

Salbutamol and hallucinations

Introduction

Salbutamol is a selective bèta-2-adrenoreceptoragonist with effect on bèta-2-adrenoreceptor of the bronchial muscles, resulting in bronchodilatation [1]. Salbutamol is indicated for *the treatment of bronchospasm in asthma and COPD and prophylaxis of exercise-induced asthma* [1,2].

Salbutamol was granted marketing authorization in the Netherlands in 1973 [1].

A hallucination is the perception of a stimulus, where none exists but that are perceived as real stimuli. Hallucinations can have various causes including neurological, psychiatric or local sense organ disorders [3].

Reports

From 9 October 1995 to 12 July 2017 the Netherlands Pharmacovigilance Centre Lareb received nine reports of hallucinations associated with the use of salbutamol. Eight reports concerned an aerosol and one report inhalation powder. Six reports concerned children aged nine years or younger.

Latencies were very diverse and varied from 15 minutes to hours in three cases, 6 days in one case, and one or more months in three cases. In two cases the latency was not reported.

There were positive dechallenges in six cases, one patient recovered despite continuation of salbutamol, and in two cases outcomes were unknown.

In one report concerning an adult (case A), the patient previously experienced episodes of hallucinations after the use of alcohol; before the current hallucinations he had consumed two glasses of beer. Another adult (patient D) experienced a psychosis during the use of a corticosteroid, ten years before current reaction. In two cases concerning children, the patients had symptoms which could indicate a respiratory tract infection (E and I), where the hallucinations could also indicate symptoms of delirium due to an infection. In the other reports no other causes possible of hallucinations were specifically described, but cannot be ruled out either. The reports gave no indications for possible overdosing of the drug.

More details of the reports are described in table 1.

Table 1. Reports of hallucinations associated with the use of salbutamol.

Patient, Sex, Age (years), Source	Drug Indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset, Action with drug Outcome
A 12257 M, 11-20 years General practitioner	Ventolin Rotacap inhalpdr 400 mcg, 4 dd 1 Allergic rhinitis due to pollen	Xylometazoline Cetirizine nasal spray	Palpitation Anxiety attack Hallucination visual	Unknown Dose reduced Unknown
B 19560 F, 5-7 years General practitioner	Ventolin 100 aer 100 mcg/do + Babyh, 1 dd 1 Unknown indication		Hallucination auditory	Unknown Drug withdrawn Recovered
C 40154 M, 5-7 years Pharmacist	Ventolin 100 aer 100 mcg/do + Inhal, 4 dd 1 CARA	Salmeterol/fluticason	Hallucination auditory	6 days Drug withdrawn Recovered
D 55133 M, 61-70 years Physician	Salbutamol Mylan aer CFKV 100 mcg/do + Inhal. 2 dd 1 Unknown indication	Local corticosteroids (not specified)	Delusion Psychosis Hallucination	a few months Dose not changed Unknown
E 78996 M, 2-4 years Consumer	Ventolin 200 aer 200 mcg/do + Inhal 1 dd 1 Cough		Hyperactivity Hallucination Aggression	2 months Drug withdrawn Recovered

Patient, Sex, Age (years), Source	Drug Indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset, Action with drug Outcome
F, 84164 M, 5-7 years Pharmacist	Ventolin 100 aer 100 mcg/do + Inhal, 2 dd 1 Asthma		Hallucinations	1 month Drug withdrawn Recovering
G, 171172 F, 21-30 years Consumer	Ventolin 100 aer 100 mcg/do + Inhal, if necessary Hay fever/asthma		Hallucination (sometimes after using maximum dose of 6 puffs)	1 hour Dose not changed Recovered
H, 206862 M, 2-4 years Consumer	Salbutamol aer 100 mcg/do, 4 dd 1 Asthma		Hallucination	15 minutes Drug withdrawn Recovering
I, 236801 F, 2-4 years Pharmacist	Salbutamol Mylan aer CFKV 100 mcg/do + Inhal, 4 dd 1 Dyspnoea and throat complaints, happens when having a cold		Hallucinations	Hours Drug withdrawn Recovered

Other sources of information

SmPC

There are 29 registered products concerning salbutamol available on the Dutch market, excluding the combination preparations. In the salbutamol product with the lowest RVG number, that is Ventolin® 5 mg/ml verneveloplossing (RVG 06676), hallucinations is labelled as a rarely occurring adverse drug reaction. However, in other Ventolin® dosage forms hallucinations are not described; for instance in the SmPC of Ventolin® 2,5 and 5 Nebules, verneveloplossing 1 mg/ml (RVG 12587), hallucinations are not described.

In the Dutch SmPCs of nine other salbutamol products hallucinations is also described as an adverse drug reaction [4]. The salbutamol products and their RVG numbers that describe hallucinations as a labelled adverse reactions in the SmPCs are listed in table 2.

Table 2. Salbutamol product and RVG number, where "hallucination" is listed as adverse drug reaction in the SmPC. [4].

Product	RVG number
Ventolin 5 mg/ml verneveloplossing	RVG 06676
Salamol Steri-Neb 2,5 mg/2,5 ml, verneveloplossing	RVG 100332
Salamol Steri-Neb 5 mg/2,5 ml, verneveloplossing	RVG 100333
Salbutamol 100 Redihaler 100 microgram/dosis, aërosol, suspensie	RVG 26971
Salbutamol 5=1 PCH, inhalatievloeistof 5 mg/ml	RVG 56751
Salbutamol CF 2 mg, tabletten	RVG 57411
Salbutamol CF 4 mg, tabletten	RVG 57412
Salbutamol CF 5 mg/ml, inhalatievloeistof	RVG 57416
Salbutamol Novolizer 100 microgram, inhalatiepoeder	RVG 29458
Salbutamol Sandoz aërosol 100 microgram/dosis, aërosol, suspensie	RVG 34424

Furthermore in several SmPCs hallucinations or psychotic reactions after drug overdose are described in section 4.9 of the SmPC.

Literature including mechanism

Concerning neurocognitive effects, a previous study in rats showed that after intravenous administration, salbutamol rapidly penetrated the 'blood-brain barrier' and reached brain concentrations amounting to about 5% of the plasma concentrations [10]. Hall *et al* described that sympathomimetic amines including salbutamol (reported as albuterol in the United States) with a phenylethylamine nucleus, resembling catecholamines, may stimulate β -receptors in the brain that are thought to mediate anxiety resulting in behavioural changes [11]. A case concerning an eight-year-old child was described, where hallucinations occurred after excessive use of salbutamol [12], but this preparation contained fluorocarbon as propellant, which is not the case for the currently in the Netherlands registered salbutamol products.

Databases

Table 3. Reports of the PT "hallucination" associated with salbutamol, in the Lareb [5], WHO [6] and Eudravigilance database [7].

Database	MedDRA PT	Drug	Number of reports	ROR (95% CI)
Lareb	Hallucination	Salbutamol	6	2.2 (1.0-5.0)
WHO	Hallucination	Salbutamol	140	0.79 (0.66-0.93)
Eudravigilance	Hallucination	Salbutamol	49	1.2 (0.9-1.6)

Prescription data

The number of patients using salbutamol in the Netherlands is shown in table 4 [8].

Table 4. Number of patients using salbutamol in the Netherlands between 2011 and 2015 [8].

Drug	2011	2012	2013	2014	2015
Salbutamol	787,830	780,960	761,890	781,350	808,540

Discussion and conclusion

The Netherlands Pharmacovigilance Centre Lareb received nine cases of hallucinations associated with the use of salbutamol. Psychotic reactions in overdosing is described in several SmPCs of salbutamol, but in the cases received by Lareb concerning hallucinations, there were no indications for overdosing. Six of these cases received by Lareb concerned children, who were all nine years or younger. The current information on hallucinations is not consistent for the salbutamol SmPCs on the Dutch market. In the SmPCs of ten salbutamol products registered in the Netherlands hallucinations is labelled as an adverse drug reaction. The SmPCs of the other nineteen products of salbutamol (excluding products with combinations of drugs), do not report hallucinations as an adverse drug reaction.

References

- SmPC salbutamol Ventolin 5 mg/ml verneveloplossing. (version date: 15-12-2016, access date: 12-7-2017) <https://db.cbg-meb.nl/IB-teksten/h06676.pdf>.
- KNMP Kennisbank [Dutch Pharmacy Database]. (version date: 2017, access date: 12-7-2017) https://kennisbank.knmp.nl/article/Informatarium_Medicamentorum/S1228.html.
- UptoDate. (version date: 2017, access date: 12-7-2017) <https://www.uptodate.com/contents/approach-to-the-patient-with-visual-hallucinations>.
- Geneesmiddeleninformatiebank (version date: 2017, access date: 12-7-2017) www.cbg-meb.nl.
- Lareb databank. (version date: 2017, access date: 12-7-2017) www.lareb.nl.
- WHO Global Individual Case Safety Reports database (Vigilyze). (version date: 2017, access date: 12-7-2017) <https://tools.who-umc.org/webroot/> (access restricted).
- Eudravigilance database. (version date: 2017, access date: 12-7-2017) <http://bi.eudra.org> (access restricted).
- GIP databank. (version date: 2017, access date: 12-7-2017) <https://www.gipdatabank.nl>.

9. College voor Zorgverzekeringen. GIP Databank. (version date: 2017, access date: 12-7-2017) <http://www.gipdatabank.nl/>.
10. Caccia S, Fong MH. Kinetics and distribution of the beta-adrenergic agonist salbutamol in rat brain. J Pharm Pharmacol. 1984;36(3):200-2.
11. Hall RC, Beresford TP, Stickney SK, Nasdahl CS, Coleman JH. Psychiatric reactions produced by respiratory drugs. Psychosomatics 1985;26(7):605-8, 615-6.
12. Schnapf BM, Santeiro ML. Beta-agonist inhaler causing hallucinations. Pediatr Emerg Care 1994;10(2):87-8.

This signal has been raised on August 23, 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