Labetalol during pregnancy and nipple pain

Introduction

Labetalol is a selective α_1-blocker and non-selective β-blocker which was granted marketing authorization in the Netherlands in 1977. It is indicated for the treatment of *mild, moderate or severe hypertension, patients with angina pectoris in combination with hypertension and hypertension during pregnancy* [1]. By blocking α_1- and β_1/β_2-receptors, labetalol causes a decrease of peripheral resistance and cardiac output. The ratio of α_1- to β-blockade have been estimated to be approximately 1:3 and 1:7 following oral and intravenous administration, respectively. Labetalol is completely absorbed from the gastrointestinal tract with peak plasma levels occurring 1-2 hours after administration [1].

Methyldopa is first choice for the treatment of hypertension during pregnancy. If mono-therapy with methyldopa leads to high daily doses, the frequency of adverse drug reactions increases disproportionate. Addition of a second drug, labetalol or nifedipine, is then preferred [2].

The current observation describes the possible association between labetalol during pregnancy and nipple pain. Nipple pain has been described in breastfeeding woman [3,4]. Common causes of nipple pain include milk letdown pain, problems with infant latch-on and positioning, plugged lactiferous ducts, atopic dermatitis, allergic or irritant contact dermatitis, psoriasis, secondary infections with organisms such as Candida albicans, and Raynaud phenomenon of the nipple [3].

Reports

In the period from May 7th 2012 until January 10th 2013, the Netherlands Pharmacovigilance Centre Lareb had received 3 reports concerning nipple pain associated with the use of labetalol.

Case A (138585)
This non-serious report from a consumer concerned a female aged 21-30 years with nipple pain following administration of labetalol 200mg with a latency of 30 minutes after start. Labetalol was administrated for hypertension during pregnancy, the patient was pregnant for 31 weeks. The dose for labetalol was decreased and the intake frequency increased, maintaining the daily dose of 200 mg. The nipple pain recovered. Concomitant medication was methyldopa. The patient has no known medical history or past drug therapy. She is a non-smoker and is not familiar with Raynaud's syndrome.

Case B (141890)
This non-serious report from a pharmacist concerned a pregnant female aged 31-40 years with nipple pain following administration of labetalol 200 mg for unknown indication with a latency of 1 hour after each dose. The dose for labetalol was not changed. The nipple pain spontaneously recovered 30 minutes after start. Concomitant medication was insulin. The patient has no known medical history or past drug therapy.

Case C (157410)
This non-serious report from a consumer concerned a female aged 31-40 years with nipple pain and discoloration of the nipple from white to purple/blue following

administration of labetalol 200 mg and methyldopa 500 mg with a latency of respectively 1 hour and 6 months after start. Both drugs were administrated for hypertension during pregnancy. Labetalol was withdrawn, the dose for methyldopa was unchanged. The patient recovered. Concomitant medication was not reported. The patient has no known medical history or past drug therapy.

Other sources of information

SmPC

Nipple pain is not mentioned in the SmPC of labetalol [1].

Literature

In literature one case report was found concerning a 37 year old woman who experienced Raynaud's phenomenon of her nipples after administration of labetalol during both of her previous two pregnancies. The complaints recovered after withdrawal of labetalol [5]. Raynaud's phenomenon is a well-described pathologic state which is characterized by vasospasm of arterioles, causing intermittent ischemia, and subsequent reflex vasodilatation. It is described most commonly in the fingers and toes but also has been shown to affect the nipple vasculature [3,5,6].

Databases

For all reports of the Lareb database is known that the patients were pregnant during the use of labetalol. For the patients out of the other two databases this is not known. The reports of the database of the WHO, with the exception of the Dutch reports, concerned two females aged 27 and 40 years. The Eudravigilance database contains the three Dutch reports, 1 report from Denmark (woman 40 years old who is breastfeeding) and two reports from the UK (both pregnant women, ages 37 and unknown).

Table 1. Number of reported cases of nipple pain associated with the use of labetalol in the dataset of Lareb, the WHO and Eudravigilance

Drug	Number of reports	ROR (95% CI)
labetalol	Lareb: 3	231.9 (68.8-781.8)
	WHO: 5	17.1 (7.1-41.2)
	Eudravigilance:	160.3 (70.9 – 362.2)

Prescription data

There are no prescription data available of patients using labetalol tablets (for hypertension during pregnancy) in the Netherlands [7].

Mechanism

The exact mechanism by which labetalol can cause nipple pain is unknown. Both, selective and non-selective β-blockers are associated with cold extremities due to peripheral vasoconstriction. Labetalol is a blocking agent of α_1- and β_1/β_2-receptors [1]. β_2-receptors blockage would result in vasoconstriction and bronchodilatation. However, α_1-receptor blockage would result in vasodilatation [8]. During pregnancy the woman's breasts grow and the breasts' blood circulation is increased. No literature was found on whether these circumstances influence the α_1- and β_1/β_2-receptor blockage effect of labetalol.

Class effect

Besides the described cases of nipple pain associated with the use of labetalol, the Lareb database contains 1 report of nipple pain associated with sotalol. This report

concerned a 44-year old female with nipple pain and dysgeusia 4 days after start of sotalol. The dose for sotalol is not changed and the patient had not recovered.
The database of the WHO also contains a few reports of nipple pain associated with β-blockers: 3 reports on carvedilol, 2 reports on sotalol and 2 reports on metoprolol. The reports of sotalol concerned women, the other reports concerned men.
Since all described cases in this quarterly report concern pregnant women, and this is not known or not the care for the reports of nipple pain in association with other β-blockers, a class effect cannot be assumed.

Conclusion

The Netherlands Pharmacovigilance Centre Lareb received three reports of nipple pain associated with the use of labetalol administrated in pregnant women. Nipple pain started 30 to 60 minutes after administration of labetalol. This correspondents with the peak plasma levels of labetalol. This association is disproportional present is the database of Lareb, the WHO and Eudravigilance. One possible similar case report was found in literature.

- Nipple pain during pregnancy should be mentioned in the SmPC of labetalol

References

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This signal has been raised on May 2014. It is possible that in the meantime other information became available. For the latest information please refer to the website of the MEB www.cbgmeb.nl/cbg/en/default.htm or the responsible marketing authorization holder(s).