Lareb
Nederlands Bijwerkingen Centrum
Netherlands Pharmacovigilance Centre

Cisapride and cardiac arrhythmia: what advice should be given on the frequency of ECG-check?

Introduction

Cisapride (Prepulsid®) is a gastro-intestinal prokinetic drug which has been approved for the Dutch market on September 11, 1989. It is known for its risk on *prolongation of the QT-interval and/or severe or fatal cardiac arrhythmias, such as torsade-de-pointes, ventricular tachycardia and ventricular fibrillation.* It is therefore restricted in its prescription and may only be used with certain precautions.

The SPC of Prepulsid® mentions that it *should be prescribed only by experienced medical specialists* and *only for a short period of treatment.* As a special warning is stated: *it is necessary, before prescribing cisapride, to consider if the patient is at risk for severe or even fatal arrhythmias*. And also: *all patients should be laboratory and ECG tested before and during treatment* [1,2].

A recent report to Lareb showed arrhytmia with a latency of a few days after start. The short latency warrants a more specific advice in the SPC concerning ECG checks.

Reports

Up to August 2004, Lareb received 13 reports on cardiac arrhythmias and 1 on sudden death associated with the use of cisapride. The most recent report was from a consumer who stated that even though the pre-treatment ECG was normal and she had no cardiac risk factors, she developed severe tachycardia. The latency was 5 days after start of cisapride, and she was hospitalized on ICU 4 days later. She already had an appointment for a control ECG planned 6 weeks after start of therapy.

Details of the reports are shown in table 1. Of these 14 reports, 9 were classified as serious by the reporter. The latency period is unknown in 5 cases, and varies from hours to 5 days in the other cases. Exceptions to this latency were seen in the cases A,C,K. In case (A) the latency was 3 months after start of cisapride but on the same day that ketoconazol was added. Ketoconazol is known for its interacting effect on cisapride. Case C reports atrial fibrillation, which is a type of cardiac arrhythmia that is not typical for cisapride, with a latency of 17 days. In another case (K) the latency after start of cisapride was 5 months, but palpitations were seen 5 days after addition of amoxicillin/clavulanic acid. An interacting effect of amoxicillin/clavulanic acid on cisapride is not known, there might have been other triggering factors (fever?) involved.
In some cases there was a medical history of cardiac disease, or other suspect medication was reported.

Table 1. reports of cardiac arrhythmias or sudden death associated with the use of cisapride

Patient, Sex, age	Serious	Suspected ADR	Other suspect medication	Time to onset	Outcome at moment of reporting
A: M, 69	yes	cardiac arrhythmia NOS	ketoconazol	hours#	recovery
B: M, 80	yes	death NOS		2 days	fatal
C: F, 55	yes	atrial fibrillation		17 days	recovery with therapy
D: F, 61	yes	arrhythmia		unknown	not recovered
E: M, 74	yes	torsade de pointes	ketanserine	unknown	recovery
F: M	yes	torsade de pointes		4 days	recovery
G: F, 0	yes	QT prolonged		unknown	recovery
H: F, 47	yes	arrhythmia, QT prolonged		5 days	recovery
I: M, 14	yes	QT prolonged	fluconazole, sevoflurane	unknown	recovery
J: F, 51	no	palpitation		unknown	recovery
K: F, 58	no	palpitation	amoxicillin + clavulanic acid	5 days *	recovery
L: F, 62	no	palpitation		1 day	recovery
M: F, 45	no	palpitation		hours	recovery
N: F, 74	no	cardiac arrhythmia NOS	flecainide	hours	recovery

latency 3 months after start cispride, but hours after addition of ketoconazol

* latency 5 months after start cisapride, 5 days after addition of amoxicillin/clavulanic acid.

Other sources of information

Literature

The risk of QT prolongation and ventricular arrhythmias of cisapride has been extensively described in literature and has led to the withdrawal of cisapride from the USA market [3]. Risk factors for arrhythmias are cardiac disease (for instance poor left ventricular function and genetic long-QT syndrome) and the use of concomitant medication that has also an effect on the QT interval, or that inhibits the metabolisation of cisapride through CYP3A4. Most review articles do not give information on latency periods. Wysowski *et al.* describe arrhythmias reported to the FDA from 1993-1999. For 215 individuals without concomitant use of enzyme inhibitor drugs, the median time from use of cisapride to onset of the event was 14 days. Three patients developed the event after one dose and 26 additional patients within 2 days of beginning cisapride. For 126 individuals who got as concomitant medication a cytochrome P450 3A4 enzyme inihibitor drug, the median time from use of cisapride or the inhibitor drug (whichever occurred later) to the onset of the event was 5 days. Two patients developed the problem after one concomitant dose and 24 patients developed the event within 2 days of concomitant dosing [3].
In an overview on drug-related cardiac arrhythmias, Colin Doig states that as a preventive measure in prescribing drugs that are known for their effect on the QT-interval, frequent ECG recording must be performed, in some cases, this will be needed daily [4].

Mechanism

Cisapride is an agonist of serotonin 5HT-4 receptor, that stimulates the physiological release of acetylcholine in the myenteric plexus. It does not stimulate muscarin or nicotin receptors. It does not inhibit the activity of acetyl cholinesterase. After oral administration it is quickly and completely absorbed. Due to first pass effect, the biological availability is 40-50%. Peak plasma levels are reached after 1 to 2 hours. Elimination halftime is approximately 10 hours. With repeated use, the metabolism is not influenced and there is no accumulation. Liver dysfunction can cause a longer elimination halftime, with no influence on the biological availability. The steady state plasma levels are usually higher in elderly patients, the therapeutic dose is the same as in younger patients [1,2].
Cisapride is metabolized through CYP 3A4. Strong inhibitors of this enzyme are contraindicated because they can lead to higher plasma levels of cisapride and thus to a higher risk of cardiac arrhythmias [1,2].
The arrhythmic effect of cisapride is due to a prolongational effect on the repolarization of ventricular cardiac muscle, through an effect on potassium, sodium and calcium channels in the cardiac muscle cell membranes. This can lead to triggered activity, such as polymorphic ventricular tachycardia or torsade-de-pointes [4].

Prescription data

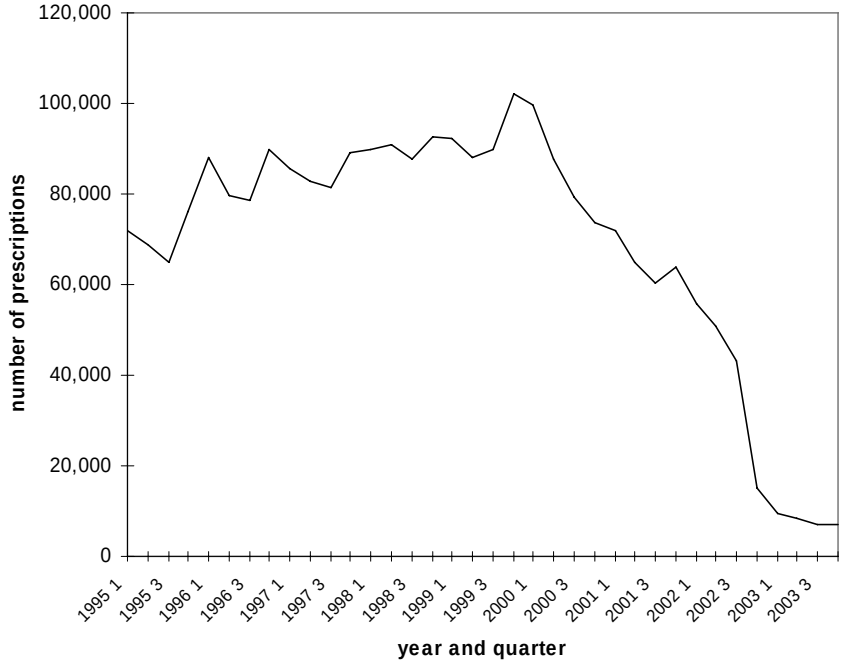

Figure 1. Total number of cisapride prescriptions per quarter since 1995 (Source: GIP College voor Zorgverzekeringen, Diemen).

Conclusion

The SPC of cisapride states that this drug should be prescribed only under certain conditions and with certain precautions. Several cases of cardiac arrhythmias were reported to Lareb. The latency period in these cases indicate that arrhythmias might already take place within days after start of the therapy. Pharmacokinetics of the drug do not contradict such an early effect. Therefore it is necessary to adapt the SPC to advice prescribing physicians on how early and how often they should have an ECG made in their patients.

References

1. Dutch SPC Prepulsid®. (version date 11-02-2003) http://www.cbg-meb.nl/IB-teksten/12466-12467.pdf.
2. Dutch SPC Prepulsid® pediatrie. (version date 11-6-2002) http://www.cbg-meb.nl/IB-teksten/27808.pdf.
3. Wysowski D, Corken A, Gallo-Torres H, Talarico LREM. postmarketing reports of QT prolongation and ventricular arhythmia in association with cisapride and Food and Drug Administration regulatory actions. Am j Gastroenterol 2001;96(6):1698-703.
4. Colin Doig J. drug-induced cardiac arrhythmias, incidence, prevention and treatment. Drug Safety 1997;17(4):265-75.