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A combination of metoclopramide and selective serotonin reuptake inhibitors: additional extrapyramidal effects?

Introduction

Metoclopramide (Primperan®) is a prokinetic agent, which increases gastrointestinal motility. It was approved in the Netherlands in 1968. Metoclopramide possesses central and peripheral dopamine antagonistic properties and it acts on the peripheral 5HT₄-receptors, which results in acetylcholine release from the myenteric plexus [1]. The serotonin reuptake inhibitors (SSRIs) are widely used as antidepressants. SSRIs inhibit the presynaptic reuptake of serotonin. Some of the SSRIs have some acetylcholine antagonistic properties [1].

Extrapyramidal reactions occur during metoclopramide therapy due to the dopamine antagonism of metoclopramide. Extrapyramidal reactions have also been reported during the use of SSRIs. These reactions are probably caused by a serotonergic inhibition of the dopamine neurotransmission in the striatum [2,3]. The SPCs of metoclopramide and most of the SSRIs [4-11] do mention extrapyramidal symptoms as adverse drug reaction. However an additive effect or an interaction between metoclopramide and SSRIs is not mentioned in the SPC of either metoclopramide or the SSRIs [4-10].

Reports

Lareb received 6 reports of extrapyramidal symptoms during combined use of metoclopramide and SSRI's (table 1). All cases were reported by a health professional. In cases A and B the reporting health professional recognized the interaction between the SSRI and metoclopramide, in cases C, D and E the SSRI was mentioned as concomitant medication and in case F metoclopramide was considered as concomitant medication. The symptoms started within a few hours after metoclopramide was administered in cases A,B,C,D and E. In case B and case E the patient was admitted to the hospital because of the extrapyramidal reaction.

Table 1. reports of extrapyramidal reactions with metoclopramide and a SSRIs

Patient, Sex, age	Existing therapy/ time to onset	Additional therapy/ time to onset	Adverse drug reaction	Action taken, outcome
A, F, 32	fluvoxamine 50mg*/ 3 days	metoclopramide 10mg*/ hours	akathisia	both drugs withdrawn, recovered
B, F, 35	fluvoxamine 50mg*/ days	metoclopramide 10mg*/ hours	tardive dyskinesia, trismus	hospitalisation, both drugs withdrawn, recovered
C, F, 38	fluoxetine 20mg/ concomitant	metoclopramide 10mg*/ 1 day	dyskinesia	?, recovered
D, F, 44	paroxetine 20mg/ concomitant	metoclopramide 20mg*/ 6 hours	akathisia, dystonia	?, ?
E, F, 38	paroxetine 20mg/ concomitant	metoclopramide 20mg*/6 hours	extrapyramidal reaction	metoclopramide withdrawn, biperidene, recovered
F, F, 49	metoclopramide 10mg/ concomitant	sertraline 50mg*/ 3 days	dystonia, tinnitus	sertraline withdrawn, recovered

*suspected medication according to health professional

Other sources of information

Literature

In the Dutch interaction-reference-works the interaction between metoclopramide and SSRIs is not mentioned [13,14]. According to Stockley the additive effect of fluoxetine, fluvoxamine and sertraline and metoclopramide was reported in a few isolated case reports [15]. Fisher and Davis published two cases of a serotonin syndrome with serious extrapyramidal movement disorders. The symptoms appeared in two patients on chronic treatment with sertraline or venlafaxine after a single dose metoclopramide [16].

Mechanism

An explanation for these extrapyramidal symptoms is a pharmacodynamic interaction. SSRIs increase the serotonin activity, which inhibits the dopaminergic system, leading to severe extrapyramidal symptoms in combination with the antidopaminergic activity of metoclopramide.

In addition, a pharmacokinetic interaction should be taken into account. Metoclopramide is a known substrate for cytochrome P450 2D6. Citalopram, fluoxetine, paroxetine and sertraline are (weak) inhibitors of this enzyme [1,12]. A decreased metabolism of metoclopramide could enhance the interaction between metoclopramide and SSRI's.

Conclusion

Lareb received 6 reports of a possible interaction of metoclopramide and a SSRI shortly after start of the metoclopramide and some publications suggest that such interaction may occur. SSRIs and metoclopramide both have the potential to cause extrapyramidal reactions by itself. It is conceivable that the combination increases the risk for extrapyramidal symptoms.

References

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