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DEPARTMENT OF HEALTH
DRUG OFFICE
DRUG REGISTRATION AND IMPORT/EXPORT CONTROL DIVISION
3/F., Public Health Laboratory Centre,
382 Nam Cheong Street, Kowloon, Hong Kong

29 December 2014

Dear Healthcare Professionals,

Health Sciences Authority:
Risk of hypoglycaemia associated with hydroxychloroquine or chloroquine

Your attention is drawn to the Singapore Health Sciences Authority's (HSA) advice that healthcare professionals should be aware of the risk of hypoglycaemia associated with the use of hydroxychloroquine or chloroquine.

Hydroxychloroquine and chloroquine are anti-malarial drugs used for the suppression and treatment of malaria. Hydroxychloroquine is also indicated for the treatment of rheumatoid arthritis, juvenile chronic arthritis, discoid and systemic lupus erythematosus and dermatological conditions caused or aggravated by sunlight.

Hydroxychloroquine is known to potentiate the hypoglycaemic effects of anti-diabetic agents. However, it has been reported in the literature that the risk of hypoglycaemia with hydroxychloroquine was also observed in patients who were not on concomitant hypoglycaemic agents. Two such case reports are highlighted below in patients who were prescribed hydroxychloroquine for the treatment of rheumatic diseases. In these case reports, hydroxychloroquine had been identified as the most likely cause of hypoglycaemia in these patients.

One overseas case report described a 62-year-old male patient with rheumatoid arthritis who was on sulphasalazine, methotrexate, prednisolone and leflunomide. Two months after hydroxychloroquine 200mg daily was added to his therapy, he developed hypoglycaemia (blood glucose level 10mg/dL or 0.56mmol/L) leading to unconsciousness. This patient was assessed to have developed hypoglycaemia secondary to hydroxychloroquine therapy after all predisposing conditions which could have led to the hypoglycaemic episode (e.g., insulinoma, ethanol intake, oral anti-diabetics, exogenous insulin usage) were ruled out. A second case report involved an 80-year-old female who reportedly had four events of hypoglycaemia leading to abrupt syncope and loss of consciousness. These events had all occurred within the four-month window period during which she was taking hydroxychloroquine 400mg daily. Her concomitant medications did not include any oral anti-diabetics or insulin. Upon discontinuation of hydroxychloroquine, no recurrence of the hypoglycaemia was reported in the 24-month follow-up period.

There was also a published overseas case report of hypoglycaemia associated with the use of chloroquine. In the report, the patient's blood glucose level repeatedly fell below 36mg/dL (or 2mmol/L) despite repeated infusions with dextrose. While the dose and indication for chloroquine use was unknown, a post-mortem toxicological examination found levels of chloroquine to be within the range associated with death from chloroquine poisoning (57.2mg of chloroquine per 100g liver tissue). The authors postulated that the hypoglycaemia was associated with chloroquine poisoning.

The possible mechanisms by which hydroxychloroquine or chloroquine can lead to hypoglycaemia are supported by *in vitro* and animal studies. *In vitro* evidence has shown that chloroquine reduces intracellular insulin degradation, increases intracellular insulin accumulation, slows receptor recycling and stimulates insulin-mediated glucose transport. In animal studies, chronic chloroquine treatment was found to enhance insulin release in rats while treatment of diabetic rats with hydroxychloroquine led to higher insulin levels and lower glucose concentrations.

In October 2013, following the European Medicines Agency's review of information available in EudraVigilance and the literature, it was recommended that the product labelling for hydroxychloroquine and chloroquine should be strengthened on the risk of hypoglycaemia associated with their use. More recently, in July 2014, Health Canada has also concluded from its assessment that there is sufficient evidence to support a causal association between hydroxychloroquine use and the onset of hypoglycaemia, including serious cases involving a loss of consciousness and hospitalisation.

HSA advises healthcare professionals to be vigilant to possible signs and symptoms of hypoglycaemia in patients prescribed hydroxychloroquine or chloroquine, regardless of concomitant use of hypoglycaemic agents. HSA is working with the drug companies to strengthen existing warnings in the local package inserts for hydroxychloroquine- or chloroquine-containing products regarding the additional information on the risk of hypoglycaemia.

Please refer to HSA's website for details:
http://www.hsa.gov.sg/content/hsa/en/Health_Products_Regulation/Safety_Information_and_Product_Recalls/Product_Safety_Alerts/2014/risk-of-hypoglycaemiaassociatedwithhydroxychloroquineorchloroqui.html

In Hong Kong, there are three registered pharmaceutical products containing hydroxychloroquine and one containing chloroquine. All of them are prescription-only medicines. So far, the Department of Health has not received any adverse drug reaction report on the drugs related to hypoglycaemia. The matter will be discussed in the meeting of the Registration Committee of the Pharmacy and Poisons Board. The Department of Health will remain vigilant on safety updates of the two drugs. Healthcare professionals are advised to balance the risk of possible adverse effects against the benefit of treatment.

Please report any adverse events caused by drugs to the Pharmacovigilance Unit of Department of Health (tel. no.: 2319 2920, fax: 2186 9845 or email: adr@dh.gov.hk). For details, please refer to the website at Drug Office under "ADR Reporting": http://www.drugoffice.gov.hk/adr.html. You may wish to visit the Drug Office's website for subscription and browsing of "Drug News" which is a monthly digest of drug safety news and information issued by Drug Office.

Yours faithfully,

(Grant NG)
for Assistant Director (Drug)