

Hydroquinine hydrobromide and hypoglycaemia

Introduction

Hydroquinine hydrobromide (Inhibin®) has been approved for marketing in the Netherlands for the treatment of *nocturnal cramps when treatment with drugs is considered necessary*. It is available in the Netherlands since March 1990 as an over-the-counter drug with a dose of 200 mg with the evening meal and a further 100 mg at bedtime for 14 days. According to the Summary of Product Characteristics (SmPC), hydroquinine hydrobromide can be re-administered when nocturnal cramps return [1]. Traditionally, quinine and its derivatives such as hydroquinine have been used for the prevention of nocturnal cramps but there has been concern over their efficacy and potential for adverse drug reactions (ADRs), especially in the elderly. However, in a randomized, double-blind, placebo-controlled trial, conducted in the Netherlands, 300 mg hydroquinine hydrobromide was considered safe if used for a short period and significantly more effective than placebo in the prevention of frequent, ordinary muscle cramps [2]. The most frequently reported ADRs are nausea, dry mouth, vomiting, and tinnitus [1]. Although hypoglycaemia is not mentioned in the SmPC, Lareb received three spontaneous reports of lowered blood glucose levels associated with the use of hydroquinine.

Drugs are the most frequent cause of hypoglycaemia in adults. Hypoglycaemia is a well-known adverse effect of antidiabetic agents and it may occasionally develop in the course of treatment with drugs used in everyday clinical practice such as analgesics and antibacterials. The incidence of hypoglycaemia induced by non-antidiabetic drugs is unknown, due to several factors, including the lack of a standardized definition of hypoglycaemia, lack of data from clinical trials, under-reporting of adverse drug reactions by physicians, and the lack of evidence of a causal relation between hypoglycaemia and the suspected drug. Drug-induced hypoglycaemia has a substantial clinical impact in terms of mortality. In diabetic patients, it also prevents optimal glycaemic control. Severe hypoglycaemia is considered a contributing factor towards death in 2–6% of diabetic patients [3].

The current observation describes the association between hydroquinine bromide and hypoglycaemia.

Reports

From 18 July 2001 until 14 January 2014, the Netherlands Pharmacovigilance Centre Lareb received a total of 3 reports concerning hypoglycaemia associated with the use of hydroquinine. The reports are described below.

Case A(66560)

This serious spontaneous report from a pharmacist concerns a female aged 70 years and older, with hypoglycaemia (2.1 mmol/L) following administration of hydroquinine for muscle cramps with a latency of 4 hours after start. A few days after cessation the hypoglycaemia was still present. Concomitant medications were simvastatin, glibenclamide, losartan, pantoprazole, temazepam, metformin, salmeterol/fluticasone, tiotropium, insulin glargin, diltiazem. The medical history indicates that the patient has type 2 diabetes mellitus.

Case B(156127)

This serious spontaneous report from a consumer concerns a male aged 70 years and older, with nerve pain in the wrist and hand following administration of hydroquinine for nocturnal muscle cramps with a latency of 2 months after start. The reporter was treated with morphine and also indicated that his blood glucose levels lowered with 3 mmol/L due to hydroquinine; the latency is unknown. The patient recovered after hydroquinine was withdrawn and his blood glucose increased with 3 mmol/L. The medical history indicates that the patient has type 1 diabetes mellitus.

Case C (32512)

This serious spontaneous report from a consumer concerns a female aged 70 years and older who experienced hypoglycaemia after 8 days of treatment for restless legs with hydroquinine 100 mg a day. The patient was treated by withdrawing the hydroquinine and by temporarily changing the insulin medication she used. She recovered without sequelae. Concomitant medication consisted of human insulin, isosorbide mononitrate, diltiazem, triamterene, atenolol, acetylsalicylic acid, and diclofenac.

Although the use of antidiabetic agents in the three cases may weaken the association, one should keep in mind that a lowering in blood glucose level is only noticed by measuring it and only diabetic patients do this regularly.

Other sources of information

SmPC

The SmPC of hydroquinine does not mention hypoglycaemia. Some of the SmPCs of other quinine derivatives, such as quinine and hydroxychloroquine, describe hypoglycaemia as a possible ADR [1,4,5].

Literature

PubMed shows about 150 publications on hydroquinine and only three publications on hydroquinine hydrobromide. None of them mentions hypoglycaemia. Because hydroquinine is a quinoline the search was broadened to quinoline antimalarials. Hypoglycaemia can occur in patients with falciparum malaria, either spontaneously or during treatment with antimalarial agents. Hypoglycaemia induced by quinine may also occur in persons not infected with malaria. It has been reported occasionally following the use of oral quinine for leg cramps [3]. Hydroxychloroquine, in addition to its use as an antimalarial agent, has become one of the most commonly prescribed drugs in the treatment of many rheumatic diseases such as rheumatoid arthritis and systemic lupus erythematosus. In a prospective, multicentre, observational study involving 4905 patients with rheumatoid arthritis, Wasko *et al.* reported that the use of hydroxychloroquine was associated with a reduced risk of diabetes [6]. Hydroxychloroquine may induce hypoglycaemia in both diabetic and non-diabetic patients with rheumatoid arthritis [7,8].

Databases

Table 1. Reports of hydroquinine associated with hypoglycaemia in the Lareb database

| ADR (MedDRA PT) | Drug | Number of reports | ROR (95% CI) |
|-----------------|--------------|-------------------|----------------|
| Hypoglycaemia | Hydroquinine | 3 | 6.8 (2.1-21.3) |

The WHO-database of the Uppsala Monitoring Centre contained only 1 report of hypoglycaemia associated with the use of hydroquinine. The Eudravigilance database contained 2 reports of hypoglycaemia in association with hydroquinine. Due to the low number of reports disproportionality could not be assessed.

Prescription data

Hydroquinine hydrobromide was the second best provided pharmacy only (UA) drug in 2012. Despite the UA status, more than 70% of this agent is prescription based. It is not reimbursed by health insurances, therefore there is no prescription data available via the GIP database from the College for Health Insurers [9].

Mechanism

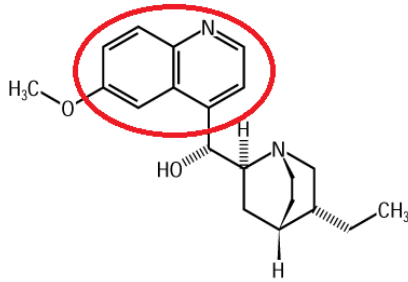
Quinoline antimalarial drugs can stimulate insulin release from the pancreas, probably through the activation of voltage-sensitive calcium channels by inhibition of potassium conductance in both diabetic and non-diabetic patients. In addition to the enhanced insulin release by antimalarial drugs, a marked glucose uptake by parasitized red cells can lead to severe hypoglycaemia in treated patients with falciparum malaria [3].

Octreotide, a somatostatin analogue, is considered to be effective in the treatment of profound hypoglycaemia induced by quinine. It inhibits insulin release and reduces the need for large volumes of intravenous dextrose [3].

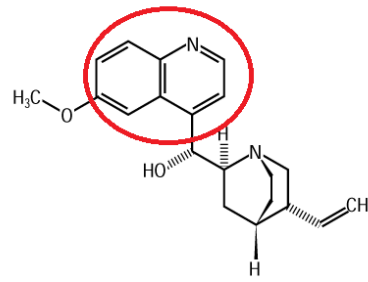
Class effects

Not only quinoline antimalarial agents used for the treatment of malaria and rheumatic disorders are known for their hypoglycaemic effects, other compounds with the 4-quinoline or very similar 4-quinolone nucleus such as fluoroquinolones are also well known for their effect on the blood glucose level. The structure relationship is emphasized by the fact that the first quinolone, nalidixic acid, was isolated as a byproduct from the synthesis of chloroquine [10]. In retrospect, the early and unrecognized structure-activity relationship that we now know exists, might have provided some initial evidence that compounds with this nucleus may be associated with hyperinsulinaemia and hypoglycaemia [11].

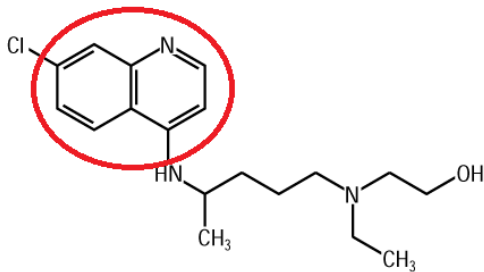
Hydrokinine



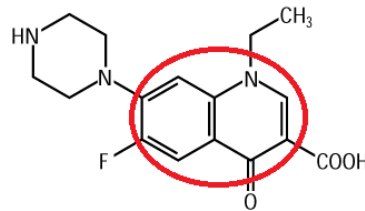
Kinine



Hydroxychloroquine



Norfloxacin



Discussion and conclusion

Lareb received only 3 cases of hypoglycaemia associated with hydroquinine. However, according to the suspected structure-activity relationship of the quinolone and quinoline nucleus with hypoglycaemia it is possible that hydroquinine has the ability to lower blood glucose levels. Additionally, patients, like the one we described in Case B, may use hydroquinine for a longer period than the indicated 2 weeks. Since the drug is obtainable without a prescription in pharmacies and hypoglycaemia can result in unfavourable outcomes, it is important to draw the attention of diabetic patients to this possible adverse drug reaction.

- Hypoglycaemia should be mentioned in the SmPC of hydroquinine hydrobromide

References

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This signal has been raised on May 2014. It is possible that in the meantime other information became available. For the latest information please refer to the website of the MEB www.cbgmeb.nl/cbg/en/default.htm or the responsible marketing authorization holder(s).