



LETTER TO THE EDITOR—BRIEF COMMUNICATION

Labetalol for hypertension during pregnancy and nipple pain



Dear Editors,

We would like to raise awareness of the occurrence of nipple pain and the possible association with the use of labetalol during pregnancy. Labetalol is an antihypertensive drug with α - and β -blocking properties [1]. It is the only β -blocker that is indicated for the treatment of hypertension during pregnancy. Nipple pain is not described in the Summary of Product Characteristics of labetalol [1]. Nipple pain has several etiologies. Common causes include milk letdown pain, problems with infant latch-on and positioning, plugged lactiferous ducts, dermatitis, psoriasis, secondary infections with organisms such as *Candida albicans* and Raynaud phenomenon of the nipple [2].

The Netherlands Pharmacovigilance Centre Lareb maintains the voluntary adverse drug reaction reporting system in The Netherlands. Lareb received three reports of pregnant women who experienced nipple pain during the use of labetalol. In the presented cases a causal relation with the use of labetalol seems plausible.

All three women had been using labetalol for hypertension during pregnancy. None had a relevant medical history or past drug therapy. The first case concerns a 30-year old gravida with nipple pain starting 30 min after administration of labetalol 200 mg. She was 31 weeks pregnant. The patient recovered after the dose for labetalol was decreased and the intake frequency increased. Methyldopa was used as concomitant medication. She did not smoke and does not have Raynaud's phenomenon in her medical history. The second case concerns a 31-year old gravida who experienced nipple pain 1 h after administration of labetalol 200 mg, three times a day. The dose for labetalol was not changed. The nipple pain spontaneously recovered each time 30 min after labetalol administration. Concomitant medication was insulin. The last case concerns a 38-year old gravida with nipple pain and discoloration of the nipple from white to purple/blue one hour after administration of labetalol 200 mg and methyldopa, three times a day 750 mg. Methyldopa was used for 5 months, and the nipple pain started after addition of labetalol. During previous use of these drugs she also experienced nipple pain. The dose for methyldopa was not changed and the patient recovered after withdrawal of labetalol.

The time to onset of nipple pain in all three women corresponds with the maximum plasma concentration (T_{max}) of labetalol, which is reached after 30–60 min [1]. In addition, the course of the nipple pain in the first and second case—recovery after dose reduction and spontaneously recovery after 30 min—may suggest a dose-related pharmacological effect of labetalol. The elimination half-time of labetalol was found to be shorter in women during the third trimester of pregnancy (1.4–2 h) compared to non-pregnant hypertensive patients (approximately 4 h) [1,3]. This supports

the idea that nipple pain is caused by a dose-related pharmacological effect of labetalol. In the third case the symptoms seem to fit Raynaud's phenomenon of the nipple. In the literature one similar case report was described [4]. Raynaud's phenomenon is a well-described pathologic state, characterized by vasospasm of arterioles, causing intermittent ischemia and subsequent reflex vasodilatation. It is most commonly located in the fingers and toes but also has been shown to affect the nipple vasculature [2,4,5].

The exact mechanism of how labetalol can cause nipple pain or Raynaud's phenomenon is unknown. β -blockers are known to cause peripheral vasoconstriction. Since labetalol is a combined α - and β -blocker it is less likely than other β -blockers to decrease utero-placental blood flow. During pregnancy the woman's breasts grow and blood circulation is increased. Whether these circumstances influence the α - and β -blockage effect of labetalol is unknown.

The presented cases suggest a causal relation between labetalol use during pregnancy and nipple pain. Adjustments to dose and intake frequency of labetalol may have a positive effect.

Competing interests

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References

- [1] Dutch SmPC of labetalol. <http://db.cbg-meb.nl/IB-teksten/h11106.pdf> [version date: 2009, access date: 10.01.14].
- [2] Barrett ME, Heller MM, Stone HF, Murase JE. Raynaud phenomenon of the nipple in breastfeeding mothers: an underdiagnosed cause of nipple pain. *JAMA Dermatol* 2013;149(3):300–6.
- [3] Rogers RC, Sibai BM, Whybrew WD. Labetalol pharmacokinetics in pregnancy-induced hypertension. *Am J Obstet Gynecol* 1990;162(2):362–6.
- [4] McGuinness N, Cording V. Raynaud's phenomenon of the nipple associated with labetalol use. *J Hum Lact* 2013;29(1):17–9.
- [5] Hardwick JC, McMurtrie F, Melrose EB. Raynaud's syndrome of the nipple in pregnancy. *Eur J Obstet Gynecol Reprod Biol* 2002;102(2):217–8.

Leàn Rolfes^{a,b,*}

^aNetherlands Pharmacovigilance Centre Lareb,
's-Hertogenbosch, The Netherlands

^bUniversity of Groningen, Department of Pharmacy,
Pharmacotherapy and Pharmaceutical Care,
Groningen, The Netherlands

Irene de Swart-Ruijter

Teratology Information Service of the Netherlands
Pharmacovigilance Centre Lareb, 's-Hertogenbosch,
The Netherlands

Florence van Hunsel^{a,b}

^a*Netherlands Pharmacovigilance Centre Lareb, 's-Hertogenbosch,
The Netherlands*

^b*University of Groningen, Department of Pharmacy,
Pharmacotherapy and Pharmaceutical Care,
Groningen, The Netherlands*

*Corresponding author at: Netherlands Pharmacovigilance Centre
Lareb, Goudsbloemvallei 7, 5237 MH 's Hertogenbosch, The
Netherlands. Tel.: +31 73 6469700; fax: +31 73 6426136
E-mail address: l.rolfes@lareb.nl (L. Rolfes).

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