

1.1. Noscapine and angioedema

Introduction

Noscapine is an Over-The-Counter (OTC) drug. It is a cough medicine with a central mechanism of action. Noscapine has a cough depressant effect by blocking the receptors in the reflex centers in the medulla oblongata. It doesn't have an analgesic effect [1]. *Noscapine is registered for the treatment of (a nonproductive) tickling cough* and is also the drug of first choice when a cough depressant is required. Noscapine is available as a syrup and a tablet [2].

Angioedema is a self-limiting, localized swelling of the skin or mucosal tissues. It results from leakage of fluid through the small vessels into surrounding tissues. Exposure of the vasculature to inflammatory mediators causes dilatation and increased permeability of capillaries and venules. It typically affects the face, lips, tongue, throat, ears, hands, feet and genitalia. Angioedema may occur in isolation, accompanied by urticaria, or as a component of anaphylaxis. The known causes of angioedema can be subdivided into three groups, depending upon the underlying mechanism:

- Mast cell-mediated: angioedema results from release of mast cell-derived mediators that increase vascular permeability. Mast cell-mediated angioedema is associated with urticaria and/or pruritus in most cases. Examples are angioedema as reaction to nonsteroidal anti-inflammatory drugs
- Bradykinin-mediated: angioedema results from the generation of bradykinin, which increases vascular permeability. These forms of angioedema are not associated with urticaria and/or pruritus.

The remaining form of angioedema has an underlying mechanism that is not yet clarified [3]

Reports

Between September 29th 1987 and September 12th 2013, the Netherlands Pharmacovigilance Centre Lareb received 10 reports of (symptoms consistent with) angioedema associated with the use of noscapine.

Table 1. Reports of angioedema associated with the use of noscapine

Patient, Sex, Age, Source	Drug, dosage, indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset, Action with drug, outcome
A 4707, M, 2-4 years, General Practitioner	noscapine syrup (1mg/ml; 15 ml), 2dd1, indication unknown		face oedema (red swollen eyelids)	1 day, drug withdrawn, unknown
B 3912, F, 41-50 years, General Practitioner	noscapine syrup (1mg/ml; 8 ml), 3dd1, indication unknown	beclometasone nasal spray	face oedema (swelling eyelids)	1 day, drug withdrawn, unknown
C 19042, F, 31-40 years, General Practitioner	noscapine capsule (15mg), as necessary, cough	ethinylestradiol/levonorgestrel	angioedema	unknown, drug withdrawn, recovered

Patient, Sex, Age, Source	Drug, dosage, indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset, Action with drug, outcome
D 30947, F, 71 years and older, General Practitioner	Noscapine syrup (1mg/ml; 15 ml), 1dd1, indication unknown	diclofenac; alendronate; captopril/hydrochlorothiazide tablet; acetylsalicylic acid	urticaria; periorbital oedema; oedema mouth	2 days, drug withdrawn, unknown
E 31037, F, 51-60 years, Pharmacist	Noscapine syrup (1mg/ml; 15 ml) 2dd, cough	oxymetazoline nasal spray	tongue oedema (swelling tongue and the inside of the mouth)	< 12 hours, drug withdrawn, recovered within 1 week after withdrawal
F 40362, M, 8-10 years, Specialist doctor	noscapine capsule (15mg; 1 DF), dosage unknown, cough		laryngeal oedema; respiratory failure	< 1 day, unknown, not recovered/not resolved
G 154841, F, 21-30 years, Consumer	Noscapine syrup (1mg/ml; 1 DF) dosage unknown, tickling cough		angioedema (swelling tongue and swallowing difficulties) faeces pale	10 minutes, drug withdrawn, recovered/resolved 12 hours, drug withdrawn, recovered/resolved
H 117709, F, 11-20 years, Pharmacist	Noscapine syrup (1mg/ml; 1 DF), dosage unknown, tickling cough		urticaria; angioedema (swelling of lips and throat)	1 hour, Drug withdrawn, unknown
I 159480, F, 71 years and older, Pharmacist	noscapine syrup (1mg/ml; 1 DF), dosage unknown, indication unknown	sumatriptan; paroxetine	swelling face; lip swelling	4 days, drug withdrawn, unknown
J 129261, M, 11-20 years, Consumer	noscapine syrup (1mg/ml; 15 ml) 4dd1, cough		pruritus (hands and feet); peripheral swelling (hands and feet); pharyngeal oedema	4 days, drug withdrawn, recovered/resolved

Case C: the reporter mentioned that the angioedema was life-threatening and has been treated with clemastine.

Case E: was treated with miconazole oral gel.

Case F: was hospitalized and treated with clemastine because of the respiratory insufficiency that occurred following laryngeal oedema.

Case G: visited the emergency room and was treated with clemastine.

Case H: visited the emergency room.

Case I: the reporter mentioned that the swelling of the face and lips was treated. It is unknown which treatment the patient received at that time.

Case J: the reporter mentioned that the adverse drug reaction was life-threatening and was treated with a prednisone injection and bronchodilators.

Other sources of information

SmPC

Angioedema is not mentioned in the SmPC of noscapine syrup and noscapine tablets. The SmPC does mention hypersensitivity reactions like rhinitis, conjunctivitis and rash [1].

Literature

Literature describes hypersensitivity reactions like rhinitis, conjunctivitis and rash. Toxic concentrations of noscapine can lead to histamine-effects including bronchoconstriction, dyspnea, blushing, tachycardia and hypotension [2].

Databases

Table 2. Reports of angioedema (and angioedema associated symptoms) associated with the use of noscapine in the databases of the Netherlands Pharmacovigilance Centre Lareb [4], the WHO- and Eudravigilance (EMA) database [5,6].

Database	Averse drug reaction (ADR)	Number of reports	ROR (95% CI)
Lareb	Angioedema	3	3.86 (1.21-12.27)
	Tongue oedema	1	15.20 (2.10-110.16)
	Periorbital oedema	1	15.31 (2.11-111.00)
	Face oedema	2	8.70 (2.13-35.58)
	Pharyngeal oedema	1	9.81 (1.36-70.91)
WHO	Angioedema	8	3.57 (1.77-7.21)
	Tongue oedema	2	5.00 (1.24-20.09)
	Periorbital oedema	1	1.17 (0.16-8.35)
	Face oedema	2	0.89 (0.22-3.57)
	Pharyngeal oedema	3	9.04 (2.90-28.19)
EV	Angioedema	2	-
	Tongue oedema	0	-
	Periorbital oedema	0	-

Database	Averse drug reaction (ADR)	Number of reports	ROR (95% CI)
	Face oedema	1	-
	Pharyngeal oedema	2	-

Prescription data

Because noscapine is an OTC-drug, there is no information available in the GIP-database regarding the number of patients using noscapine in the Netherlands. However literature shows that 28 percent of cough medications, that are provided without prescription in pharmacies, concerns noscapine [7].

Mechanism

As described above, one of the underlying mechanisms causing angioedema is the mast cell-mediated etiology. Often mast cell-mediated angioedema is associated with urticaria and/or pruritus. This form of angioedema is pathologically similar to urticaria, although it takes place in the deeper levels of the dermis and subcutaneous tissues. Activated mast cells release inflammatory mediators including histamine. Histamine causes dilation of venules in the dermis and enhance venule permeability, with resultant tissue edema [3]. In the literature is described that noscapine causes release of histamine [8]. These mechanisms support the causal relationship between noscapine and angioedema. Literature doesn't mention angioedema as an ADR of noscapine. However the finding that noscapine can stimulate histamine release and the fact that histamine release plays an important role in the pathophysiology of angioedema, support the causal relation between this ADR and noscapine. Mast cell-mediated angioedema caused by histamine release usually begins within minutes after exposure to the provoking substance or stimulus (in this case noscapine). The angioedema builds over a few hours and typically resolves in 24-48 hours. In 6 out of 10 reports the ADR occurs within 24 hours after first use of noscapine. In 3 reports the latency period lies between 2 and 4 days, in 1 report the latency period is unknown.

Conclusion

The Netherlands Pharmacovigilance Centre Lareb received 10 reports of angioedema and angioedema associated symptoms in relation to the use of noscapine syrup or tablets.

The association of these ADR's and noscapine is supported by a statistically significant disproportionality in the database of Lareb. This disproportionality is also shown in the WHO database, except for face oedema (ROR 0.89 (0.22-3.57 CI)). Angioedema isn't described in the SmPC of noscapine. The reported latencies are relatively long and make a causal relationship between noscapine-administration and the onset of angioedema less plausible. It should be taken into account that the concomitant medication that is used by Case D and I are also known for causing angioedema. In these two cases it concerns diclofenac, captopril, acetylsalicylic acid, sumatriptan and paroxetine. It is not clear whether noscapine can safely be readministered when a patient has developed angioedema on previous use.

- Angioedema should be mentioned in the SmPC of noscapine

References

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8. Seth V. Seth S.D., Seth V., editors. Textbook of pharmacology. 3 ed. Elsevier, a division of Reed Elsevier India Private Limited; 2009; 52, Pharmacotherapy of cough.

This signal has been raised on July 2015. 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.cbg-meb.nl