

Promethazine and hallucinations

Introduction

Promethazine belongs to the group of the phenothiazines and has anticholinergic, local anesthetic and α -sympatholytic effects. Promethazine is a competitive antagonist of histamine at the H1 receptor and has no effect on the H2 receptor. It also has anti-emetic, sedative and cough suppressive properties (1). The central sedative action may be due to an anticholinergic effect (affinity for muscarinic receptors) and action on other receptors, especially 5-HT (serotonin) receptors (2). Promethazine is registered in the Netherlands in generic forms as tablets, injections and syrup for symptomatic treatment of *allergic diseases based on histamine release such as: hay fever, perennial allergic rhinitis, urticaria and other dermatoses based on direct allergic reaction (prurigo, insect bites), drug exanthems and as an adjuvant in other forms of eczema and allergic asthma and motion sickness* (1, 3-6). Promethazine was granted marketing authorization in the Netherlands in June 1992.

Hallucination is defined by the Diagnostic and Statistical Manual of Mental Disorders DSMV as "a sensory perception that has the compelling sense of reality of a true perception but that occurs without external stimulation of the relevant sensory organ (7). They are associated with psychiatric disease but can also be related to organic disease and drug or toxic exposure (8).

Reports

Between October 1987 and April, 2020 the Netherlands Pharmacovigilance Centre Lareb received 11 reports of hallucinations associated with the use of promethazine. Of these reports, 1 report (Case 6) is based on a publication submitted by the pharmaceutical industry.

Table 1. Reports of hallucinations associated with promethazine

Case	ID (NL-LRB-) sex, age, primary source	Suspect drugs	Dosage	Indication	Concomitant medication	Reported adverse drug reaction	Latency after start	Action taken with the drug/ dose	Outcome
1	3818 F, 20-30 Y Physician Pharmacist	Sirupus Promethazini 1mg/ml Ex Fna	15 ml/ 1 Day	Unknown	noscopine	Hallucination	12 Hours	Unknown	
2	116540 M, 7-10 Y Consumer	Promethazine Comp Pch Stroop 1mg/ml	6 ml / 1 Day	Cough		Hallucination	2 Hours	Withdrawn	Recovered
3	151607 M, 30-40 Y Pharmacist	Promethazine Tablet Omhuld 25Mg	25 mg / 1 Day	Insomnia	paroxetine lithium carbonate olanzapine	Confusion, Hallucination	3 Days 3 Days	Withdrawn	Recovered,
4	161364 F, 70 Years and older Pharmacist	Promethazine Tablet Omhuld 25Mg	25 mg / 1 Day	Cough		Hallucination, Nightmares	3 Days 3 Days	Withdrawn	Recovering
5	178052 F, 10-20 Y Physician	Bupropion Tablet Mga 150Mg (la) ----- Promethazine Tablet Omhuld 25Mg	150 mg / 1 Day 25 mg / 1 Day	Depression Sleep disorder	lorazepam olanzapine	Auditory and visual hallucinations Sensory hallucinations Drug interaction NOS	1 Days 2 Months 1 Day 2 Months 1 Day 2 Months	Withdrawn ----- Not Changed	Recovered
6	GLAXOSMIT HKLIN- NL2016GSK0 54255	Promethazine Capsule 12,5Mg ----- Tramadol		Suicide attempt Suicide attempt	venlafaxine omeprazole irbesartan paracetamol/	Anticholinergi c syndrome, Suicide attempt, Urinary retention,		Withdrawn, -----	Recovered

	F, 40-50 Y Other health professional	Capsule Mga 50Mg			cafeine xylometazolin e	Behavior abnormal, Confusion, Temporospatial disorientation Slurred speech Pupils dilated Tongue dry Skin red Visual Hallucinations		Withdrawn	
7	225918 F, 40-50 Y Physician Physician	Amitriptyline Hydrochloride ----- Promethazine Tablet Omhuld 25Mg ----- Valproinezuur Tablet Mga 500Mg	5 dosage form / 1 Day ----- 25 mg / 1 Day ----- 1150 mg / 1 Day	Complex regional pain syndrome ----- Bipolar affective disorder ----- Bipolar affective disorder	methylphenidate metoprolol	Sleep decreased Itchy rash Hallucination auditory Dreaming excessive Drug interaction	3 Days ----- 2 Days 3 Days ----- 3 Days ----- 2 Days	Dose Reduced ----- Withdrawn ----- Dose Increased	Not Recovered Recovering Not Recovered Not Recovered Recovering
8	227286 M, 70 Years and older Physician	Promethazine Hydrochloride	3 dosage form / 1 Day	Pruritus	pipamperone oxazepam risperidone	Psychotic reaction Hallucination Ataxia	1 Day ----- 1 Day 1 Day	Withdrawn	Recovered
9	248382 M, 10-20 Y Pharmacist	Promethazine Tablet Omhuld 25Mg	25 mg / 1 Day	Sleepless		Palpitations, Tachycardia, Dyspnea, Hallucination	20 Min 20 Min 20 Min 20 Min	Withdrawn	Recovered
10	00327576 F, 70 Years and older Consumer	Promethazine Stroop 1Mg/ml	15 ml / 1 Day*	Sleep disorder	flecainide acenocoumarol	Hallucination Near death experience	30 Minu 30 Minu	Dose Reduced	Recovered
11	00338752 F, 30-40 Y Physician	Promethazine Tablet Omhuld 25Mg	75 mg / 1 Day**	Insomnia		Self injurious behavior Hallucination Confusion Exposure during pregnancy Overdose Off label use	2 Hours ----- 2 Hours 2 Hours	Withdrawn	Recovering

Additional information on the cases:

Case 2: concerns a promethazine syrup compositum, a combination of promethazine hydrochloride with sulphoguaiacolate potassium and Ipecacuanha tincture, administered in an 7-10 year old child.

Case 6: the patient was admitted for observation and recovered within 24 hours. Diagnostics was performed to find a causative agent for strongly suspected anticholinergic poisoning. Blood test revealed supra-therapeutic concentrations of promethazine and tramadol range.

Cases 10 and 11 concern an overdose which may play a role in the occurrence of hallucination.

Case 10: * the dose was probably too high because the patient took a gulp of the syrup from the bottle
The report concerns a 70 years and older female, who experienced hallucination during the night (like hanging on the ceiling and watching herself sleep interpreted as near death experience) 30 minutes after taking promethazine syrup 1mg/ml straight out of the bottle for sleep disorder. She recovered after 8 hours. Concomitant medication was flecainide tablet 50mg and acenocoumarol tablet 1mg. The later investigation showed the abnormality (not specified) in CYP19 and CYP6 enzyme.

Case 11: ** the patient accidentally took 3 tablets instead of 1
This serious report reported by the physician concerns a 30-40 year old pregnant women, known with cycloid psychosis, who was treated with promethazine for insomnia with an upcoming psychotic episode. Two hours after mistakenly taken 3 instead of 1 tablet of promethazine 25mg she experienced confusion and hallucinations with self-injurious behavior (stabbing her stomach

with a knife). The patient was admitted to the hospital due to safety risk. She was treated with olanzapine and was recovering. According to her psychiatrist the symptoms were different from previous psychotic reactions. The patient described the event as feeling jittery, restlessness and feeling paralyzed.

Other sources of information

SmPC

The Dutch official product information of promethazine (1, 3-5) mentions anticholinergic syndrome as an adverse drug reaction but does not specifically mention hallucination. In the SmPC of the promethazine syrup from the manufacturer Teva hallucination is mentioned as a symptom of overdose occurring in children (6). In the US SmPC (9, 10) of promethazine hallucination is mentioned at both therapeutic doses as well as overdose.

Literature

Several case reports are described in the literature of hallucinations and psychosis related to the use of promethazine (11-14). Zametkin *et al* describe a case report of a 9-year old boy with visual and auditory hallucinations during promethazine (and paracetamol) therapy (15).

Page *et al* describe a case series of 199 patients experiencing delirium related to promethazine poisonings. 57 of these 199 patients ingested promethazine alone with no co-ingestants (medication or other toxic products) (16).

A pharmacoepidemiological study of the spontaneous-reporting French Pharmacovigilance Database looking at drug-induced hallucinations, describes promethazine, among other drugs, as hallucination inducing (8).

Databases

Table 2. Reports of hallucinations associated with the use of promethazine in the Lareb, WHO and Eudravigilance database (17, 18).

Database	Drug	ADR	Number of reports	ROR (95% CI)
Lareb	Promethazine	Hallucinations (HLT)	10	12.5 [6.5 - 23.9]
WHO	Promethazine	Hallucination	375	8.7 [7.8 - 9.6]
	Promethazine	Hallucinations mixed	16	13.7 [8.4 - 22.4]
	Promethazine	Formication	39	8.2 [6.0 - 11.3]
	Promethazine	Hallucination visual	61	7.1 [5.5 - 9.1]
	Promethazine	Hallucination auditory	19	3.1 [2.0 - 4.8]
	Promethazine	Hallucination tactile	2	9.8 [2.5 - 39.4]
Eudravigilance	Promethazine	Hallucinations	62	1.8 [1.4 - 2.4]
	Promethazine	Hallucination auditory	4	6.1 [2.3 - 16.2]
	Promethazine	Hallucination visual	6	6.1 [2.7 - 13.5]
	Promethazine	Hallucinations mixed	1	

For Lareb cases, HLT Hallucinations (excl. sleep-related), case no.1 excepted
For the WHO cases, there were 95 cases with a de-challenge.

Prescription data

Table 3. Number of users of promethazine (19)

Drug	2014	2015	2016	2017	2018
R06AD02 Promethazine	38,132	38,352	39,132	38,599	39,448

Mechanism

Promethazine is a first generation H1-antihistaminic drug. Those drugs have prominent anticholinergic actions, due to the affinity for muscarinic receptors, which may contribute to the CNS stimulation seen in some patients (20). Central anticholinergic effects range from concentration problems, sedation and confusion to agitation, hallucinations, delirium and severe cognitive decline. The chance of anticholinergic side effects is increasing with increasing age, because the amount of acetylcholine decreases with ageing and is reduced in patients with Alzheimer's and other dementias (21, 22). The incidence of side effects, especially sedation and antimuscarinic effects, is relatively high (up to 50%) (20). Overdose of various classic H1 antagonists was repeatedly reported to result in toxic psychoses with hallucinations. The elderly and those with a previous history of psychiatric illness are at increased risk of drug-induced hallucination. Hallucinations caused by those drugs are commonly visual (8).

Discussion and conclusion

The Netherlands Pharmacovigilance Centre Lareb received eleven reports of hallucinations in association with the use of promethazine. Ten reports concern an adult patient; one concerns an 7-10 year old child. The latency time in all reports is short (hours- days) and nine patients recovered from the hallucinations after withdrawal or dosage decreasing, some of them after treatment.

The majority of the patients used promethazine for sleeplessness, which is "off label" use. It is known that sleep deprivation can cause hallucinations (23). It is unknown whether and to what extent sleep disorders in the reported cases could have contributed to the occurrence of the hallucinations. In addition, overdose, elderly age and history of psychiatric illness are also considered as a risk of drug-induced hallucination (8). In three of the Lareb cases (Case 6, 10 and 12) an overdose of promethazine was reported. Three patients were older than 70 year (Case 4, 8 and 10). Of the eleven patients, six have a history of mental illness that could contribute to the occurrence of hallucinations: bipolar disorder (Case 3 and 7), schizoaffective disorder (Case 11), dementia (Case 8), depression and alcohol use (Case 6).

Co-medication with anticholinergic drugs, such as some antidepressants, enhances the anticholinergic effect (20). Four patients (Case 3, 5, 6 and 8) used antipsychotics or antidepressants that could be a confounding factor. In Case 7, a recently used amitriptyline ointment for neuropathic pain appears to be the trigger for hallucinations.

The association of promethazine and hallucinations is supported by a statistically significant disproportionality in the databases of Lareb, Eudravigilance and WHO. The WHO database contains 511 cases of hallucinations (HLT) in association with promethazine. The co-reported terms show that overdose probably plays a role. The Preferred Term (PT) intentional overdose is co-reported 155 times (31%).

In the US SmPC (9, 10) of promethazine hallucination is mentioned at both therapeutic doses and overdose. In the SmPCs of promethazine products registered in the Netherlands hallucinations are not specifically labelled as an adverse drug reaction (1, 3-6). Only the SmPC of the Promethazine syrup from the manufacturer Teva (6) describes hallucinations in section 4.9, as a symptom of overdose, occurring in children.

The current information on hallucinations is not consistent for the promethazine SmPCs on the Dutch market. The warning of hallucinations is warranted, in particular in overdose and in combination with anticholinergic comedication or psychiatric comorbidity.

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This signal has been raised on May 20, 2020. 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