1.1. Tramadol and anorgasmia

Introduction

Tramadol (Tramal®, Tramagetic®, generics) is registered since 1993 in the Netherlands. Since 2003, tramadol is available in combination with paracetamol (Zaldiar®) as well. The analgesic ladder, originated by the World Health Organization (WHO), advices tramadol use in addition or in replacement of non-opioid agents like paracetamol or NSAID. Tramadol is a weak μ-opioid receptor agonist and indicated *for acute and chronic pain with mild-to-severe pain from nature, such as caused by surgery, trauma or malignancy* [1,2]. Tramadol is a racemic mixture. The (+)-isomer has a 20 fold higher affinity for the μ-opioid receptor than the (-)-isomer. The (+)-isomer inhibits the re-uptake of serotonin (5-HT) as well. The (-)-isomer inhibits the reuptake of norepinephrine and potentiates the analgesic effect of the (+)-isomer [3]. The most common ADRs include nausea, dizziness, constipation, sweating, headache are opioid related [1,2].

Anorgasmia, is a sexual dysfunction in which a person cannot achieve an orgasm despite adequate stimulation. In males it is associated with delayed or lack of ejaculation even though in the presence of an erection. Any psychological or medical disease or surgical procedure that interferes with either central control of ejaculation or the nerve supply to related organs can result in anorgasmia. As such, the causes of anorgasmia are e.g. spinal cord injury, urethritis, transurethral resection of prostate, hypogonadism and antidepressants like selective serotonin reuptake inhibitors (SSRIs) [4].

Reports

In the period from December 23th 1996 until January 19th 2015, the Netherlands Pharmacovigilance Centre Lareb received seven reports of anorgasmia with the use of tramadol. The details of these reports are presented in table 1.

Table 1. Reports of anorgasmia 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, 15957, M, 41-50, pharmacist	tramadol 50mg, 4 times a day 100 mg, pain	ranitidine	anorgasmia, ejaculation failure	2 weeks, drug withdrawn, recovered
B, 27836, M, 41-50, general practitioner	tramadol 50 mg, as needed 3 times a day 50 mg, pain	ibuprofen	anorgasmia	15 days, no change, recovered
C, 66301, M, 31-40, consumer	tramadol 100 mg, as needed 3 times a day 100 mg, back pain	testosterone injection sumatriptan injection, paracetamol	anorgasmia, insomnia, dizziness, nausea, constipation, fatigue, logorrhoea,	5 hours, drug withdrawn , recovered

			hyperacusis, decreased respiratory rate, tremor, pruritus, dry mouth, hyperhidrosis, headache	
			anorgasmia, erectile dysfunction	
			anorgasmia, restlessness, nausea, hyperventilation	
D, 92996, M, 61-70, pharmacist	tramadol 50 mg, 5 to 7 times a day 50 mg, pain in leg tramadol 50 mg, 2 times a day 50 mg, pain		anorgasmia, dysuria, haematuria, vomiting, , psychomotor hyperactivity, prostatic disorder, euphoric mood	1 day, no change , not recovered
E, 106191, M, 41-50, consumer	tramadol 50 mg, 3 times a day 50 mg, back pain	diazepam, codeine	anorgasmia, decreased appetite	days, dose increased, not recovered
F, 112642, M, 21-30, consumer	tramadol 50 mg, 1 time a day 50 mg, postoperative pain	naproxen		8 weeks, drug withdrawn, not recovered
G, 178916, M, 21-30, consumer		paracetamol, ibuprofen		2 weeks, drug withdrawn , not recovered

Cases A, B and C describe a positive dechallenge, dechallenge/rechallenge and dechallenge, respectively. In case B there was no change in drug use because tramadol was used as necessary, combined with the alternative ibuprofen.

The indication of the testosterone injection in case C is unknown. A possible indication could be hypogonadism , which may by itself also cause anorgasmia. Potential confounding by indication could therefore not be excluded.

Case E describes a dose increase due to habituation of tramadol. Codeine was used for an unknown indication.

Case F mentioned abuse of tramadol for personal thrill and the patient had not recovered at the time of reporting, twelve days after withdrawal of tramadol.

In case G, the patient had not recovered at the time of reporting, which was one day after withdrawal of tramadol.

Other sources of information

SmPC

Anorgasmia or related ADRs, are not mentioned in the Dutch SmPC of tramadol [1,2]. However, the US SmPC mentioned sexual function abnormality [5].

Literature

No previous cases of anorgasmia associated with tramadol were found in the literature. However it is well known that SSRIs can delay or prevent male orgasm [6]. Due to the pharmacological actions of tramadol, similar sexual adverse reactions could possibly occur.
Remarkable is the available literature on premature ejaculation (PE) and treatment with both SSRIs and tramadol as well [7]. The evidence of SSRIs is noted and again because of the inhibited characteristics on the re-uptake of 5-HT by tramadol the systematic review and meta-analysis of Yang *et al.* concludes that tramadol may be effective in PE treatment [8].

Databases

Table 2. Reporting odds ratios of tramadol and anorgasmia in the database of the Netherlands Pharmacovigilance Centre Lareb, the WHO and the Eudravigilance (EMA) database [9-11]

Drug and ADR	Number of reports	ROR (95% CI)
Tramadol and anorgasmia	Lareb: 7	22.1 (10.0-48.7)
	WHO: 13	1.1 (0.7-1.9)
	Eudravigilance: 5	3.1 (1.3-7.6)

Prescription data

Table 3. Number of tramadol users in the Netherlands between 2010 and 2013 [12]

Drug	2010	2011	2012	2013
Tramadol	379,090	403,350	416,310	427,400

Mechanism

The orgasm involves a complex neurochemically interplay between central serotonergic and dopaminergic neurons and secondary involvement of cholinergic, adrenergic, oxytocinergic, and gamma aminobutyric acid (GABA)-ergic neurons [4,7]. Many authors have reported anorgasmia due to psychotropic drugs [13]. This effect, for example in SSRIs, is attributed to the serotonergic activity, where the orgasm is negatively affected by excessive stimulation of 5-HT2C-receptors in the spinal cord. The (+)-isomer of tramadol inhibits the re-uptake of 5-HT. Based on the mechanism, anorgasmia due to tramadol is therefore likely.

From opposite perspective, although SSRIs affects sex drive, premature ejaculators could benefit from SSRI use. Further research has shown that SSRIs are effective in the treatment of PE. This effect occurs 1-2 weeks and 2-3 weeks maximum after start with SSRI therapy. The time to onset of effect looks similar to the latency of some received reports of anorgasmia. Tramadol may be effective, whereby it is theoretically reasonable that tramadol could cause anorgasmia as well.

Additionally, opioids are associated with delay of orgasm in men [14]. The association is poorly studied and how opioids contribute to ejaculatory control is unknown. A possible mechanism could be the inhibitory actions of opioids on testosterone. Additional data obtained from a study of Ahmed *et al*. shows that tramadol significantly reduced plasma levels of testosterone ($P < 0.05$) in rats [15]. Theoretically, the actions of tramadol at the μ-opioid receptor could therefore contribute to the negative effects on achieving an orgasm.

Finally, sexual desire and response are usually inhibited in patients with severe pain [14]. Confounding by indication could therefore not entirely be excluded.

Discussion and conclusion

The Netherlands Pharmacovigilance Centre Lareb received 7 reports of anorgasmia associated with the use of tramadol. Anorgasmia was mostly presented after two weeks and 3 patients recovered on the date of reporting after withdrawal or dose reduction of tramadol. The Lareb cases describe two positive dechallenges and one positive rechallenge. The association is not supported by studies described in the literature. However, the association is supported by a possible pharmacological mechanism and a statistically significant disproportionality in the databases of Lareb and Eudravigilance. Tramadol treatment for an opposite disorder like premature ejaculation suggests that tramadol might have a causative role in the occurrence of anorgasmia.

- Further investigation of the information of the marketing authorization holders and other national centers is needed to strengthen the signal.

References

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This signal has been raised on July 2015. 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.cbg-meb.nl