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EDITORIAL

More safety data: what about efficacy of sildenafil?

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In this issue of the *Journal of Perinatology*, Samiee-Zafarghandy *et al*. report results of their multi-center retrospective study investigating the risk of severe retinopathy of prematurity in a large cohort of very low birth weight infants exposed to treatment with sildenafil.[1] The authors matched 81 infants who received sildenafil with 243 non-exposed infants. Infants on sildenafil were born at a very low gestational age (median 25 weeks), and received more intensive care support compared with non-exposed infants. The study did not show an increased risk for severe retinopathy of prematurity for very low birth weight infants on sildenafil, and confirms results from a previous small single-center study of preterm infants born < 30 weeks gestational age with bronchopulmonary dysplasia (BPD)-associated pulmonary hypertension (PH).[2] Also, a study in a cohort of term and near-term newborns treated with sildenafil did not show an association with ocular complications.[3]

BPD-associated PH is a common morbidity in extremely preterm infants. Two recent large prospective observational studies investigated late PH in the clinical course of preterm infants with evolving BPD. The incidence for BPD-associated PH was 11.7 and 14%, respectively, and mortality in early infancy was high, reportedly 10.3 and 11.5%.[4,5] An effective and safe treatment would obviously be desirable to decrease mortality and the burden for affected infants and their parents.

So what about efficacy of sildenafil in very preterm infants suffering from BPD-associated PH? Unfortunately, studies and data in this population are still very scarce. Nyp *et al*. reported retrospective data of 21 preterm infants with a median gestational age of 27 weeks who received sildenafil for BPD-associated PH. Although they were able to show a reduction of pulmonary artery pressures (PAP) in their cohort, this did not translate into an improvement in pulmonary gas exchange or oxygen requirement.[6] Tan *et al*. recently reviewed 22 very preterm infants (median gestational age 25.6 weeks) receiving sildenafil for BPD-associated PH in their neonatal intensive-care unit. A decrease in PAP was demonstrated, and also a small but significant decrease in oxygen requirement from 0.57 to 0.42.[7] Similarly, Wardle *et al*.[8] showed an effect of sildenafil on PAP in another case series of 14 extremely preterm infants. An earlier study addressed long-term follow-up over 2.5 years of 25 preterm and term infants with PH receiving sildenafil, and again an effect on hemodynamic parameters was demonstrated.[9] Adverse effects were rare in all studies.

However, whether treatment with sildenafil reduces mortality or improves long-term outcome remains unknown. The above mentioned studies demonstrate that sildenafil is commonly prescribed in preterm infants, despite the well-known controversy about a previous Food and Drug Administration (FDA) warning regarding the use of sildenafil in children with PH following publication of the Barst trial.[10] Surprisingly and also disappointingly, a search in a number of international trial registries did not reveal a single study currently registered with the aim to investigate the effect and safety of sildenafil in BPD-associated PH in preterm infants (www.clinicaltrials.gov, www.clinicaltrialsregister.eu, www.anzctr.org.au). We still do not know whether sildenafil is a therapeutic option for this specific population. Large prospective trials investigating the efficacy and safety of sildenafil in extremely preterm infants, addressing mortality and major morbidities are desperately needed before sildenafil can be safely recommended in this fragile population.

CONFLICT OF INTEREST

The author declares no conflict of interest.

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