Case Report

Hypoglycemia, polycythemia and hyponatremia in a newborn exposed to nebivolol during pregnancy

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Received: 04-02-2014 **Revised: 15-03-2014** **Accepted: 28-06-2014**

ABSTRACT

Nebivolol is a third-generation beta blocker that exerts selective antagonistic activity on β_1 receptors. It has vasodilating properties that result from direct stimulation of endothelial nitric oxide synthase. Nebivolol is indicated for the treatment of hypertension and heart failure, and is generally well tolerated. In this article, we report a case of an infant who was admitted to the Pediatrics and Neonatology Unit of the Moscati Hospital (Aversa, Italy) about 24 hours after birth. The reason for hospitalization was persistent severe hypoglycemia (blood glucose = 30 mg/dL) and jaundice (total bilirubin = 12.5 mg/dL, indirect bilirubin 11.75 mg/dL). He was born by spontaneous delivery after a normal term pregnancy. Birth weight was 3040 g and the Apgar score was 6-9. The mother reported taking nebivolol 5 mg/day for unspecified tachycardia in the last 4 months of pregnancy. Clinical and instrumental investigations carried out during hospitalization did not reveal any congenital or perinatal abnormalities. After treatment for metabolic and electrolyte imbalance, he was discharged on the 10th day of hospitalization, in good clinical condition and with normalization of clinical and laboratory parameters. Currently, there are no specific studies on nebivolol tolerability during pregnancy. Our data suggest that the risk profile of nebivolol during pregnancy is the same as that of other β-blockers. Therefore, further studies are required to determine the safety of β-blockers during pregnancy and the risks to the unborn child.

Key words: Adverse drug reactions, nebivolol, newborn, pregnancy

INTRODUCTION

Nebivolol is a third-generation β1-selectiveblocker that is indicated for the treatment of hypertension and heart failure.[1] It has vasodilatory properties mediated by direct stimulation of the endothelial nitric oxide synthase (eNOS).[2] Nebivolol is a racemic mixture of two enantiomers in a 1:1 ratio,[3] namely a d-and an l-isomer. The D-isomer selectively blocks the β_1 receptor and has mild vasodilatory properties, while the L-isomer stimulates eNOS, thereby resulting in vasodilatation.[4] The hemodynamic changes induced by nebivolol may lead to a negative chronotropic effect, inhibition of sympathetic outflow from cerebral vasomotor centers, inhibition of peripheral β_1-adrenoceptors,[5] suppression of renin activity, and decreased peripheral vascular resistance. The very high selectivity of the nebivolol D-isomer for β_1- versus β2-adrenergic receptors involves the limited effects on airway reactivity, insulin sensitivity[6,7] and

Access this article online	
Quick Response Code:	Website: www.jpharmacol.com
	DOI: 10.4103/0976-500X.149148

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the lesser negative inotropic effect of nebivolol in patients with heart failure.[8,9] Although nebivolol has no intrinsic sympathomimetic activity, it exerts an agonistic effect on β_3-receptors, which may partially explain its effects on the endothelium.[5]

Nebivolol is well tolerated. The most frequently occurring adverse events (AEs) associated with nebivolol reported in clinical trials are fatigue (4-79%), headache (2-24%), paresthesia (7-13%), bradycardia (6-11%), rhinitis (1-7%), and dizziness (2-5%). Other commonly reported (>1%) nebivolol-associated AEs are diarrhea (2-3%) and nausea (1-3%), both of which are consistent with AEs reported for other β-blockers. Adverse events reported in <1% of patients are insomnia, asthenia, hypercholesterolemia, and hyperuricemia.[2] The following AEs were communicated to the manufacturer after nebivolol became commercially available: abnormal hepatic function, acute pulmonary edema, acute renal failure, atrioventricular block, bronchospasm, erectile dysfunction, hypersensitivity, myocardial infarction, pruritus, psoriasis, Raynaud's phenomenon, intermittent claudication, somnolence, syncope, and thrombocytopenia.[2] Nebivolol is contraindicated in patients with severe bradycardia, atroventricular nodal block greater than first degree, cardiogenic shock, decompensated heart failure, and severe liver disease. Like the use of other β-blockers, abrupt cessation of nebivolol therapy is not recommended because it may lead to a rebound effect and to the precipitation of severe angina, myocardial infarction, and ventricular arrhythmias.[2]

Like most antihypertensive agents used in pregnancy, nebivolol is designated a pregnancy category C medication (no human data supporting safety or toxicity during pregnancy). Category C includes drugs for which human studies are lacking but animal studies showing a fetal risk. Category C drugs should be administrated only if the potential benefits outweigh the potential risks to the fetus. This category is difficult to interpret because there is no evidence of risk and it is so broad to be preclude usefulness in practice.[10]

CASE REPORT

Here we report the case of an infant who was admitted to the Pediatrics and Neonatology Unit of the Moscati Hospital (Aversa, Italy) about 24 hours after birth. The reason for hospitalization was persistent severe hypoglycemia (blood glucose = 30 mg/dL) and jaundice (total bilirubin = 12.5 mg/dL, indirect bilirubin 11.75 mgl/dL). He was born at term by spontaneous delivery after a normal pregnancy. Birth weight was 3040 g and the Apgar score was 6-9. The mother reported taking nebivolol 5 mg/day for unspecified tachycardia in the last 4 months of pregnancy. Because of jaundice and hypoglycemia, the infant immediately underwent phototherapy and intravenous administration of 10% glucose solution. The laboratory tests carried out at admission revealed polycythemia with hematocrit 63.7%, red blood cells count of 6,230,000/mm^3, mild hyponatremia (132 mEq/L) and mild thrombocytopenia (platelets = 99,000/mm^3) with prolongation of prothrombin time and activated partial thromboplastin time. Tests during hospitalization showed blood glucose level within normal limits, despite treatment with intravenous glucose solution, and coagulation remained deranged without overt clinical manifestations, and hyponatremia became more pronounced.

Urinary electrolytes were below normal, hence it was decided to reduce fluid intake and increase the administration of sodium chloride. Abdominal ultrasonography, cardiology consultation, electrocardiography, echocardiography, and brain CT scan were unremarkable. Serial C-reactive protein, urinalysis, urine cultures and blood cultures were also unremarkable.

The clinical condition of the newborn gradually improved and coagulation test and the levels of blood glucose, bilirubin and serum sodium normalized. Consequently, the patient was discharged on the 10th day, in a good clinical condition and with normalization of clinical and laboratory parameters.

DISCUSSION

The detection of adverse drug events (ADEs) is crucial to improving the quality of health care system both in adults and, especially in pediatrics. To date, pharmacovigilance studies on vaccine and drug safety are still not enough in pediatric population.[11-14] Moreover, pregnant women are often excluded from clinical studies, and this could induce an inadequate pharmacological treatment which could compromise both fetal and maternal well-being.

In this scenario, we report the first case, to our knowledge, of nebivolol induced a hypoglycemia, polycythemia and hyponatremia in a newborn after a spontaneous at-term delivery. During pregnancy, the mother received an off-label prescription of nebivolol for unspecified tachycardia. The consequences of β-blocker treatment during pregnancy are debated. Some studies found an association between β-blocker treatment and small for-gestational-age (SGA) newborns and preterm births,[15-19] but not others.[20,21] A study conducted in a cohort of all births in Denmark between 1995 and 2008 revealed an association between exposure to β-blockers and preterm birth and perinatal mortality. When the analysis was adjusted for maternal comorbidity, co-medication and smoking, only labetalol was found to be associated with perinatal mortality.[22] However, other studies show that labetalol is safer than other β-blockers during pregnancy,[10,23] thus this drug is becoming the first-line choice for hypertension and

other chronic conditions during pregnancy. In any event, the risk of SGA, preterm birth and perinatal mortality following exposure to β-blockers could be a class effect.[22]

Our patient was affected by hypoglycemia, polycythemia and hyponatremia after being exposed to nebivolol during the last 4 months of pregnancy. There are numerous reports of hypotension, bradycardia and hypoglycemia in infants after administration of β-blockers, particularly labetalol, during pregnancy.[24] In particular, a cohort study showed that exposure to β-blockers in the last trimester of pregnancy is associated with an increased risk of hypoglycemia in infants. In fact, β-blockers spread through the placenta, and can increase insulin levels and decrease glucagon levels in the fetus, thereby resulting in hypoglycemia in the newborn.[25] However, hypoglycemia is common in neonates and usually occurs in the first 48 hours after birth. The risk of hypoglycemia in newborns is increased by prematurity, perinatal stress or asphyxia, small size for gestational age and being born to diabetic mothers.[26] Hypoglycemia can be transient or persistent. The persistent form may be due to metabolic diseases, such as hyperinsulinism and hypopituitarism, or hereditary hepatic enzyme deficiencies.[27] Instead, the transient hypoglycemia could represent a metabolic mechanism of adaptation to extrauterine life[28] and is commonly observed in at-risk infants.[29] Moreover, transient low blood glucose concentrations are frequently observed in healthy newborns[30] and, unlike in our case, it is a transient phenomenon.[28] Therefore, it is conceivable that exposure to nebivolol has favored the onset and persistence of hypoglycemia in our patient.

There are no reports of hyponatremia or polycythemia consequent to exposure to nebivolol. In our case, polycythemia may have resulted from placental insufficiency induced by nebivolol. In fact, β-blockers reduce placental perfusion.[24] The effects on placental hemodynamics have been observed in both human and animal studies. It has been suggested that β-blockers without intrinsic sympathomimetic activity cause selective vasoconstriction of placental vessels.[31] Placental insufficiency can lead to chronic or acute fetal hypoxia with birth asphyxia and hypothermia, neonatal hypoglycemia, polycythemia and coagulopathy.[32] Hyponatremia could be the consequence of increased blood viscosity resulting from polycythemia and thus it would be a pseudohypontremia.

CONCLUSION

To our knowledge, this is the first case of hypoglycemia, polycythemia and hyponatremia in a newborn exposed to nebivolol during the last 4 months of pregnancy.

The safety profile of beta blockers (β-blockers) used in pregnancy is still unclear and controversial. There is a lack of studies on the tolerability and safety of nebivolol during pregnancy. However, it appears that the risk profile of nebivolol for pregnancies is the same as that of other β-blockers. Therefore, there is a need for studies designed to assess the tolerability profile of this class of drugs when used in pregnancy in order to minimize risks both for the unborn that for pregnant women. For this reason pharmacovigilance post-marketing studies are key elements to monitor the safety and effectiveness of approved drugs,[33-37] especially when used in special conditions such as pregnancy.

ACKNOWLEDGEMENT

The authors thank Jean Ann Gilder (Scientific Communication srl., Naples, Italy) for text editing.

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How to cite this article: Sullo MG, Perri D, Sibilio M, Rafaniello C, Fucile A, Rossi F, *et al*. Hypoglycemia, polycythemia and hyponatremia in a newborn exposed to nebivolol during pregnancy. J Pharmacol Pharmacother 2015;6:45-8.

Source of Support: Nil, **Conflict of Interest:** None declared.