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An overview of reports on tiotropium bromide

Introduction

Tiotropium bromide (Spiriva®) is a once-daily long-acting anticholinergic bronchodilator. It was granted a marketing authorisation on 9 October 2001 as *bronchodilator for maintenance treatment of chronic obstructive pulmonary disease*[1]. The Netherlands act as RMS. Tiotropium is considered a new chemical entity that exerts its action by competitive binding to all three muscarinic receptor sub-types that control smooth muscle function in human airways [2]. Tiotropium exhibits a kinetic receptor subtype selectivity, dissociating rapidly from M_2 receptors but slowly from M_1 and M_3 receptor subtypes hence preventing stimulation of acetylcholine release by negative feedback modulation [3,4]. Tiotropium bromide differs from ipratropium bromide in its longer duration of action and its more rapid M_2 receptor dissociation. Like ipratropium bromide it has a quaternary structure which limits absorption and hence systemic bioavailability. Therefore adverse drug reactions based on local anticholinergic reactions will prevail above systemic effects. Adverse drug reactions listed in the SPC include: dry mouth, constipation, moniliasis, sinusitis and faryngitis [1]. The Netherlands Pharmacovigilance Centre provides an overview of the reports it received during the first 1.5 year after approval.

Reports

Until 1 March 2003 the Netherlands Pharmacovigilance Centre Lareb received 41 reports concerning 66 adverse drug reactions (table 1.). Four of these reports originated from the marketing authorisation holder.

Two cases of death were reported. One 66-year-old female patient with chronic heart failure and an ejection fraction of 20%, died 10 days after start of tiotropium bromide. The reporting general practitioner considered causality unlikely. In the same week Lareb received a report from the marketing authorisation holder describing a patient of unknown age and sex with cardiac complaints who died while taking tiotropium bromide in the Netherlands. Follow up information was never received. It cannot be excluded that these 2 reports refer to the same patient.
The 4 additional reports that were classified serious included urinary tract infection and sepsis in a patient with prostatitis, urinary retention, chest pain and headache, and a patient with vomiting, dizziness, diarrhoea, and nausea.

Other sources of information

Literature

Most studies describe a dry mouth as the most common adverse drug reaction occurring in 6 to 15% of the patients[2-5]. A search in literature reveals no other adverse drug reactions as mentioned in the SPC.

Databases

The WHO adverse drug reactions database contains no information on tiotropium.

Mechanism

The pharmacological mechanism by which tiotropium bromide perceives its effectiveness in the human airways may facilitate anticholinergic adverse drug reactions. It is suggested that structural features limit absorption into the circulation and that the rapid dissociation of the M_2 receptor reduces these anticholinergic adverse drug reactions[5].

Table 1. Adverse drug reactions on tiotropium use reported to Lareb per MedDRA system organ class

S & O class	ADR	n
Card	Angina pectoris	1
	Palpitation	1
Eye	Dry eyes	1
	Vision abnormal	1
	Vision blurred	3
	Visual disturbance	1
Gastr	Abdominal discomfort	1
	Constipation	1
	Diarrhoea	1
	Gingivitis	1
	Mouth dry	2
	Nausea	1
	Oedema mouth	1
	Throat sore	1
	Vomiting	2
Genrl	Chest pain	3
	Chest pressure	1
	Death NOS	2
	Feeling strange	1
	Malaise	3
	Mucosal swelling	1
Infec	Sepsis	1
	Urinary tract infection	1
Inv	Weight increase	1
Metab	Anorexia	2
Nerv	Burning sensation	1
	Dizziness	4
	Drop attacks	1
	Headache	3
	Migraine aggravated	1
	Somnolence	1
Psych	Agitation	1
	Paroniria	1
Renal	Urinary retention	2
Resp	Asthma aggravated	1
	Dyspnoea	3
	Hoarseness	1
Skin	Hyperpigment. skin	1
	Itching	1
	Pruritus	2
	Rash	3
	Rash psoriaform	1
	Sweating increased	1
	Vesicular eruption	1
	Vesicular rash	1
Total		66

Conclusion

During the first 1.5 year after granting a marketing authorisation in the Netherlands, 41 reports on tiotropium were received, including 6 serious reports. The pattern of reported adverse drug reactions on tiotropium bromide reflect described adverse drug reactions in SPC and literature. Many of them can be classified as an anticholinergic reaction. However little information from literature is available until now.

References
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