

1.1. Mirtazapine and constipation

Introduction

Mirtazapine (Remeron[®]) belongs to the group of other antidepressants, together with agomelatine, bupropion, duloxetine, trazodone and venlafaxine. It acts as an antagonist at central presynaptic α_2 adrenergic receptors, an action that results in an increase in central noradrenergic and serotonergic activity. Furthermore, mirtazapine is a potent histamine H1, serotonin 5-HT₂ and 5-HT₃ antagonist [1]. Mirtazapine has been approved for the Dutch market since March 1994. It is indicated for the treatment of *major depressive disorder* [1].

The current observation describes the association between mirtazapine and constipation. Constipation is seen in 10% of the Dutch population. It occurs in men and women of all ages, however it is most frequent in women of older age. Depression is a known risk factor for constipation [2,3].

Reports

On January 16th, 2012, the database of the Netherlands Pharmacovigilance Centre Lareb contained ten reports of constipation associated with the use of mirtazapine. The reports are listed in Table 1.

Table 1. Reports of constipation associated with the use of mirtazapine

Patient, Sex, Age, Source	Drug Indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset, Action with drug outcome
A 32564 F, 41 – 50 years Specialist doctor	mirtazapine 1 dd 30mg depressive episode	oxazepam, flurazepam	constipation, abdominal pain upper, diabetes mellitus non- insulin-dependent	2 weeks discontinued recovering
B 20800 F, 51 – 60 years General Practitioner	mirtazapine 1 dd 30mg depressive episode	metoprolol, terfluzine, tramadol, amitriptyline	constipation, nightmares	12 hours dose reduction not reported
C 25114 F, 41 – 50 years General Practitioner	mirtazapine 1 dd 30mg depressive episode		constipation	days no change not reported
D 27611 F, 71 years and older Consumer	mirtazapine 1 dd 30mg depressive episode	oxazepam, tamoxifen, carbasalate calcium	constipation	1,5 month discontinued not reported
E 42742 F, 31 – 40 years Specialist doctor	mirtazapine 1 dd 30mg dysthymia		constipation, photopsia	4 weeks no change recovered
F 56122 F, 71 years and older Pharmacist	mirtazapine 1 dd 15mg	pantoprazole, anastrozole, triamterene/ epitizide, magnesium- hydroxide, beclometasone	constipation	2 days no change not recovered

Patient, Sex, Age, Source	Drug Indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset, Action with drug outcome
G 64642 F, 41 – 50 years Consumer	mirtazapine 1 dd 30mg depression, nitrofurantoin prophylaxis		restless legs, constipation, nightmares, oedema periorbital, mental deterioration	days no change not recovered
H 66210 F, 21 – 30 years General Practitioner	mirtazapine depression		constipation	2 weeks no change unknown
I 86109 F, 61 – 70 years Pharmacist	mirtazapine depression	movicolon, oxazepam	constipation, flatulence	hours unknown unknown
J 126898 F, 51 – 60 years Pharmacist	mirtazapine 1 dd 30mg depression	conjugated estrogens, psyllium containing laxans, tramadol, propranolol, omeprazole, domperidone	constipation	2 days no change unknown

Other sources of information

SmPC

Constipation is not mentioned in the Dutch SmPC of mirtazapine [1]. The US SmPC of mirtazapine describes adverse events seen in patients who participated in short-term US placebo-controlled trials in which patients were dosed at a range of 5 to 60 mg/day. Constipation occurred in 13% of patients who received mirtazapine (n=453) compared to 7% of patients who received placebo (n=361) [4]. The difference is statistically significant (Pearson Chi-Square test p=0.004).

Literature

A systematic review that studied the safety and adverse-event profile of mirtazapine described that in randomized controlled trials constipation was observed in 11.1% of the patients treated with mirtazapine. This was not significantly different compared with tricyclic antidepressants (TCA's), which are also known to cause constipation, and selective serotonin reuptake inhibitors (SSRI's) [5].

Chung et al [6] studied the efficacy and tolerability of mirtazapine and sertraline in 51 Korean veterans in an randomized open label trial (not placebo-controlled). The main side effect for the mirtazapine treated group was constipation (19.6%).

Databases

On January 16th, 2012, the database of the Netherlands Pharmacovigilance Centre Lareb contained ten reports of constipation associated with the use of mirtazapine. The association between mirtazapine and constipation was reported disproportionally with a Reporting Odds Ratio (ROR) of 2.0 (95% CI 1.0-3.7). The WHO database of the Uppsala Monitoring Centre contained 92 reports of constipation associated with the use of mirtazapine with a ROR of 1.1 (95% CI 0.9-1.3), which was not disproportional.

On 30 January 2012, the Eudravigilance database contained 32 reports of constipation associated with the use of mirtazapine, of which 25 were classified as 'serious'. In one case the outcome was fatal. However, in this case several suspect drugs and several ADRs were present, making it difficult to determine which was the causal agent, if any, and which ADR was responsible for the fatal outcome. The reports concern 21 females and 11 males. The median age of the patients was 62 years (range 21 – 91 years). In two cases, the age was not reported. Constipation was not reported disproportionately (ROR = 0.8 , 95% CI: 0.6 – 1.2).

Prescription data

The number of patients using mirtazapine in the Netherlands is shown in Table 2.

Table 2. Number of patients using mirtazapine in the Netherlands between 2006 and 2010 [7].

Drug	2006	2007	2008	2009	2010
Mirtazapine	85,513	90,189	92,152	93,589	98,803

Mechanism

Mirtazapine is a moderate antagonist at muscarinic receptors [4]. Antagonism of muscarinic receptors in the gut wall leads to a decrease in motility and tone [8].

Class-effects

Mirtazapine belongs to the group of other antidepressants. This is a heterogeneous group with drugs with various mechanisms of action. Therefore, a class-effect is not reported for this association.

Discussion and conclusion

Lareb received ten reports of constipation associated with the use of mirtazapine; A positive dechallenge was reported in one patient; the remaining patients were not yet recovered at the time of reporting. Although there were several confounding factors (concomitant medication known to cause constipation, medical history of constipation, a higher risk of constipation in depressed patients) in most cases the constipation worsened since the start of mirtazapine and the constipation occurred soon after start of mirtazapine.

Constipation is already described in the US SmPC of mirtazapine [4]. Studies published in the literature describe constipation as a common adverse event seen with mirtazapine treatment [5,6]. The association of constipation with mirtazapine use is supported by a statistically significant disproportionality in the Lareb database, which could be explained by the anticholinergic effect of mirtazapine. Consideration should be given to updating the Dutch SmPC of mirtazapine to include constipation.

- Consider to mention constipation in the SmPC of mirtazapine

References

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6. Chung MY, Min KH, Jun YJ, Kim SS, Kim WC, Jun EM. Efficacy and tolerability of mirtazapine and sertraline in Korean veterans with posttraumatic stress disorder: a randomized open label trial. *Hum. Psychopharmacol.* 2004;19(7):489-94.
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