

## Tramadol and hiccups – an update

### Introduction

Tramadol (Tramal<sup>®</sup>, Tramagetic<sup>®</sup>, Theradol<sup>®</sup>, Tramajuna<sup>®</sup> and generic) is indicated for treatment of acute and chronic pain, such as pain due to surgery, trauma or malignant diseases and was granted marketing authorisation in the Netherlands in 1992 [1]. Since 2003 tramadol is also registered in combination with paracetamol (Zaldiar<sup>®</sup>).

Hiccups are involuntary, brief contractions of the diaphragm. These contractions lead to sudden inspiration followed by sudden closure of the glottis which generates the characteristic 'hic' sound. The pathophysiology of hiccups is unknown. Hiccups can be acute or persistent. Persistent hiccups may continue for more than 48 hours and can lead to severe complications including dehydration, insomnia, eating disorders, depressed mood and exhaustion. Acute hiccups are usually caused by gastric distention from overeating or carbonated beverages, excessive alcohol use or stress. Persistent hiccups can be caused by tumor growth (abdominal, cervical or cerebral), an infection (eg, meningitis, encephalitis) or electrolyte disturbance (eg hypocalcemia, hyponatremia or uremia). But also several drugs can also cause hiccups. [2,3]

In May 2007 Lareb described the association between hiccups and the use of tramadol in a quarterly report [4]. The current observation is an update of this association.

### Reports

In the period from April 27<sup>th</sup> 1998 until October 24<sup>th</sup> 2014, the Netherlands Pharmacovigilance Centre Lareb received seven reports of hiccups associated with the use of tramadol. The reports are listed in table 1.

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

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, 20900 M, 71 years and older, General Practitioner	tramadol 1dd 50mg pain		hiccups	unknown, discontinued, recovered
B, 43012 M, 51-6- years, Pharmacist	tramadol 3dd 50 mg pain	rosuvastatin, diazepam	hiccups	1 day, discontinued, recovered
C, 51061 M, 51-60 years, General Practitioner	tramadol 4dd 50mg supraspinal syndrome	pantoprazole	hiccups	unknown hours, discontinued, recovered
D, 110169 F, 21-30 years, Pharmacist	tramadol 3dd 50mg indication unknown, tramadol retard 3dd 100mg indication unknown	ethinylestradiol/ levonorgestrel	hiccups	1 week, dose increased, unknown
E, 123217 M, 71 years and older, Pharmacist	tramadol p.r.n. 3dd 50mg pain		hiccups	1 day, discontinued, 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
F, 130143 M, 31-40 years, General Practitioner	tramadol daily dose unknown indication unknown		hiccups	30 minutes, unknown, recovered
G, 139265 F, 21-30 years, General Practitioner	tramadol 3dd 100 mg pain		hiccups	3 months, discontinued, recovered

p.r.n. = as necessary

Patient B experienced hiccups up to seven hours a day. Sometimes the hiccups disappeared for some hours and then returned spontaneously. After discontinuation of tramadol the hiccups were less severe and one day later the patient had made a full recovery.

Patient C has reflux complaints for which he uses pantoprazole.

Patient G experienced persisting hiccups.

## Other sources of information

### SmPC

In the Dutch SmPCs of various brands hiccups are not mentioned as adverse drug reaction. Except for the SmPC of Tramagetic® were hiccups are mentioned as a very rare (< 1/10,000) adverse reaction [5-17].

### Literature

Several articles describe opiate-related hiccups and myoclonus [18,19]. Vickers et al mention hiccups in association with intravenous administration of tramadol. During a multi-centre, double-blind, randomized study the analgesic effect on post-operative pain of intravenous tramadol was compared to that of intravenous morphine. A high incidence of gastrointestinal adverse events were observed with both treatments mostly consisting of mild nausea, dry mouth, vomiting, dyspepsia and hiccups [20].

Two articles mention persistent hiccups in association with intrathecal morphine infusion. Loomba et al describe a 44-year-old male with complex regional pain syndrome of bilateral upper extremities. After various unsuccessful treatments to relief pain, continuous intrathecal infusion of morphine was initiated. The patient started experiencing persistent hiccups approximately 12 hours after the initiation. Other causes for hiccups, like electrolyte imbalance, stroke, alcoholism or other drugs were ruled out. The hiccups did not resolve after trying of various non-pharmacological interventions, such as breath holding or drinking water. Also the administration of baclofen had no effect. Eventually, the morphine was replaced with hydromorphone and the hiccups resolved after 12 hours [21].

Ruan et al describe the case of a 65-year-old female with severe low-back pain and left-sided leg pain. Because all other conventional treatment had no effect, she was first started on an epidural morphine-infusion trial during which she experienced only light itching as adverse event. After starting the intrathecal infusion of morphine the patient started experiencing hiccups with a latency of 12 hours after start. There was no other intolerable adverse effects. Various non-pharmacological interventions had no effect, but administration of chlorpromazine did help her slightly. Six days after start, the intrathecal infusion was switched from morphine to hydromorphone. The hiccups resolved completely after 16 hours [22].

## Databases

Table 2. Reports of hiccups associated with tramadol in the Lareb, WHO and Eudravigilance database [23-25]

Database	Drug	Preferred terms	Number of reports	ROR (95% CI)
Lareb	Tramadol	Hiccups	7	11.0 (5.1 - 23.7)
	Paracetamol & Tramadol	Hiccups	0	
WHO	Tramadol	Hiccups	45	2.0 (1.5 - 2.7)
	Paracetamol & Tramadol	Hiccups	15	1.5 (0.9 - 2.4)
Eudravigilance	Tramadol	Hiccups	17	3.0 (1.9 - 4.9)
	Paracetamol & Tramadol	Hiccups	2	

## Prescription data

Table 3. Number of patients using tramadol in the Netherlands between 2009 and 2013 [26]

Drug	2009	2010	2011	2012	2013
Tramadol	345,220	379,090	403,350	416,610	426,910

## Mechanism

A possible mechanism through which tramadol could cause hiccups is not described in literature.

## Discussion and conclusion

The Netherlands Pharmacovigilance Centre Lareb received seven reports of hiccups associated with the use of tramadol. Five patients experienced hiccups within 30 minutes to 1 week after start of tramadol. Five patients recovered after withdrawal of tramadol. One patient used diazepam which is also known to cause hiccups. Four patients used tramadol for unspecified pain and in two cases the indication for tramadol is unknown. It is unknown if the underlying condition could have caused or aggravated the hiccups as well, for example metastatic tumor related pain.

In literature, several cases of opiate-related hiccups are described and one article mentions hiccups as adverse drug reaction of intravenous tramadol.

Hiccups are the result of stimulation of the central or peripheral components of a hiccup-reflex arc which consists of afferent and efferent limbs and central hiccup center. Both the afferent and efferent pathway consist of the phrenic nerve, the primary motor input to the diaphragm. Loomba et al describe that morphine might be able to increase phrenic nerve hyperactivity through N-methyl-D-aspartate (NMDA) receptor activation [21]. It is notable that in the two cases described by Loomba et al and Ruan et al, the hiccups disappeared when the patients switched from morphine to hydromorphone, a morphine derivative [21,22]. Hiccups caused by tramadol cannot be explained with the mechanism suggested by Loomba et al since tramadol is a NMDA-receptor antagonist. By blocking the NMDA-receptor, tramadol would decrease phrenic nerve activity and would not be likely to cause hiccups.

Although a mechanism is not described in literature, Lareb has five cases in which a positive dechallenge is prescribed, suggesting a relation between hiccups and the use of tramadol. The association of tramadol and hiccups is supported by statistical significant disproportionality in the Lareb, WHO and Eudravigilance databases. Tramadol is a drug used on a relative large scale for pain with various causes. Considering the for some patients impairing effect of long-lasting periods of hiccups, health care professionals and patients should be aware of the possible relationship between hiccups and the use of tramadol.

- Hiccups should be mentioned in all SmPCs of tramadol.

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*This signal has been raised on March 2014. 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.cbq-meb.nl](http://www.cbq-meb.nl)*