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Hydroquinine hydrobromide and visual disturbances

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* [1]. It is available on the market as an over-the-counter drug. It is given in 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, hydroquinine hydrobromide can be re-administered when nocturnal cramps return. Quinine and its derivatives such as hydroquinine have been used traditionally 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 to take in the short-term and significantly more effective than placebo in the prevention of frequent, ordinary muscle cramps [2]. The most frequently reported ADRs are nausea, somnolence, dry mouth, insomnia, dizziness, constipation, weakness, nervousness, and sweating. The SPC mentions visual disturbances only during the use of high dosages (which are not specified) as part of cinchonism, a condition produced by the excessive or long-continued use of quinine. Symptoms of cinchonism are well described and consist of headaches, tinnitus, nausea, dizziness, headache and visual disturbances. Acute intoxication with quinine has been associated with blindness, arrhythmias, acute renal failure, and death [3].

Reports

In September 2003, the database of the Netherlands Pharmacovigilance Centre contained seven reports concerning visual disturbances associated with the use of hydroquinine hydrobromide. Details concerning these reports are shown in table 1. All patients had been using hydroquinine hydrobromide in the recommended dosage of 300 mg daily or less. Report G, concerns a long term use of hydroquinine possibly associated with optic neuritis. This report will be discussed in more detail.

Patient G concerns a 51-year-old female who developed papillary edema and optic neuritis after about fifteen years of chronic hydroquinine treatment for a restless legs syndrome in a dosage of 300 mg daily. She had complaints of 'visual obscurations' of both eyes since five years, but had not visited an ophthalmologist for these complaints. On examination, her vision of both eyes was 1.0 (with the patient's own correction). Fundoscopy showed some retinal hemorrhages centered around the optic disc and papillary edema. Neurological examination revealed no explanation for her complaints. The erythrocyte sedimentation rate was slightly increased, but because she suffered from rheumatoid arthritis, this was not considered as related to the visual disturbances. Visual Evoked Potentials and colour vision were not disturbed. On perimetry, an enlarged blind spot was found. Because an optic neuritis due to hydroquinine was diagnosed, this drug was discontinued. Benign intracranial hypertension could be excluded, but nevertheless she was treated with acetazolamide after a couple of months. Although she slightly recovered, an optic neuritis due to hydroquinine could not be ruled out. Concomitant drugs were carbasalate calcium, diclofenac/misoprostol, simvastatin, diazepam and hydrocobamide.

Table 1. Reports of visual disturbances associated with the use of hydroquinine hydrobromide

Patient, Sex, age Reportnr	Daily dosage hydroquinine	medication	Suspected adverse drug reaction	Time to onset; Outcome; Remarks
A M, 67 3051	200 mg	metoprolol acenocumarol nifidepine	visual disturbances (accommodation abnormal)	directly after start; unknown
B F, 71 5577	200 mg	lactulose	blurred vision after each intake of 200 mg	2 weeks; unknown
C F, 49 12195	150 mg	not specified	abnormal vision headache	1 day; unknown
D, F,39 19637	300 mg	not specified	abnormal vision dizziness tinnitus nausea	2 days; recovered; (cinchonism?)
E, F, 68 24765	100 mg	tolbutamide flunarizine	vision decreased (known to have a diabetic retinopathy)	3 weeks; recovered
F, F, 58 26155	200 mg	zopiclon meloxicam nabumeton losartan	vision blurred	Unknown; unknown
G, F,51 39654	300 mg	carbasalate calcium diclofenac/misoprostol simvastatin diazepam hydrocobamine	optic neuritis	Fifteen years after start

Other sources of information

Literature

In a randomized, double-blind, placebo-controlled trial, in which patients used 300 mg hydroquinine daily, visual complaints occurred in one patient in the hydroquinine group (*n*=49).. This adverse drug reaction was considered 'possibly hydroquinine-related' by the investigators. The type of visual complaint was not specified in more detail [2]. Quinine, which is closely related to hydroquinine hydrobromide, seldom causes ocular side effects except in overdose situations. However, in rare instances, hypersensitivity reactions or long-term low dosages can cause significant ocular effects [4].

Databases

On September 25, 2003, the database of the Netherlands Pharmacovigilance Centre contained 76 reports on hydroquinine hydrobrominde, including the above mentioned seven reports concerning visual disturbances. The analysis of the database of the WHO Monitoring Centre was hampered by the fact that no ATC code for hydroquinine hydrobromide was available and only the Dutch brand name could be searched. On September 25, 2003, this database contained a total number of 87 reports on hydroquinine hydrobromide. Four reports concerned abnormal vision. There was one report concerning blindness on quinine hydrochloride.

Mechanism

Information about ocular side effect on hydroquinine is sparse. Since the drug is closely related to quinine, we searched the literature for ocular side effects on the latter drug. According to Fraunfelder *et al.* [4], the etiology of the toxic effect of quinine seems to involve not only an early effect on the outer layers of the retina and pigment epithelium, but probably also a direct effect on retinal ganglion cells and optic nerve fibers [4]. A toxic mechanism may be involved that interferes with cholinergic neurotransmission and causes the acute visual loss. The long term visual

disturbance is either the result of irreversible acute retinal toxicity or secondary to retinal vascular insufficiency [4].

Conclusion

The reports received by the Netherlands Pharmacovigilance Centre suggest that also during the use of hydroquinine hydrobromide in normal dosages, visual disturbances may occur, sometimes even with severe consequences.

References

1. Dutch Summary of Product Characteristics of Inhibin® (version date 14 August 1998). http://www.cbg-meb.nl (access date 25-9-2003).
2. Jansen PH, Veenhuizen KC, Wesseling AI, de Boo T, Verbeek AL. Randomised controlled trial of hydroquinine in muscle cramps. Lancet 1997;349(9051):528-32.
3. Hall AP, Williams SC, Rajkumar KN, Galloway NR. Quinine induced blindness. Br J Ophthalmol 1997;81(12):1029.
4. Fraunfelder FT, Fraunfelder FW, editors.Drug-induced ocular side effect. 5 ed. Boston: Butterworth Heineman; 2001; 1, Anti-Infectives. p. 80-4.