Fluticasone and palpitations

Introduction

Fluticasone propionate for inhalation (Flixotide®) is indicated for *prophylactic treatment of asthma and symptomatic treatment of moderate to severe COPD* [1]. In the recommended dose fluticasone propionate has an effective glucocorticosteroid activity in the lungs. This results in a reduction of the symptoms and exacerbation of asthma and symptoms of COPD, without the side effects seen with oral corticosteroids [1].

Fluticasone propionate nasal spray (Flixonase®) is indicated for the *prophylaxis and treatment of and allergic rhinitis and rhinitis vasomotorica* [2].
Fluticasone propionate has a powerful anti-inflammatory effect, but when it locally used on the nasal mucosa, it has no detectable systemic activity [2].

Fluticason furoate nasal spray (Avamys®) is indicated for the *symptomatic treatment of allergic rhinitis*, in adults, adolescents and children of six years and older) [3]. Fluticasone furoate is a synthetic trifluor substituted corticosteroid that has a very high affinity for the glucocorticoid receptor and has a potent anti-inflammatory effect [3].

Palpitations is an unpleasant awareness of forceful, rapid, or irregular beating of the heart. There are many possible causes for palpitations. In a previous study in 190 patients presenting with palpitations at an university medical center, in 84% the etiology of the palpitations could be determined after evaluation. The etiology was cardiac in 43%, psychiatric in 31%, miscellaneous in 10%, and unknown in 16% [4,5].

Reports

From 24 January 1996 until 30 June 2014 The Netherlands Pharmacovigilance Centre Lareb received thirty reports concerning palpitations or other cardiac arrhythmia's with the use of fluticasone. Of these reports 18 concerned nasal administration (12 reports of fluticasone propionate, and 6 reports of fluticasone furoate) and 12 inhalation therapy. The reported reactions were palpitations (22 reports), tachycardia (2 reports), arrhythmia (1 report), extrasystoles (3 reports), ventricular tachycardia (1 report) and increased heartrate (1 report). There were 18 women and 12 men. The ages varied between 24 and 76 years and there was one report of a 6 year old patient. The median age was 41 years. There were 13 reports from pharmacists, eight from general practitioners, eight from consumers and one from the industry (where the report originated from a pharmacist). There were 14 reports where fluticasone was the only suspect drug and the patient used no concomitant drugs. There were 6 reports with other suspect drugs and 5 where the patients used concomitant drugs of which palpitations are reported in the SmPC as an adverse drug reaction (ebastine, clemastine, fexofenadine, salbutamol, terbutaline, levocabastine, loratadine, ciclesonide, salmeterol/fluticason, formoterol/budesonide, ipratropium, quetiapine, formoterol/beclometason). The latencies varied between minutes to 2 years, with a median of 4 days. In 6 reports latencies were less than a day, in 11 reports latencies varied from 1 to 7 days, in 9 reports latencies were longer than 7 days, and in four reports the latencies were not reported. In 20 patients fluticasone was

withdrawn and the patients were recovering or had recovered. In 5 patients a positive rechallenge was reported.
In 14 reports of palpitations and 1 of extrasystoles these were the only reported reactions. In the other 15 reports other reactions were also reported, for example agitation or dyspnoea.

Other sources of information

SmPC

The Dutch SmPC's of fluticasone propionate for inhalation, fluticasone propionate nasal spray and fluticasone furoate nasal spray, do not mention palpitations as an adverse drug reaction [1-3].
When looking at other glucocorticoids available on the Dutch market, the Dutch SmPC of prednisolone for systemic use Di-Adreson-F aquosum® for injection, does not mention palpitations as an adverse reaction [6].
The US SmPC of the FDA of fluticasone propionate Flovent® for inhalation does also not mention palpitations as an adverse drug reaction [7].
In the US SmPC of the FDA of prednisone delayed-release tablets cardiac arrhythmias and tachycardia are described as adverse reactions [8]. Palpitations are not specifically described.

Literature

There is no literature available of the symptom palpitations and glucocorticosteroids. Literature is available though on atrial fibrillation and glucocorticosteroids.
Oteri *et al* [9] described a case of a 15-year-old boy with paroxysmal atrial fibrillation with fast ventricular response after the administration of fluticasone propionate, resolving after discontinuation of fluticasone propionate. The authors described that it was reasonable to hypothesize that fluticasone propionate had played a role in the appearance of atrial fibrillation in the patient. The authors mention that it remained to be established whether this effect of fluticasone underlied arrhythmogenesis as a consequence of increased potassium efflux.
In systemic glucocorticosteroid therapy an increased incidence of atrial fibrillation has also been described [10-12]. In one of these articles [11] a population-based cohort study among 7983 older adults was described, showing that only high-dose (oral or parenteral steroid at a daily dose > or =7.5 mg of prednisone equivalents) corticosteroid use was associated with an increased risk (OR, 6.07; 95% CI, 3.90-9.42), whereas low-intermediate-dose use was not (OR, 1.42; 95% CI, 0.72-2.82).
On the other hand, recently a meta-analysis [13] was published, involving 7621 participants who had been treated with cardiac surgery. Cardiopulmonary bypass and cardiac surgery are associated with a significant systemic inflammatory response that has been suggested to play a causative role in the development of perioperative atrial fibrillation [13]. In this study, glucocorticoids prophylaxis significantly lowered participants' risk of developing perioperative atrial fibrillation (Relative Risk [RR] 0.77; 95% confidence interval [CI] 0.66-0.90), P < 0.01).

Databases

Table 1. Reports of palpitations associated with fluticasone (combined reports for Flixotide®, Flixonase® and Avamys®), in the Lareb [14], WHO [15] and Eudravigilance database [16].

Database	MedDRA PT	Number of reports	ROR (95% CI)

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Lareb	Palpitations	22	2.3 (1.5-3.5)
	Extrasystoles	3	24.8 (7.7-79.6)
	Tachycardia	2	-
	Ventricular tachycardia	1	-
	Arrhythmia	1	-
	Heart rate increased	1	-
WHO	Palpitations	176	1.6 (1.4-1.9)
	Extrasystoles	16	2.0 (1.3-3.3)
	Tachycardia	56	0.5 (0.4-0.6)
	Ventricular tachycardia	5	0.4 (0.2-0.9)
	Arrhythmia	26	0.7 (0.5-1.1)
	Heart rate increased	93	2.1 (1.7-2.6)
Eudravigilance	Palpitations	14	2.2 (1.3-3.8)
	Extrasystoles	1	-
	Tachycardia	5	0.5 (0.2-1.3)
	Ventricular tachycardia	1	-
	Arrhythmia	2	-
	Heart rate increased	11	3.0 (1.7-5.4)

* For the WHO- and Eudravigilance database only PT's were selected for which Lareb also received cases

Prescription data

Table 2. Number of patients using fluticasone in The Netherlands between 2009 and 2013 [17].

Drug	2009	2010	2011	2012	2013
Fluticasone Flixotide®	275,610	262,670	255,600	241,360	224,340
Fluticasone Flixonase®	408,920	402,350	406,360	401,540	416,430
Fluticasone Avamys®	122,660	174,560	214,560	220,890	220,040

Mechanism

Oteri et al [9] postulated a possible mechanism in a case of paroxysmal atrial fibrillation as a possible effect of fluticasone, that is arrhythmogenesis as a consequence of increased potassium efflux. In none of the cases received by Lareb, though, atrial fibrillation was diagnosed.

Discussion and conclusion

The Netherlands Pharmacovigilance Centre Lareb received thirty reports concerning palpitations (22 reports) or other cardiac arrhythmia's with the use of fluticasone. Of these reports 18 concerned fluticasone nasal spray, so by accident reporting of fluticasone instead of fluticasone combined with a beta$_2$-sympathicomimeticum, where the latter could cause the palpitations, is not possible in these cases. This in contrast to fluticasone for inhalation. In the WHO database there are 176 cases present of palpitations associated with fluticasone.

In the Lareb-, WHO- and Eudravigilance databases the association is disproportionally present. The FDA SmPC of fluticasone propionate Flovent® for inhalation [7] does not mention palpitations as an adverse drug reaction. Supporting aspects of the cases received by Lareb were 20 positive dechallenges and 5 positive rechallenges, which might indicate a causal relationship. Most latencies were a few days.

A weak aspect was, that there were 11 reports with other suspect drugs or where the patients used concomitant drugs of which palpitations were a known adverse drug reaction. Also, in 15 of the thirty reports other reactions were reported, for example agitation or dyspnoea. These symptoms agitation or dyspnoea by themselves might be an explanation for the palpitations.
Besides this, psychological or behavioral effects including anxiety are known adverse reactions of fluticasone described in the SmPC [1], which might be underlying causes of palpitations although not reported in the cases.
The indications might have played a role as well in the palpitations. Psychological or physiological stress caused by COPD or allergic rhinitis might lead to palpitations by themselves. So confounding by indication can't be excluded. Unfortunately, in most cases the reaction concerned the symptom palpitations without any further information on the underlying cardiac rhythm.
A possible mechanism provided by the literature is also very limited, and only concerns atrial fibrillation which was diagnosed in none of the cases received by Lareb.

Palpitations have a high background incidence and there are many possible causes of palpitations. However, because of the many positive de- en rechallenges in the cases received by Lareb, it is suggested that fluticasone might have a causative role in the occurrence of palpitations.

- Further investigation of the information of the marketing authorization holders and other national centers is needed to confirm the signal

References

1. Dutch SmPC Flixotide 50/125/250 Inhalator CFK-vrij, aërosol, suspensie 50/125/250 microgram/dosis. (version date: 28-11-2012, access date: 17-7-2014) http://db.cbg-meb.nl/IB-teksten/h16212.pdf.
2. Dutch SmPC Flixonase® 50 microgram per dosis, neusspray suspensie. (version date: 17-12-2012, access date: 17-7-2014) http://db.cbg-meb.nl/IB-teksten/h14424.pdf.
3. Dutch SmPC Avamys® 27,5 microgram per dosis, neusspraysuspensie. (version date: 11-1-2008, access date: 17-7-2014) http://www.ema.europa.eu/docs/nl_NL/document_library/EPAR_-_Product_Information/human/000770/WC500028814.pdf.
4. Weber BE, Kapoor WN. Evaluation and outcomes of patients with palpitations. Am J Med. 1996;100(2):138.
5. UpToDate. (version date: 2014, access date: 5-8-2014) http://www.uptodate.com/contents/overview-of-palpitations-in-adults?source=search_result&search=palpitations&selectedTitle=1~150.
6. Dutch SmPC Di-Adreson-F aquosum®. (version date: 2014, access date: 5-8-2014) http://db.cbg-meb.nl/IB-teksten/h00093.pdf.
7. FDA. US SmPC Flovent®. (version date: 2010, access date: http://www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/pediatricadvisorycommittee/ucm235282.pdf.

8. FDA SmPC Rayos (prednisone) delayed-release tablets 1 mg, 2 mg, 5 mg. (version date: 2012, access date: 7-8-2014) http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/202020s000lbl.pdf.
9. Oteri A, Bussolini A, Sacchi M, Clementi E, Zuccotti GV, Radice S. A case of atrial fibrillation induced by inhaled fluticasone propionate. Pediatrics. 2010;126(5):e1237-41.
10. Huerta C, Lanes SF, Garcia Rodriguez LA. Respiratory medications and the risk of cardiac arrhythmias. Epidemiology 2005;16(3):360-6.
11. van der Hooft CS, Heeringa J, Brusselle GC, Hofman A, Witteman JC, Kingma JH, Sturkenboom MC, Stricker BH. Corticosteroids and the risk of atrial fibrillation. Arch Intern Med. 2006;166(9):1016-20.
12. Christiansen CF, Christensen S, Mehnert F, Cummings SR, Chapurlat RD, Sorensen HT. Glucocorticoid use and risk of atrial fibrillation or flutter: a population-based, case-control study. Arch Intern Med 2009;169(18):1677-83.
13. Liu C, Wang J, Yiu D, Liu K. The efficacy of glucocorticoids for the prevention of atrial fibrillation, or length of intensive care unite or hospital stay after cardiac surgery: a meta-analysis. Cardiovasc Ther. 2014;32(3):89-96.
14. Lareb database. (version date: 2014, access date: 17-7-2014) http://www.lareb.nl/Bijwerkingen/Zoek-op-geneesmiddel.
15. WHO Global Individual Case Safety Reports database (Vigibase). (version date: 2014, access date: 17-7-2014) https://tools.who-umc.org/webroot/ (access restricted).
16. Eudravigilance database. (version date: 2014, access date: 17-7-2014) http://bi.eudra.org (access restricted).
17. College for Health Insurances. GIP database. (version date: 7-3-2014, access date: 17-7-2014) http://www.gipdatabank.nl/.

This signal has been raised on November 2014. 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.cbgmeb.nl