

Hydroquinine and photosensitivity reaction

Introduction

Hydroquinine (Inhibin®) is indicated for the treatment of *nocturnal cramps when treatment with drugs is considered necessary*. It increases the contraction as response to single, maximal stimulus that is contributed to the muscle, directly or via the nerve, but it extends the refractory period of the muscle such that the response on the tetanic stimulation is decreased. Hydroquinine also reduces the irritability of the motoric nerve ending inducing decrease of reactions on repeated nerve stimulation and acetylcholine.

Hydroquinine is available in the Netherlands since 1955 and with an altered composition since 1991. It is an over the counter product, but has a dispensing status 'Pharmacy only' 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 can be re-administered when nocturnal cramps return [1;2].

The most frequently reported ADRs are nausea, dry mouth, vomiting, dyspepsia, diarrhoea, unrest and tinnitus [1]. Photosensitivity reactions are not mentioned in the SmPC, Lareb received four spontaneous reports of a photosensitivity reaction associated with the use of hydroquinine.

Photosensitivity induced by exogenous agents refers to a process in which chemicals or drugs that are ingested or applied to the skin promote a photosensitivity reaction when the individual is exposed to sunlight. Photosensitivity is usually divided into phototoxic and photoallergic reactions. Phototoxic and photoallergic reactions differ in their clinical features and causative agents. Phototoxicity results from direct tissue or cellular damage following ultraviolet irradiation of a phototoxic agent that has been ingested or applied to the skin. Phototoxicity can occur in any individual in whom an individually sufficient amount of both the chemical or drug and UV radiation is supplied. By contrast, photoallergy is a cell-mediated immune response elicited by small amounts of compound in previously sensitized individuals. Differentiation between both reactions can sometimes be difficult. The majority of drug-induced photosensitivity reactions are phototoxic, but there are also systemic or topical medications that can induce photoallergic reactions [3].

Reports

Between August 1997 and September 2017 Lareb received four reports of photosensitivity associated with the use of hydroquinine.

Table 1. Cases of hydroquinine and photosensitivity in the Lareb database

Number, Sex, Age, Reporter	Suspect drug, dose, Indication for use	Concomitant medication	Reaction	Time to onset, Action with drug, Outcome
A 18307 M, 71 years and older, General practitioner	hydroquinine dragee 100mg 2dd1 Movement disorder		photosensitivity reaction hypoacusis	Weeks Dose reduced Unknown
B 20198 F, 51-60 years, Specialist doctor	hydroquinine dragee 100mg 1dd1 Movement disorder	bumetanide doxazosin alfacalcidol temazepam ranitidine epoetin	photosensitivity reaction	1 day Drug withdrawn recovered
C 137456 M, 61-70 years, General practitioner	hydroquinine dragee 100mg, 1dd2 Cramps	carbasalate calcium bisoprolol finasteride isosorbide mononitrate gemfibrozil	photosensitivity reaction	10 days Drug withdrawn Unknown
D 246702, F, 51-60 years, Pharmacist	hydroquinine dragee 100mg, 2dd 2 - 1 Cramps legs	acetylsalicylic acid rosuvastatin metoprolol (succinate) omeprazol	photosensitivity reaction	3 days Dose not changed Recovered/reso lved

Additional information on the cases is given below:

Case A

Burned skin on uncovered skin parts like back of the hand, head, face after about 15 minutes of exposure to the sun. Feverish feeling during exposure to sun. The dose of hydroquinine was decreased to 1dd1 and 3 days later it was withdrawn. The patient's outcome is unknown.

Case B

The patient has constitutional eczema and kidney dialysis. The photosensitivity reaction, reported as photo-allergy, occurred on body parts that were exposed to the sun (neck, face, hands, arms), 1 day after cycling. There was also a slight rash on the remaining (covered part) of the body. The hydroquinine was withdrawn. The reaction was treated with a corticosteroid containing cream/ointment. After 1 week of treatment strong improvement was seen and after 2 weeks the patient had completely recovered. The patient had also recovered from the slight rash.

Case C

There was dermatitis on the sun exposed body parts like forehead, ears and hands. The hydroquinine was withdrawn. The patient was treated with an unknown corticosteroid containing cream/ointment. The patient's outcome is unknown. The medical history indicates prostatic hypertrophy, hypercholesterolemia. The patient has had a myocardial infarction. The patient is used to spend a lot of time outside, and never experienced this reaction before.

Case D

The patient experienced rash three days after start of hydroquinine and following an unknown period after the use of a tanning bed. The patient recovered after two days. When using UV radiation again, while still using hydroquinine, the reaction reoccurred. The patient used a tanning bed before taking the hydroquinine without experiencing a rash.

Other sources of information

SmPC

The SmPC of hydroquinine does not mention photosensitivity reaction nor phototoxic or photoallergic reaction as an adverse drug reaction [1].

Literature

There are no reports of hydroquinine and photosensitivity reaction in the literature. However, quinine and its analogues are known to be able to induce photosensitive reactions. Ferguson et al. describes quinine induced photosensitivity, as an infrequently described adverse effect, reported in four patients. The clinical features suggested a phototoxic effect but laboratory studies indicated that the molecular mechanisms involved are unusual. Clinical and phototest evidence of abnormal photosensitivity persisted for some months after stopping quinine. Dawson draws attention to lichenoid photosensitivity related to the use of quinine for nocturnal cramps. From 1982 until 1991 he saw nine patients affected by it. Oakley et al. describes quinine (among others) as a common photosensitizing drug in the class of drug-induced of photosensitivity [3-6].

Since the structural formulas of both agents are comparable it would therefore be plausible that hydroquinine is also able to induce a photosensitivity reaction.

Databases

Since hydroquinine (Inhibin®) is not available outside the Netherlands, the European database Vigilyze® contains very limited reports on photosensitivity reactions in association with the use of hydroquinine. Vigilyze has 56 ICRS on hydroquinine, resulting from reports from the Netherlands. Only two match the reaction photosensitivity reaction. [7]. It is not clear why the other Dutch cases cannot be found using Vigilyze®, the search tool of the WHO database.

Table 2. Reports of photosensitivity reaction associated with the use of hydroquinine in the Lareb database [8].

Database	Drug	ADR	Number of reports	ROR (95% CI)
Lareb	hydroquinine	Photosensitivity reaction	4	8.5 (3.1 – 23.0)

Prescription data

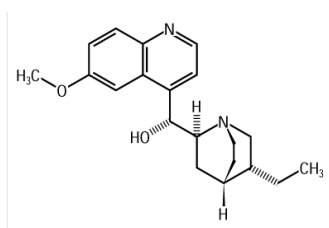
Since hydroquinine is not a prescription drug, no expenditure data are available through the Dutch GIP database.

Mechanism

The mechanism of hydroquinine-induced photosensitivity reactions is not known.

Moore described a Type II (single molecular oxygen) photosensitizing mechanism for quinine and states that a correlation appears to exist with reports of in vivo photosensitivity [9;10].

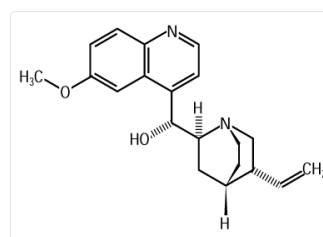
As mentioned, the structural formulas of both hydroquinine and quinine are comparable and it would therefore be possible that hydroquinine is, like quinine, also able to induce a photosensitivity reaction.



Chemische omschrijving (Ch.)

(-)-(R)-[(2S,4S,5R)-5-ethylchinuclidin-2-yl][(6-methoxy-4-chinoly)]methanol

Hydroquinine [2]



Chemische omschrijving (Ch.)

(R)-[(6-methoxychinolone-4-yl)[2S,4S,5R]-5-ethenyl-1-azabicyclo[2.2.2]oct-2-yl]methanol

Quinine [2]

Discussion and conclusion

The Netherlands Pharmacovigilance Centre Lareb received four reports of photosensitivity reaction associated with the use of hydroquinine. These reports concerned two women and two men, with ages varying from 51-60 years to 71 years and older. One patient had a history of constitutional eczema. In two cases the patient was treated with an unknown corticosteroid containing cream/ointment. In one of these cases the patient recovered, in the other case the outcome is unknown. From the patients who were not treated, one patient recovered and from the other case the outcome is unknown. In one of the cases (the most recent report) the reaction reoccurred after recurrent exposure to UV light (tanning bed).

It is difficult to make a distinction between a phototoxic and a photoallergic reaction in our cases.

Since hydroquinine (Inhibin®) is not used outside the Netherlands, there are no data in the WHO or Eudravigilance database other than two of the four Dutch cases.

Photoallergy, phototoxicity or photosensitivity reaction has not been described for hydroquinine in the scientific literature, but photosensitivity is described for quinine which is chemically related to hydroquinine. The available data suggest a causal relation for photosensitivity reactions during usage of hydroquinine.

Reference List

1. SmPC Inhibin® omhulde tabletten 100 mg. (Version date:19-03-2015, access date: 11-12-2017).
2. KNMP Kennisbank (Dutch Pharmacy Database). (Version date: 2017, access date: 11-12-2017).
3. Elmetts, C. A. Photosensitivity disorders (photodermatoses): Clinical manifestations, diagnosis, and treatment. (version date: 29-08-2017, access date: 11-12-2017) Up to Date®.
4. Ferguson J, Addo HA, Johnson BE, Frain-Bell W. Quinine induced photosensitivity: clinical and experimental studies. Br J Dermatol 1987 Nov;117(5):631-40.
5. Oakley AM, Al Aboud AM. Oakley A.M., Al about A.M. Photosensitivity. Stat Pearls (electronic book available through Pub Med, version date: 06-10-2017, access date 11-12-2017).
6. Dawson TA. Side effect of quinine for nocturnal cramps. BMJ 1995 Mar 18;310(6981):738.
7. WHO Global Individual Case Safety Reports database (Vigilyze). (Version date: 2047, access date: 11-12-2017).
8. Lareb databank. (Version date: 2017, access date: 11-12-2017)
9. Moore DE. Photosensitization by drugs. J Pharm Sci 1977 Sep;66(9):1282-4.
10. Moore DE. Drug-induced cutaneous photosensitivity: incidence, mechanism, prevention and management. Drug Saf 2002;25(5):345-72.

This signal has been raised on April 9, 2018. It is possible that in the meantime other information became available. For the latest information, including the official SmPC's, please refer to website of the MEB www.cbg-meb.nl