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LETTER TO THE EDITOR

Doxazosin treatment of phaeochromocytoma during pregnancy: placental transfer and disposition in breast milk

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Information on transfer of drugs and metabolites into placental blood and breast milk is based on modelling, animal experiments and clinical observations due to lack of experimental evidence in humans. We describe the use of doxazosin in a pregnant woman with a phaeochromocytoma. Treatment of a phaeochromocytoma in pregnancy consists of α-adrenergic receptor blockade followed by surgical excision either during pregnancy or directly after delivery. We measured doxazosin concentrations before and after delivery in maternal and umbilical cord blood sampled from the umbilical vein and breast milk using a validated toxicology liquid chromatography-mass spectrometry method. The patient approved these additional tests and publication of her case.

A 35-year-old Caucasian woman (gravida 3, para 2; two first pregnancies without complications) was diagnosed as having a phaeochromocytoma in her right adrenal gland at the end of the second trimester of pregnancy. Her blood pressure was well-controlled using doxazosin 4 mg once daily, probably as a consequence of only mildly elevated catecholamines. Because of the advanced pregnancy we decided to follow-up in the outpatient setting with regular home blood pressure measurements. At week 37, she was admitted to the hospital for intensification of her antihypertensive therapy prior to induction of labour at week 38 (+2 days). Her mean arterial blood pressure (MAP) was targeted to be ≤100 mmHg.

A 24 hr blood pressure measurement showed a mean MAP during daytime of 104 mmHg. The doxazosin dosage was increased (Table 1) and metoprolol 12.5 mg was added 2 days before delivery because of tachycardia (heart rate > 100 beats min^{-1}). Vaginal delivery was without complications.

A boy was born with a good start (Apgar score of 9 and 10 after 1 and 5 min) and a birth weight of 4210 g. Physical examination did not show any abnormalities including dysmorphic features and kidney function was normal. He was monitored at the neonatal intensive care unit for 30 h. His blood pressure, measured every hour, was normal, MAP around 50 mm Hg. Three days after delivery, his mother underwent adrenalectomy. The diagnosis of a phaeochromocytoma with a diameter of 7.5 cm was confirmed. Directly after surgery, doxazosin and metoprolol were stopped.

Based on the small molecular size but high level of protein binding (98%) it was hard to make a prediction about the placental transfer of doxazosin. We hypothesized that it would be limited, based on data in rabbits and rats and no reported serious adverse events in human newborns [1]. In our patient, we found a doxazosin fetal : maternal ratio of 0.8, indicating exposure of the fetus to therapeutic doxazosin concentrations (Table 1). One could argue that some placental transfer of an α-adrenergic receptor blocker is appropriate to prevent adrenergic stimulation of the fetus. However, earlier studies in phaeochromocytoma during pregnancy and one unpublished case in our hospital showed low levels of catecholamines (adrenaline and norepinephrine) in umbilical cord blood (<10% of maternal levels) [2]. This is due to high activity of catecholamine transporters (most importantly: norepinephrine transporters) and metabolizing enzymes such as catechol-O-methyltransferase in the placenta probably to protect the fetus against elevated catecholamine levels during delivery [2]. The umbilical cord plasma concentrations of metanephrine and normetanephrine we measured were approximately half of the maternal levels (Table 1). We do not know whether these levels were completely of fetal origin or also in part from maternal origin, following crossing of the placenta of either free metanephrines or rapidly degraded catecholamines.

The other α-adrenergic receptor blocker that has been used during pregnancy is phenoxybenzamine that binds irreversibly [3]. The fetal : maternal plasma ratio of phenoxybenzamine is 1.6, suggesting accumulation in the fetus. Neonatal hypotension

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Table 1

Plasma concentrations of doxazosin and (nor)metanephrine at different time points

	Doxazosin dose (mg)					
	a.m.	p.m.	Plasma	Doxazosin (μg l^{-1})	Metanephrine (nmol l^{-1})	Normetanephrine (nmol l^{-1})
−1 month	4 mg	-	Maternal		1.15	6.9
−1 week (hospital admission)	6 mg					
−3 days	6 mg	2 mg	Maternal	45 (peak concentration)		
Day 0 (delivery)	6 mg	2 mg	Maternal	48 (12 h after drug intake)	1.23	6.8
			Umbilical	40	0.48	3.77
+2 days	6 mg	4 mg	Maternal	72 (trough concentration)		
+3 days (surgery)	8 mg	-	Maternal	95 (trough concentration)		
+2 weeks	-	-	Maternal		<0.06	0.22

Therapeutic range for trough concentration of doxazosin: 10–150 μg l^{-1}. Lower limit of quantification plasma assay 25 μg l^{-1}. Metanephrine normal <0.3 nmol l^{-1}; Normetanephrine normal <0.6 nmol l^{-1}

and respiratory depression after maternal use of phenoxybenzamine during pregnancy has been reported, although in this case report the mother also used a low dose of labetalol and in most cases also phenoxybenzamine appeared safe [4].

Doxazosin has earlier been described to transfer into breast milk [5]. Our first breast milk sample (mixed foremilk and hindmilk) could be obtained 30 h after the last dose and did not show any doxazosin disposition. Given the plasma half-life of 16–30 h, maternal plasma concentrations of doxasozin are expected to be still in the therapeutic range at that time. Therefore, we assume that transfer into breast milk was low during doxazosin use. Also for phenoxybenzamine a low percentage of transfer into breast milk has been described, around 1% [1, 3].

Our results support earlier evidence that doxazosin is a safe α-adrenegic receptor blocker to use in pregnant women with a phaeochromocytoma. Although it passes the placenta, the fetal drug concentration remained lower than the maternal concentration, at least for the relatively low dose of 8 mg. We cannot recommend its use during breastfeeding, but based on our data it seems safe to start breastfeeding 1 day after the last doxazosin dose.

Competing Interests

All authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare no support from any organization for the submitted work, no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years and no other relationships or activities that could appear to have influenced the submitted work.

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