Lareb
Nederlands Bijwerkingen Centrum
Netherlands Pharmacovigilance Centre

Tramadol and hiccups

Introduction

Since 1993 tramadol (Tramal®, Tramagetic®) is available in the Netherlands and since 2003 tramadol is also available in combination with paracetamol (Zaldiar®). Tramadol is a centrally acting analgesic, which is indicated *for acute and chronic pain, such as pain due to surgery or trauma, and malignant diseases* [1]. Tramadol is a racemate of two enantiomers. The cis-enantiomer binds to the μ-opiate-receptor and inhibits the serotonin-reuptake. The trans-enantiomer inhibits the norepinephrine-reuptake and stimulates α_2-receptors [2]. Nausea, vomiting, constipation, sweating, dry mouth and headache are the most frequently occurring adverse drug reactions. Respiratory depression may occur only when high dosages of tramadol are used [1,2] or when concomitant drugs with centrally inhibiting effects are used [1]. Tramadol has almost no effect on the gastrointestinal motility [2].

Hiccups (singultus) are involuntary, brief contractions of the diaphragm, followed by a sudden closure of the glottis. The pathophysiology of hiccups is unknown. Hiccups can be acute or persistent. In most cases acute hiccups disappear spontaneously. Persistent hiccups may continue for more than 48 hours and can lead to severe complications, such as sleeping disorders, eating disorders, exhaustion and depressed reactions.
Patients suffering from hiccups also have remarkably often gastrointestinal complaints but a causal relationship has not been proved. Furthermore, men suffer more frequently from hiccups than women.
There is no clear treatment for hiccups; chlorpromazine is the only drug that is registered for treatment of hiccups.
Several drugs, for example benzodiazepines, can cause hiccups [3,4]. Hiccups are not described in the Dutch SPC of tramadol [1].

Reports

On March 6 2007 the database of the Netherlands Centre contained three reports of tramadol and hiccups (Table 1). All three patients were male and they recovered after withdrawal of tramadol. One patient used concomitantly diazepam, which is also known to cause hiccups.

Table 1. Reports of hiccups associated with the use of terbinafine

Patient, Sex, age	Drug Indication for use	Concomitant medication	ADR	Time to onset outcome
A M, 81	tramadol 50 mg od pain	not reported	enduring hiccups	unknown recovered after withdrawal of tramadol
B M, 55	tramadol 50 mg tdd not reported	rosuvastatin, diazepam	severe hiccups	1 day recovered after withdrawal tramadol and diazepam
C M, 58	tramadol 50 mg qid not reported	pantoprazol	hiccups	several hours recovered after withdrawal

Other sources of information

Literature

Literature about hiccups associated with the use of tramadol is rare, however, a few articles about opiate-related hiccups and myoclonus were found.
Vickers *et al.* compared the analgesic efficacy of intravenous tramadol and morphine for post-operative pain. In a double blind, randomised study involving 523 patients they found no substantial differences in analgesia between tramadol and morphine. Adverse drug reactions observed during this study were for both drugs gastro-intestinal complaints, such as dyspepsia, nausea and vomiting, dry mouth and hiccups [5].
Lauterbach described a case report of a 55-year-old man with hiccups and focal rhythmic diaphragmatic myoclonus after hydrocodone administration for dental pain. The symptoms appeared shortly after starting with hydrocodone. Every day the hiccups started about two hours after intake of hydrocodone. After hydrocodone discontinuation the symptoms disappeared. Patient concomitantly used penicillin, sertraline, bupropion, trazodone, flurazepam, digoxin and warfarin. Continuation of these drugs after withdrawal of hydrocodone did not elicit the hiccups [6].

Wilcox reports a case of a 63-year-old man with transient hiccups associated with the use of oral morphine solution. Due to the hiccups the oral morphine solution was changed into sustained release morphine. He suffered from hiccups within one hour after the first intake. Morphine intake was discontinued after 24 hours of persistent hiccups. The hiccups disappeared within 48 hours after discontinuation. Patient refused readministration of the drug and commenced a fentanyl patch and oxycodone, which he tolerated without developing hiccups [7]

Databases

On March 6th 2007 the database of the Netherlands Pharmacovigilance Centre Lareb contained 815 reports on tramadol and 42 reports of hiccups. The association tramadol and hiccups is disproportionally present in the Lareb database (ROR 4.5; 95% CI 1.4 -14.4).
The database of the Uppsala Monitoring Centre (UMC) of the WHO contained 35 reports of hiccups of which 12 concerned the use of tramadol, which is also disproportional (ROR 3.4; 95%CI 1.9-5.9).

Prescription data

Table 2. Total number of users of tramadol and tramadol/paracetamol per year since 2001 (Source: GIP College voor Zorgverzekeringen)

	2001	2002	2003	2004	2005
Tramadol (Tramagetic®)	234,620	250,970	266,270	230,257	279,980
Tramadol/paracetamol (Zaldiar®)			7,187	30,257	72,871

Discussion and conclusion

The pathophysiology of hiccups is still poorly described. The Netherlands Pharmacovigilance Centre Lareb received three reports of hiccups associated with the use of tramadol. The positive dechallenge in all three cases and the availability of several articles concerning opiate-related hiccups suggest a causal relationship between tramadol and hiccups.
Considering the for some patients impairing effect of longlasting periods of hiccups, health care professionals and patients should be aware of the possible relationship between hiccups and the use of of tramadol.

References
1. Dutch SPC Tramal®. (version date 2006) http://www.cbg-meb.nl/IB-teksten/18941-18942-18943-18944.pdf.
2. Winap, editor. Informatorium Medicamentorum 2007. Den Haag: 2006.
3. Weda M. Persisterende Hik. Pharm Weekbl 1994;129((22/23)):572-6.
4. Ten Holter JBM. De Hik. Ned Tijdschr Geneeskd 2005;149(48):2659-62.
5. Vickers MD, Paravicini D. Comparison of tramadol with morphine for post-operative pain follwing abdominal surgery. Eur J Anaethesiol 1995;12(3):265-71.
6. Lauterbach EC. Hiccup and apparent myoclonus after hydrocodone: review of the opiate-related hiccup and myoclonus literature. Clin neuropharmacol 1999;22(2):87-92.
7. Wilcox SK. Persistent hiccups after slow-release morphine. Palliat Med 2005;19(7):568-9.

- Hiccups are not listed in the Dutch SPC of tramadol.