Letters to the MEB

Overview of reports of adverse drug reaction associated with clioquinol

Introduction

Clioquinol was introduced as oral treatment for *amoebiasis* in 1929. In the 1950s the indication was extended to *prevention and treatment of diarrhoea* which led to increased use of clioquinol and therefore more exposure in the population. By the end of the 1960s the first reports from Japan about subacute-myelo-optic-neuropathy (SMON) associated with the use of clioquinol appeared. The first symptoms of SMON are gastrointestinal complaints followed by neurological symptoms. Neurological symptoms only appeared if a total dose of 10-50 gram clioquinol was administered and have not been seen after a 10-day-course with a daily dose of 750mg. Also outside Japan cases of SMON were reported. Many countries, including the Netherlands, banned clioquinol for systemic use and in 1985 all oral formulations of clioquinol were worldwide taken of the market by Ciba-Geigy [1-3].

In the Netherlands, clioquinol for systemic use is no longer registered through the Medicines Evaluation Board. Therefor it is currently only available as a compounded drug. It is used for *amoebiasis and infections with dientamoeba fragilis*. To prevent accumulation of clioquinol, it is advised for adults not to use more than 750mg clioquinol per day for more than 10 consecutive days with a maximum of three courses a year. Between each course the interval should be at least two months [4-6].

In the last year, Lareb has noticed an increase in reports concerning adverse drug reactions associated with the systemic use of clioquinol. The sum of reports in 2011, 2012 and 2013 was 11 reports, while in 2014 alone Lareb received 12 reports. Because of this observation, Lareb wants to inform the Dutch Medicines Evaluation Board and the Dutch Health Care Inspectorate about all reports concerning clioquinol with this general overview.

Reports

From 1 February 2001 until 31 December 2014 the Netherlands Pharmacovigilance Centre Lareb received 33 reports concerning adverse drug reactions associated with the systemic use of clioquinol.

Table 1. Reports of adverse drug reactions associated with the systemic use of clioquinol

Patient, Number, Sex, Age, Source	Drug, daily dose Indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset, Action with drug, outcome
A, 30907, M, 21-30 years, Specialist doctor	clioquinol, 3dd250mg, amoebiasis		rash erythematous	1 day, discontinued, recovered
B, 53425, F, 41-50 years, Pharmacist	clioquinol, 3dd250mg, infection parasitic		Amnesia	1 day after discontinuation, -, recovering
C, 51228, M, 41-50 years, General Practitioner	clioquinol	thiamazole levothyroxine	pallor, confusional state	1 day, discontinued, unknown
D, 66439, F, 51-60 years, Consumer	clioquinol, 3dd250mg, infection parasitic		diarrhoea	2 days, not applicable, not recovered

Patient, Number, Sex, Age, Source	Drug, daily dose Indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset, Action with drug, outcome
E, 71953, M, 51-60 years, Consumer	clioquinol, 3dd1DF±, infection parasitic		neuralgia	5 days, dose not changed, not recovered
F, 74435, M, 41-50 years, Consumer	clioquinol, 3dd 250mg, infection parasitic		rash generalised, pyrexia, hypotension, arrhythmia, hyperglycaemia	7 days, unknown, recovered with sequel
G, 106538, F, 11-20 years, Pharmacist	clioquinol, 3dd140mg, amoebiasis esomeprazole, 1dd10mg		rash generalised, pruritus	clioquinol 3 days, discontinued, recovering esomeprazole 1 day after discontinuation, -, recovering
H, 107531, F, 51-60 years, Consumer	clioquinol, 3dd250mg, amoebiasis	Vogel Passieflora complex*	crying, panic reaction	7 days, dose not changed, recovered
I, 110743, M, 61-70 years, Pharmacist	clioquinol, 3dd250mg, fungal infection	retinol	hypoacusis	unknown, discontinued, unknown
J, 112711, F, 41-50 years, Consumer	clioquinol, 3dd1DF, amoebiasis		visual acuity reduced, neuralgia, proctalgia, vulvovaginal burning sensation	3 days, discontinued, recovering
K, 115760, F, 41-50 years, Consumer	clioquinol, 3dd250mg, amoebiasis		palpitations, nausea, dizziness, diarrhoea, abnormal dreams, headache	1 day, discontinued, not recovered
L, 118942, F, 61-70 years, Pharmacist	clioquinol, 3dd250mg, amoebiasis		flatulence	3 days, dose not changed, recovered
M, 121221, F, 11-20 years, Specialist doctor	clioquinol, 3dd250 mg, gastrointestinal infection		paraesthesia, photopsia, dizziness	8 days, discontinued, recovered
N, 133341, F, 5-7 years, Consumer	clioquinol, 3dd125mg, amoebiasis		abdominal pain, headache, diarrhoea	abdominal pain, diarrhoea 3 days, dose not changed, not recovered headache 4 days, dose not changed, not recovered
O. 136784, F, 41-50 years, Consumer	clioquinol, 3dd250mg	ethinylestradiol, plantago ovata	rash pruritic	1 day, discontinued, recovering
P, 145963, F, 61-70 years, Pharmacist	clioquinol, 3dd250mg	ezetimib, dabigatran, perindopril, verapamil, flecainide, rabeprazole	therapeutic response unexpected, abdominal discomfort	1 day, discontinued, unknown

Patient, Number, Sex, Age, Source	Drug, daily dose Indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset, Action with drug, outcome
Q, 150079, M, 11-20 years, Hospital Pharmacist	clioquinol, 3dd150mg, amoebiasis		pyrexia, abdominal pain, paraesthesia, visual impairment	2 days, discontinued, recovered
R, 152001, F, 11-20 years, Pharmacist	clioquinol, 3dd250mg	ethinylestradiol/ levonorgestrel	rash generalised	10 days, discontinued, recovered
S, 150710, F, 31-40 years, Specialist doctor	clioquinol, 3dd250mg, amoebiasis	salbutamol, ethinylestradiol/ drospirenone	hepatic enzyme abnormal	4 days, discontinued, recovered
T, 154581, M, 31-40 years, General Practitioner	clioquinol, 3dd1DF, diarrhoea		therapeutic response unexpected	2 days, discontinued, recovered
U, 155942, F, 4-6 years, Specialist doctor	clioquinol, 3dd1000mg, blastocystis hominis infection		vomiting, gait disturbance, medication error, subacute myelo-opticoneuropathy. overdose	2 days, unknown, recovering
V, 166720, F, 41-40 years, Pharmacist	clioquinol, 3dd250mg, infection parasitic	spirulina	pharyngeal oedema, dyspnoea	12 hours, dose not changed, not recovered
W, 166542, F, 31-40 years, Consumer	clioquinol, 3dd250mg, amoebiasis		dizziness	1 day, dose not changed, recovered
X, 168923, F, 4-6 years, Consumer	clioquinol, 3dd75mg, amoebiasis		rash	6 days, discontinued, unknown
Y, 178462, F, 41-50 years, General Practitioner	clioquinol, 3dd250mg, amoebiasis	ethinylestradiol/ desogestrel	loss of consciousness	3 days, dose not changed, recovered
Z 180237, F, 71-years and older years, Consumer	clioquinol, 3dd1DF, amoebiasis		varicose vein	2 days, dose not changed, recovered with sequel
AA,181303, F, 31-40 years, General Practitioner	clioquinol, 3dd250mg, amoebiasis		neuralgia, disturbance in attention	10 days, discontinued, not recovered

Patient, Number, Sex, Age, Source	Drug, daily dose Indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset, Action with drug, outcome
AB,182434, M, 31-40 years, Consumer	clioquinol, 3dd250mg, amoebiasis		faeces discoloured, diarrhoea, dry mouth, anorectal discomfort, erectile dysfunction, disturbance in attention, somnolence	faeces discoloured, diarrhoea 2 days, dose not changed, recovered dry mouth, anorectal discomfort, erectile dysfunction 3 days, dose not changed, recovered disturbance in attention, somnolence 3 days, dose not changed, recovering
AC, 183257, M, 61-70 years, General Practitioner	clioquinol, 3dd250mg, amoebiasis	salbutamol, budesonide, mometasone	balance disorder, double vision	1 day, discontinued, recovered with sequel
AD, 183425, F, 61-70 years, Consumer	clioquinol, 3dd250mg, amoebiasis	glutamine, Vogel Dormeasan Forte‡	stomach pain	4 days, dose not changed, recovered
AE, 183723, M, 31-40 years, Consumer	clioquinol, 3dd250mg, amoebiasis		dizziness	5 minutes, dose not changed, recovered
AF, 183726, F, 41-50 years, Consumer	clioquinol, 3dd250mg, amoebiasis		dizziness	10 minutes, dose not changed, recovered
AG, 184278, M, 61-70 years, Specialist doctor	clioquinol, 3dd250mg, amoebiasis	carbasalate calcium, pravastatin, candesartan, pantoprazole, ezetimibe	renal function disorder	11 days, drug withdrawn, outcome unknown

± 1DF = 1 dosage form. Patient E and J reported 3dd250ml as daily dose. It seems unlikely that they actually used this daily dose since a bottle of clioquinol suspension only contains 100ml.
* Vogel® Passieflora-complex contains passiflora, melissa officinalis and valeriana officinalis
‡ Vogel® Dormeasan Forte contains passiflora, melissa officinalis, valeriana officinalis, avena sativa and humulus lupulus.

Patient D used clioquinol for 7 days. Due to the parasitic infection the patient already had diarrhoea which worsened after start of clioquinol. The patient was hospitalised for 4 weeks. A colonoscopy showed inflammations.
Patient E received a second 10-day-course after the first course had no effect. The complaints started during the second course. Her general practitioner diagnosed neuralgia and the patient is being treated with pregabalin, amitriptyline, oxycodone and paracetamol.
Patient F was admitted to the ICU and treated with prednisolone.
Patient H experienced the reactions on the last day of the course. The next day, the reactions disappeared. Fatigue and tensions in her social and professional life could have played a role in the occurrence of the reaction and the use of Vogel® Passieflora-complex aggravated the reactions.
Patient I used the clioquinol during 2 months.
Patient L recovered after using Rennie deflatine® (consisting of calcium carbonate, magnesium carbonate and dimeticon).

The reactions experienced by Patient M could have been caused by hyperventilation after reading the leaflet.
Patient N already had abdominal pain and diarrhoea due to amoebiasis. The patient also had a cold.
Patient O was treated with an unspecified drug.
Patient P experienced an unexpected therapeutic effect, namely better circulation which decreased his bowel problems and he was less confused.
Patient T experienced an unexpected therapeutic effect (the disappearance of his eczema).
Patient U received an accidental overdose; instead of 0.3 gram/day, 3 gram/day was administered.
Patient W recovered 3 days after discontinuation. Possible other causes for the reactions are the abdominal cramps and low blood pressure (100/65 mm/mol).
Patient Y experienced two short periods of absence while driving her car. Her daughter was also treated with clioquinol and had the same reaction.
Patient Z has painful varicose veins. The 7-day-course was finished, but four months later the patient has not recovered.
Patient AA experienced the reactions at the end of the course. Two weeks after the course, the patient has not recovered.
Patient AD had various gastrointestinal complaints due to the parasitic infection, but only experienced stomach cramps while using clioquinol. The patient received pantoprazole which had no effect.
Patient AE experienced dizziness during the first two days of the seven-day-course. The dizziness occurred 5 minutes after administration of the suspension and disappeared during the following hour.
Patient AF experienced dizziness which occurred 10 minutes after every administration of the suspension and disappeared after 4 hours. The last two days of the seven-day-course the dizziness had almost disappeared.
Patient AG used clioquinol for 10 days and experienced renal function disorder with creatinine that increased over a short period from 92 to 182. The patient had low intake because of malaise, other prerenal and renal causes were excluded.

Other sources of information

SmPC
Because clioquinol is no longer registered through the Dutch Medicines Evaluation Board, a Summary of Product Characteristics (SmPC) is not available. There is a leaflet available of the clioquinol oral suspension which is provided by Apotheek De Magistrale Bereider, one of the large compounding pharmacies in the Netherlands. Both the leaflet and the Farmacotherapeutisch Kompas describe the following adverse reactions:

- Green discoloration of tongue, urine and faeces which disappears after the course
- Gastrointestinal complaints, like diarrhoea
- Hyperthyroidism
- Allergic reaction, like pruritus, swelling or rash
- Intake of a cumulative dose of 10-50 gram can lead to subacute-myelo-optico-neuropathy. Symptoms are abdominal pain and diarrhoea followed by sensomotoric disturbance. Also visual disturbances and blindness can occur [5,6].

The Informatorium Medicamentorum and Kinderformularium mention only the risks of SMON when using a cumulative dose of 10-50 gram clioquinol after oral administration [7,8].

Literature

Among other ADRs, Lareb received reports of neurological symptoms associated with the use of clioquinol. Neurotoxicity and SMON associated with the systemic use of clioquinol have been described in various articles [9-16]. Neurological symptoms, such as paresthesia and visual disturbance, are due to degeneration of the long fibres of the spinal cord and the optic nerve [1]. Neurological symptoms only appeared if a total dose of 10-50 gram clioquinol was administered. If a daily dose of 600mg was used neurological symptoms would occur after 48.8 days on average, and twice as fast if the daily dose was doubled. Neurological symptoms have not been reported after a 10-day-course with a daily dose of 750 mg [1,3]. In the Netherlands, cases of neurotoxicity possibly related to clioquinol use

were also described. Drukker *et al*. mentions the occurrence of bilateral optic atrophy in a one and one-half-year-old child possibly a result of administration of 12 gram iodochlorhydroxyquinoline (clioquinol) [17]. Bron *et al.* describes two cases of female patients who both developed severe myeloneuropathy after protracted use of fairly large doses iodochlorhydroxyquinoline [18].
A number of articles published in the last ten years, describe the effect of treatment with clioquinol on Dientamoeba fragilis infections [19-22]. Bosman *et al.* mention that no notable adverse drug reactions were reported in children with Dientamoeba fragilis after treatment with clioquinol (15 mg/kg/day for 5-7 days) [20].

Prescription data

Table 2. Number of patients using clioquinol in the Netherlands between 2009 and 2013 [23]

Drug	2009	2010	2011	2012	2013
Clioquinol	3,732	4,330	5,484	6,968	8,621

Discussion and conclusion

Neurotoxicity and the occurrence of SMON have been associated with systemic administration of clioquinol with doses of 10 gram or higher. If systemic clioquinol is used for treatment of amoebiasis and dientamoebe fragilis infections in the advised dosage regimen (max 750 mg a day for no more than 10 days), no neurological reactions have been described in literature. Nevertheless, Lareb received 16 reports of neurological symptoms associated with the use of clioquinol. The neurological symptoms varied from dizziness to disturbance in attention or visual disturbances. In two reports accumulation of clioquinol could have played a role in the occurrence of the adverse drug reactions. The first report mentions the onset of neuralgia during the second 10-day-course of clioquinol. The second report describes a 4-year-old patient who received an overdose of clioquinol due to a medication error which led to the development of SMON. In other reports which mentioned neurological symptoms, patient used the normal advised dosage regimes. Some reports mention that the complaints recovered after discontinuation of the drug. Others mention that the dose for clioquinol has not changed but the complaints recovered or were recovering at time of reporting. Since clioquinol is given as a course, it can be assumed that these patients finished the course and the complaints recovered during or after the course.

Prescription data show that the amount of clioquinol users in the Netherlands has doubled over the past 5 years. The age of the users is unknown, but Lareb received 5 reports concerning children under 12 years.

Lareb observed an increase in use of systemic administration of clioquinol as well as an increase in reports of possible adverse drug reactions, including neurological symptoms, associated with this usage. Lareb wants to inform the Dutch Medicines Evaluation Board and Health Care Inspectorate about these findings and create awareness for possible signs of neurotoxicity during usage of normal dosage regimes.

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