

Pipamperone and increased appetite/weight

Introduction

Pipamperone (Dipiperon®) is a mild to moderately potent butyrophenone neuroleptic and is used in *the treatment of psychosis and severe agitation*. It is a 5-HT(2) receptor antagonist and demonstrates weak affinity for alpha1-adrenergic and D2-receptors. Pipamperone has not been associated with anticholinergic effects. Pipamperone has been approved for the Dutch market since 1968[1].

Weight gain is a well-known side-effect of antipsychotics, alone or part of a metabolic syndrome. Weight gain, diabetes, dyslipidemia, diabetic ketoacidosis, and cardiovascular disease constitute a metabolic syndrome usually associated with second-generation antipsychotics, presenting with comparable frequency in first-generation antipsychotics. The mechanism by which these symptoms are produced is not entirely clear. There is some evidence for both increased appetite and altered metabolic control with these drugs. Patient-related factors include pre-existing metabolic issues. Those who are obese, diabetic or prediabetic, or have high-risk lipid profiles are more likely to experience problems with these medications than other patients. Increased susceptibility for metabolic side effects in patients with some of the disorders they are treated for, particularly schizophrenia, may also play a role [2].

Reports

Between April 1989 and April 2017 Lareb received 12 reports of weight increased and/or increased appetite associated with the use of pipamperone.

Table 1. Cases of pipamperone and increased weight/appetite in the Lareb database

Patient, Sex, Age	Drug Indication for use	Concomitant medication	Suspected adverse drug reaction	Weight gain	Time to onset, Action with drug outcome
A 5073 M, 5-7 years, General practitioner	pipamperone, drug use for unknown indication		weight increased	5 kg	9 weeks, unknown, unknown
B 6253 F, 31-40 years, Pharmacist	pipamperone, 40 mg 2 dd 1, drug use for unknown indication		increased appetite, genital pruritus	not reported	5 days, drug withdrawn, recovered, positive rechallenge
C 19589 F, 5-7 years, General practitioner	pipamperone, hyperactivity		weight increased, hirsutism	8 kg	3 months, dose not changed, unknown
D 25761, F, 41-50 years, General practitioner	pipamperone, obsessive-compulsive disorder		weight increased, hirsutism, breast enlargement, oedema peripheral	not reported	1 week, dose not changed, unknown
E 29382, F, 5-7 years, General practitioner	pipamperone 40 mg 1 dd 1, drug use for unknown indication		weight increased	9 kg in 6 months	6 months, drug withdrawn, unknown
F 36701, F, 41-50 years, Pharmacist	pipamperone 40 mg 1 dd 1, restlessness	trazodone, clorazepic acid, lithium carbonate, propranolol	increased appetite, dyspepsia	not reported	1 day, drug withdrawn, recovered
G 37822, F, 5-7 years, Specialist doctor	pipamperone, sleep and behavioral problems	lamotrigine, ethosuximide	weight increased	14.5 kg in 14 months	6 months, dose not changed, not recovered

Patient, Sex, Age	Drug Indication for use	Concomitant medication	Suspected adverse drug reaction	Weight gain	Time to onset, Action with drug outcome
H 40951, M, 5-7 years, Pharmacist	pipamperone, drug use for unknown indication	valproic acid	increased appetite	not reported	hours, dose not changed, unknown
I 102046, M, 11-20 years, Pharmacist	pipamperone 40 mg 1 dd 1, drug use for unknown indication		increased appetite	not reported	unknown, drug withdrawn, recovered
J 133464, M, 41-50 years, Consumer	pipamperone, manic depression, valproic acid, manic depression, methylphenidate, ADHD	fluticasone, salbutamol/ipratropium	increased appetite, weight increased, abscess, unresponsive to stimuli, suicidal ideation, palpitations	45 kg in 6 months	1 year, drug withdrawn, not recovered
K 236628, M, 2-4 years, Consumer	pipamperone, aggression	methylphenidate	weight increased, increased appetite, urinary incontinence, anal incontinence	10 kg in 1 year	4 weeks, dose not changed, recovering
L 237751, F, 11-20 years, Consumer	pipamperone 40 mg 2 dd 1, anxiety		weight increased, increased appetite	27 kg	4 weeks, drug withdrawn, recovering

Additional information on the cases is given below:

Case G

Medical history of epilepsy and mental retardation.

Case L

The patient has family members with obesity and diabetes.

Other sources of information

SmPC

The SmPC of pipamperone does not mention increased appetite or weight [1].

Literature

There are no reports of pipamperone and increased weight/appetite reported in literature. However, weight gain is a well-known side-effect of several first- and second-generation antipsychotics and the proposed mechanisms could apply for pipamperone as well [3,4]. Furthermore, the national Child and Adolescent Psychiatry Organization mentions weight gain as an important side-effect of pipamperone on their website [5].

Databases

Table 2. Reports of increased weight and/or appetite associated with the use of pipamperone in the Lareb, WHO and Eudravigilance database [6, 7].

Database	Drug	ADR	Number of reports	ROR (95% CI)
Lareb	pipamperone	weight increased	7	5.1 [2.4-11.0]
	pipamperone	increased appetite	7	33.3 [15.5-71.8]
WHO	pipamperone	weight increased	23	1.6 [1.1-2.5]
	pipamperone	increased appetite	12	8.0 [4.6-14.2]
Eudravigilance	pipamperone	weight increased	15	1.2 [0.7-1.9]

Database	Drug	ADR	Number of reports	ROR (95% CI)
	pipamperone	increased appetite	7	7.2 [3.4-15.2]

Prescription data [8]

Drug	2011	2012	2013	2014	2015
pipamperone	21,831	20,071	19,196	18,501	16,664

Mechanism

The mechanism of pipamperone-induced appetite stimulation and weight gain is uncertain, but probably resembles that of risperidone since they both antagonize the alpha1 and 5HT2 receptor. Weight gain is a well-known side-effect of risperidone [9]. Baptista et al. [3] stated that appetite stimulation is probably the main mechanism of body weight gain and this is strongly correlated with the antipsychotic drugs affinity for H1 (histaminergic) and alpha1 (adrenergic) receptors. Furthermore, studies show that the serotonin pathway is closely involved with appetite, feeding and weight gain. Of the serotonin receptors, it appears that 5-HT2A and 5-HT2C are prominent in contributing to weight gain [10]. Pipamperone is a 5-HT2 receptor antagonist and demonstrates a weak affinity for alpha1-adrenergic receptors which may be in part responsible for the weight gain seen in these patients.

Discussion and conclusion

The Netherlands Pharmacovigilance Centre Lareb received 12 reports of increased appetite/weight associated with the use of pipamperone. These reports concerned seven women and five men, with ages varying from 3 to 49 years. Half of the reports are from children aged 3 to 7 years. The weight gain is large (5-45 kg). In three cases, comedication (lithiumcarbonate, clorazepic acid and valproic acid) with known side-effect of increased weight was reported. However, in one of these valproic acid had been used for years without notice of weight increase. Two patients also used methylphenidate of which decreased weight is a known side-effect. Case D also mentions peripheral oedema which could have caused the weight gain, since the reported time to onset for this patient was only one week. Four patients had recovered or were recovering from increased appetite (and one of these four patients was also recovering from increased weight) after drug withdrawal. However it might be difficult to lose weight once it's gained.

The association of pipamperone and increased weight/appetite is supported by a statistically significant disproportionality in the database of Lareb, WHO and Eudravigilance (only for increased appetite). It should be noted that the number of cases in the WHO database is limited, but the total number of reports on this drug is 1 791. Pipamperone is only marketed in Belgium, Denmark, France, Germany, Greece, Japan, the Netherlands, Switzerland and Tunisia.

Weight gain has not been described for pipamperone in literature yet, but it has for other antipsychotics with mechanisms that could apply to pipamperone as well. The available data, especially the amount of weight gained by patients, warrants further attention for this association.

References

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This signal has been raised on December 4, 2017. 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.cbq-meb.nl