

## 1.1. Tramadol and myoclonus

### Introduction

Tramadol (Tramal<sup>®</sup> and generics) is available on the Dutch market since 1992. The current therapeutic indication is: *Treatment of acute and chronic moderate and severe pain caused by surgery, trauma or malignancies*. Tramadol is a weak  $\mu$ -opioid receptor agonist and also inhibits the reuptake of noradrenaline and serotonin. Undesirable effects include many opioid related effects. Because of its inhibitory effect on serotonin reuptake, tramadol should not be used in patients taking MAO-inhibitors or other serotonin reuptake inhibitors. Finally, tramadol can cause seizures and possibly exacerbate seizures in patients with predisposing factors [1,2].

### Reports

Lareb has received four reports of myoclonus in association with tramadol.

Patient 2 used also paroxetin, thereby increasing the serotonin reuptake inhibition of tramadol.

Patient 3 used also amitryptilin, thereby amplifying the serotonin reuptake inhibition of tramadol.

None of the patients was familiar with epilepsy.

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

Patient, Sex, age	Drug, dosage Indication for use	Concomitant medication	Suspected adverse drug reaction	Latency, outcome
1 F, 41	tramadol 1dd 150 mg not specified	nabumeton	involuntary muscle contractions	few days, unknown
2 M, 47	tramadol retard 1dd 150 mg not specified	paroxetin, cerivastatin, salicylic acid, verapamil, paracetamol, folic acid, omeprazol, ledertrexate, fibers	myoclonic jerks	unknown, no neurological cause
3 M, 41	tramadol retard 300+200 mg chronic pancreatitis	prednisolon, midazolam, amitryptilin, omeprazol	myoclonic jerks	unknown, unknown
4 F, 64	tramadol retard 1dd150 mg, pain in neck	omeprazol, erytromycin course, metronidazol course	myoclonic jerks	one day, positive dechallenge

### Other sources of information

#### Literature

Myoclonus is a recognised adverse drug reaction of morphine, especially in patients on chronic opioid therapy, and it seems to be dose related in an unpredictable manner [3]. This is confirmed by a Medline search on myoclonus and morphine/adverse effects with nearly 30 hits. However, the same search with tramadol yields only one hit, dealing with myoclonus as part of the serotonergic syndrome during use of tramadol and iproniazide, a MAO-inhibitor [4].

#### Databases

The WHO-combinations database yields statistically significant reporting odds ratio's on involuntary muscle contractions (including myoclonic jerks) and the following opioids (ATC N02A): pentazocine, morphine, tramadol, fentanyl, meperidine (pethidine) and hydromorphone (table 2).

Table 2: WHO-combinations database: statistically significant disproportionality of associations between various opioids and involuntary muscle contractions

drug	Ncomb	ROR (CI <sub>95</sub> )
pentazocine	21	2.15 (1.40-3.30)
morphine	61	2.26 (1.75-2.91)
tramadol	65	2.48 (1.94-3.17)
fentanyl	67	2.78 (2.18-3.54)
meperidine	82	3.38 (2.71-4.20)
hydromorphone	21	10.94 (7.06-16.94)

Ncomb: number of reports with association ROR: reporting odds ratio; CI<sub>95</sub>: 95% confidence interval

### Mechanism

In 1999, Lauterbach has reviewed the literature on the opiate-related hiccup and myoclonus [5]. He differentiates opiate related myoclonus (ORM) into various types of myoclonus that are characterised by clinical properties: opiate induced myoclonus (OIM), intrathecal opiate induced myoclonus (intrathecal OIM), and opiate withdrawal myoclonus (OWM). Concerning the mechanism, several hypotheses are put forward:  $\mu$ -receptor activity, an opiate-serotonergic interaction, and seizure related myoclonus. The author concludes: *An understanding of opiate related myoclonus from the literature is confounded by diagnostic ambiguities and the multiple actions of opiates at various sites in the nervous system. More rigorous description and systematic study are needed.*

### Conclusion

Four cases of myoclonus during use of tramadol have been reported to the Netherlands Pharmacovigilance Centre Lareb. Myoclonus is statistically significant associated with the use of tramadol in the WHO-combinations database. Literature supports an association between opiates and myoclonus, although the pharmacological mechanism is not yet clear. Concomitant medication with a serotonin increasing effect may contribute to the association.

### References

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