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Mirtazapine SolTab and mouth paraesthesia/anaesthesia

Introduction

Mirtazapine (Remeron®) is a tetracyclic piperazinoazepine analogue of mianserin, a chemical structure unrelated to TCAs, MAO-inhibitors or SSRIs. Similar to mianserin, mirtazapine displays pre-synaptic alpha-2 receptor blocking activity, thereby enhancing serotonergic neurotransmission. Unlike mianserin it has no effect on the synaptic reuptake of norepinephrine. Preclinical studies have demonstrated antihistaminic (H1) and antiserotonergic properties of mirtazapine, but hardly any anticholinergic activity. The drug mainly affects serotonin (5-HT) receptors of the 5-HT2 and 5-HT-3 subtypes, possessing low affinity for 5-HT1A, 5-HT1B, and 5-HT1C receptors. The increased serotonergic neurotransmission therefore results in a selective activation of 5-HT1 receptors [1,2]. Remeron® tablets were approved for the Dutch market in 1994 for *the treatment of an episode of depression, especially with vital sign*s [3].
Commonly observed ADRs are drowsiness, dizziness, headache, increased appetite, local or generalised oedema and weight gain [1,2]. In rare cases (0.01-0.1%) paraesthesia, restless legs, arthralgia/myalgia, fatigue, nightmares, hypotension, mania, convulsions, tremor and acute haematological abnormalities have been observed [1].
Remeron SolTab® is an orally disintegrating tablet. It is placed on the tongue, where it will disintegrate, after which it can be swallowed without the use of water [3]. Remeron SolTab® was approved for the Dutch market in June 2001 for the same indication as specified for mirtazapine tablets [3]. The adverse reactions that have been described are similar to those mentioned for the tablet form [1,3]. As soon as it was marketed, Remeron® tablets were withdrawn from the market on January 1, 2003. Consequently, many patients switched from mirtazapine tablet to mirtazapine SolTab.

Reports

Lareb received 27 case reports on mirtazapine SolTab. Twenty-two of the patients mentioned had previously used mirtazapine tablets. Paraesthesia or anaesthesia of mouth, palate or tongue was reported for 10 patients. These 10 patients (Table 1) include six patients who switched to mirtazapine SolTab and didn't had a similar reaction when on mirtazapine tablets. In two patients the problems disappeared after they had started ingesting SolTab like a tablet (by swallowing it whole), and in one patient they subsided after he had begun dissolving the tablet in a glass of water before ingestion. Besides the paraesthesia/anaesthesia, two of the patients mentioned SolTab as causing an unpleasant taste in the mouth.
One additional patient reported sensations of swelling in the tongue and palate. From the report it is not clear if the patient suffered from angio-oedema or that he also experienced a feeling of anaesthesia.

With reference to the tablet formualation, Lareb has also received two reports of paraesthesia/anaesthesia of the mouth: one mentioning numbness of the tongue, mouth, throat, nates and thighs and one describing numbness in palate, chin and skin.

Table 1: Reports of paraesthesia/anaesthesia associated with the use of mirtazapine SolTab

Sex, age	Dose Indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset Discontinuation Outcome
M, 49	30 mg Depression	None	Feelings of swollen (numb) palate, burning tongue and lips	Minutes Discontinued Recovered after 1.5 hour
M, 56	30 mg Depression	None	Numb feeling in mouth	4 weeks Discontinued Recovered
F, 71	30 mg Depression	None	Tickling and numb feeling in mouth and tongue	Starting day Discontinued Recovered
F, 26	30 mg	ethinylestradiol/ levonorgestrel	Numb feeling in tongue, bad taste	Not reported Not discontinued Not recovered
M, 48	30 mg	folic acid, methotrexate, mometason nose spray	Numb feeling in mouth, bad taste	Minutes No, SolTab dissolved in water Recovered
F, 78	30 mg Depression	oxazepam, amiloride/HCT, ureum creme	Tickling sensations in mouth and tongue, nausea, dizziness	Starting day Not discontinued Not recovered
F, 29	45 mg	None	Paralysed feeling in mouth and throat	Minutes No, swallows SolTab like a tablet Recovered
F, 49	30 mg	None	Burning feeling in mouth	Starting day No, swallows SolTab like a tablet Not reported
F, 52	30 mg	oxazepam	Burning feeling in mouth	Starting day Not discontinued Not recovered
M, 41	45 mg	oxazepam	Numb feeling in tongue, dyspepsia	Starting day Not discontinued Not recovered

Other sources of information

Literature.

In clinical trials using the traditional formulation hypaesthesia and paraesthesia occurred in at least 1 in 100 patients [2]. Additional ADRs that have occurred with mirtazapine include dry mouth, glossitis, gum hemorrhage, stomatitis, ulcerative stomatitis, tongue discoloration, tongue edema, salivary gland enlargement, increased salivation, oral moniliasis, taste loss, and parosmia [2].

A search in Medline [4] did not reveal any reports of burning mouth, mouth paraesthesia or mouth anaesthesia in association with mirtazapine, although data on dry mouth and bad taste have been published [5]. No literature on the SolTab formulation was available.

Databases

The WHO combinations database contains over a hundred reports of "paraesthesia" associated with the use of mirtazapine, but no reports of "paraesthesia mouth". It is not possible to verify whether the coded adverse drug reaction term "paraesthesia" actually refers to paraesthesia of the skin- or to mucosal paraesthesia. In addition, we were unable to distinguish the reactions on mirtazapine tablets from those caused by mirtazapine SolTab.

Mechanism

The pathogenic mechanism is unknown. The excipients in mirtazapine SolTab differ from those used in mirtazapine tablets (Table 2).

Table 2: Lists of excipients of mirtazapine formulations according to the SPCs

Remeron[O] **15 mg**	**Remeron**[O] **30 mg**	**Remeron**[O] **45 mg**	**Remeron SolTab**[O] **15, 30, 45 mg**
Maize starch	Maize starch	Maize starch	Sugar
hydroxypropylcellulose	Hydroxypropylcellulose	hydroxypropylcellulose	hydroxypropylcellulose
magnesium stearate	magnesium stearate	magnesium stearate	magnesium stearate
colloidal silicon dioxide	colloidal silicon dioxide	colloidal silicon dioxide	
lactose	lactose	lactose	
Polyethylene glycol 8000	Polyethylene glycol 8000	Polyethylene glycol 8000	
Titanium Oxide (E171)	Titanium Oxide (E171)	Titanium Oxide (E171)	
Yellow Ferric oxide (E172)	Yellow Ferric oxide (E172)		
	Red Ferric oxide (E172		
	Hydroxypropyl-methylcellulose		Povidone
			Ammonio Methacrylate Copolymer E (Eudragit E100)
			Aspartame (E951)
			Citric acid
			Crospovidone
			Manitol
			Microcrystalline cellulose
			Natural and artificial essence of orange
			Sodium bicarbonate

Possibly, a local antinociceptive effect of mirtazapine itself may play a role. Acute nociceptive pain is induced by the peripheral activation of primary sensory afferent neurons [6]. These neurons can be activated by a range of mediators such as prostanoids, bradykinin, ATP, histamine and serotonin. Peripheral nerve endings also express a variety of inhibitory neuroreceptors such as opioid, a-adrenergic, cholinergic, adenosine and canabinoid receptors. Various agents are being investigated as topical analgesics. There are also some clinical data on the analgesic use of topical antidepressants [6]. In mice, a dose-dependant antinociceptive effect was observed with mirtazapine. This effect mainly involves μ- and ?$_3$-opoid mechanisms [7].

Other sources of information

Pre-approval trials did not mention local mouth reactions with mirtazapine SolTab (personal communication A. Elferink, MEB, May 2003). Contact with the marketing authorisation holder revealed that effects of numbness with the mirtazapine tablets only occurred when it was not swallowed immediately but chewed on. To avoid the "lidocaine effect" the MAH advises not to suck the SolTab too vigorously or, alternatively, to swallow it directly on intake. This advice is not mentioned in the SPC.

Conclusion

Lareb has received 10 reports of mouth paraesthesia or mouth anaesthesia in association with Remeron SolTab®. Six of these patients mentioned had no such reactions with the tablet

formulation they had used previously. A possible explanation for this discrepancy may be found in the duration of the local exposure to mirtazapine SolTab in the mouth.

References

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