.

It is known that cases of cardiomyopathy resulting in cardiac failure have been associated with the use of chloroquine and hydroxychloroquine, in some cases with a fatal outcome. Patients should be monitored and if signs and symptoms of cardiomyopathy occur during treatment with either drug, then treatment should be stopped.

NB - These warnings are not being introduced for topical macrolide products (which are indicated for conjunctivitis or acne), as these products are used at lower doses and with very limited potential for systemic exposure, and do not list cardiovascular events as potential adverse effects associated with their use.

Reminder of previous concerns regarding psychiatric reactions - Hydroxychloroquine and chloroquine have been previously associated with psychiatric reactions, including reports of depression, anxiety, hallucinations, and psychosis. A review in November 2020 recommended updates to the warnings to include a range of psychiatric reactions, including rare cases of suicidal behaviour. It was noted that when psychiatric events occurred, they were typically within the first month of treatment.

Advice for healthcare professionals

- Carefully consider the benefits and risks before prescribing systemic azithromycin or other systemic macrolide antibiotics (erythromycin or clarithromycin) to patients being treated with hydroxychloroquine or chloroquine.
- If there is a clinical need to prescribe systemic macrolide antibiotics with hydroxychloroquine or chloroquine, use caution in patients with risk factors for cardiac events and follow advice in the product information for each medicine
- Be vigilant for psychiatric reactions associated with hydroxychloroquine or chloroquine, especially in the first month of treatment; events have been reported in patients with no prior history of psychiatric disorders.
- Report suspected adverse drug reactions on a [Yellow card](#).

To contact the Medicines Optimisation Team please phone 01772 214320

If you have any suggestions for future topics to cover in our prescribing tips, please contact Nicola.schaffel@nhs.net