

Tramadol and flushes

Introduction

Tramadol (Tramal[®], Tramagetic[®], Theradol[®], Doltard[®]) is a synthetic opioid, indicated for both chronic and acute moderate to severe pain [1]. It is registered in the Netherlands since 1992 and is marketed in both immediate and extended release oral preparations and in preparations for rectal and intravenous administration. Tramadol is advised to be used in addition to or in replacement of an initially prescribed analgesic. It is mostly used in combination with paracetamol or an NSAID [2]. In 2007 tramadol was prescribed to almost 400,000 patients in the Netherlands [3].

Flushing can be defined as transient reddening of the face due to fever, systemic disease, neurological disease, drugs, exertion, stress, or a disease process. Hot flushes are sudden, temporary sensations of heat, flushing of face of neck and can be accompanied by palpitations, hyperhidrosis and anxiety. Hot flushes are most often related to menopausal hormonal changes but can also be inflicted due to hormonal deprivation in cancer treatment in both men and women. Other causes are like those of flushing. Between both complaints there is a considerable overlap and a distinction between those two complaints is difficult to make.

This report studies the association between tramadol, flushing and hot flushes.

Reports

Until May 15 2008, the Netherlands Pharmacovigilance Centre Lareb received eight reports of flushes associated with the use of tramadol and three reports of hot flushes in relation to the use of this drug. The characteristics of these eight reports are shown in Table 1, reports of flushing and hot flushes associated with the use of tramadol.

Table 1. Reports of flushing and hot flushes associated with the use of tramadol.

Patient, Sex, age	Daily dose Indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset, action with drug, outcome
A 11898 M, 73	4 dd 50 mg not specified	flunitrazepam, sertraline, alfuzosin, finasteride, fluspirelene	flushing	ten days, withdrawn, unknown
B 15569 F, 73	4 dd 50 mg not specified	fluvastatin, acenocoumarol, famotidine, lisinopril	flushing syncope	hours, Withdrawn, Recovered
C 29017 F, 51	3x100mg pain	naproxen, diclofenac, ethinyl estradiol/levonorg estrel	flushing, nausea, headache	four days, no changes performed, recovered
D 60245 M, 54	7 x50 mg, as necessary pain	paracetamol, oxazepam	flushing, sweating increased	days, no changes performed, not recovered
E 62161 F, 59	2 x50 mg pain after surgical procedure	paracetamol	flushing, vomiting, dyspnoea, dry mouth, malaise	twelve hours, withdrawn, recovered
F	1x100mg	oestrogene/levono	hot flushes,	hours,

Patient, Sex, age	Daily dose Indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset, action with drug, outcome
59528 F, 40	not specified	rgestrel	vomiting, hyperventilation, syncope	withdrawn, unknown
G 65518 F, 67	2x 200mg rheumatoid arthritis	temazepam, prednisolone, omeprazole	hot flushes, hyperhidrosis	two years, withdrawn, recovered, positive rechallenge
H 74807 F, 47	3x 325/37.5 mg paracetamol/tamadol pain	fosinopril	hot flushes	two days, withdrawn, unknown

Other sources of information

SmPC

Neither flushing nor hot flushes are mentioned in the Dutch SmPC of immediate or extended release tramadol products and tramadol/paracetamol combination preparations [1]. The American SmPC however mentions hot flushes and estimates its incidence to at least one percent [4]. Flushes are mentioned in the SmPC of Zaldiar[®], a combination of paracetamol and tramadol, which is available in the Netherlands. The causal relationship between use of tramadol and the occurrence of hot flushes is classified in this SmPC as possible or greater.

Literature

Although no specific studies aimed to determine the incidence of flushing or hot flushes related to the use of tramadol have been published, both effects are described in two review articles as an ADR occurring both in immediate release and extended release preparation [5,6]. Scott and Perry mention an incidence of 0.6%, Hair describes a much higher incidence of at least five percent, both referring to the US product information.

Mechanism

Tramadol is a synthetic, centrally acting analgesic, which acts by multiple, distinct mechanisms of action. Tramadol has both a positive and a negative active enantiomer. Tramadol's positive enantiomer is a weak opioid agonist with selectivity for the μ -receptor and is involved in the inhibition of serotonin reuptake. Tramadol's negative enantiomer is both an inhibitor of norepinephrine reuptake and increases the release of this substance by autoreceptor activation [6]. Besides a direct opioid action, both the noradrenergic and serotonergic activity of tramadol may be related to the effects of tramadol on flushing.

In general, hot flushes are related to withdrawal of estrogens, yet this seems not to be the sole exerting mechanism. The mechanism of flushing is complex and not completely understood.

A following model for the pathogenesis of hot flushes is postulated in which norepinephrine plays a key role in exertion of hot flushes initiated by decreased levels of estrogen: decreased levels of oestrogen lead to a decrease in endorphin and catecholamine levels [7], that culminates in increased hypothalamic norepinephrine and serotonin release. These substances in their turn lower the set

point in the thermoregulatory nucleus, allowing heat loss mechanisms to be triggered by subtle changes in core body temperature [7].

The role of serotonin in hot flushes is complex: both pathogenic and therapeutic effects on hot flushes have been described. Apart from direct vasodilator effects, serotonin is also involved in thermoregulations. Increased levels can lead to a malignant rise of body temperature, yet its temperature lowering effect after single administration has been demonstrated in animal studies [7]. Stimulation of the 5HT1a receptor may be responsible for lowering of body temperature, while stimulation of the 5 HT2a may be involved in increasing body temperature [7,8]. Also the role of direct opioid activation has been mentioned as origin for the occurrence of hot flushes. In one study the administration of the opioid antagonist naloxone reduced the frequency of menopausal hot flushes [9]. This result was however not replicated in other studies and the reason for these contradictory findings is still unclear [10].

Histamine release in opioid treatment is one of the main mechanisms for vasodilatation. Tramadol is believed to have at most limited effect on histamine release [11].

Databases

On May 25, 2008, the database of the Netherlands Pharmacovigilance Centre Lareb contained five reports of flushing and three reports of hot flushes. Neither of these two reactions were reported disproportionately in the Netherlands Pharmacovigilance Centre Lareb's database. In the database of the WHO Collaborating Centre flushing was reported 99 times, and hot flushes 13 times: both associations were not disproportional.

In the Eudravigilance database flushing or hot flushes 12 cases of serious reactions in relation to the use of tramadol or tramadol/paracetamol were reported. Nine cases were rated as serious because of hospitalisation, one due to the reported disabling character of tramadol associated flushing. In two cases other causes were reason to rate these reaction as serious. In addition three Italian cases of non-serious reaction were available in the Eudravigilance database.

Discussion

Flushing or hot flushes has been reported eight times to the Netherlands Pharmacovigilance Centre Lareb. Latencies ranged mostly from hours to days, except in one case where tramadol had been used for two years. In this case a causal relation between the use of tramadol and the occurrence of flushes was supported by a positive rechallenge. In two cases symptoms resolved after withdrawal of tramadol. In one case symptoms diminished despite ongoing use of tramadol. In the remaining four cases the outcome is unknown. Five patients used tramadol in daily doses of 200mg or higher, with a maximum daily dose of 400mg, suggesting a dose dependent effect, given the low initial dose of 50-100 mg daily advised in the SmPC for tramadol. However, information on the initial dose is lacking. Three patients were middle aged females, so hot flushes due to menopausal causes cannot be ruled out in these cases. The short latency of hours in two of these cases is however fits in an adverse reaction.

A relation between the use of tramadol and occurrence of (hot) flushes seems to be recognised by the manufacturer of tramadol since the American SmPC

mentions this ADR and rates the possibility of a tramadol related effect as possible or greater. The reviews suggest that this labelling is supported by clinical studies. This relation is supported by possible mechanisms that explain the ADR by effects of tramadol through inhibition of serotonin and epinephrine reuptake. Flushing is a well recognised ADR of other opioids. These effects are mostly believed to be histamine mediated. Tramadol is believed not to exert this effect, yet to our knowledge the only study supporting this claim is a 1987 n=13 study in which effects of 100mg intravenously administered tramadol were studied in healthy subjects [11]. Effects of tramadol due to use of higher recommended doses, up to 400 mg daily, or effects, for instance by histamine release or noradrenergic action in sensitive populations cannot thus be ruled out.

Conclusion

Lareb received eight reports of hot flushes and flushing associated with the use of tramadol. These effects are not mentioned in the Dutch SmPCs of tramadol, but are described as common ADRs in the tramadol SmPC for the US market. At case level confounding could not be ruled out in all reports. The whole of reports however supports a relationship between use of tramadol and the occurrence of flushes. The effects of tramadol on the initiation of hot flushes and flushing can be explained by several pharmacologic effects of tramadol and the relation is supported by literature. Flushing and hot flushes should be mentioned in all SmPCs of tramadol.

References

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This signal has been raised on July 2008. It is possible that in the meantime other information became available. For the latest information please refer to the website of the MEB www.cbg-meb.nl/cbg/en/default.htm or the responsible marketing authorization holder(s).

- Flushing or hot flushes may be related to the use of tramadol by effects of norepinephrine reuptake or other possible mechanisms.
- Flushing and hot flushes should be mentioned in the SmPCs of all tramadol containing products.