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Sildenafil as Bridge Therapy for Inhaled Nitric Oxide in Preterm Neonates

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OBJECTIVE Inhaled nitric oxide (iNO) is a mainstay of treatment for infants with persistent pulmonary hypertension. However, abrupt discontinuation of inhaled nitric oxide can result in rebound pulmonary hypertension. The objective of this analysis is to describe the use of sildenafil to facilitate the weaning from iNO in preterm neonates.

METHODS This retrospective chart review identified all infants who were receiving iNO and subsequently received sildenafil between 2017 and 2021. Neonates were included if they met the following criteria: gestational age at birth less than 34 weeks, receiving iNO, and started on sildenafil with the indication to facilitate weaning or discontinuation of iNO. Patients were excluded if they had major congenital anomalies, including congenital heart disease or congenital diaphragmatic hernia.

RESULTS We identified 7 neonates with a gestational age range of 22 5/7 weeks to 31 0/7 weeks and birth weight range of 545 to 910 g with previously failed attempts at iNO weaning. The most common starting dose for sildenafil was 0.125 mg/kg intravenously every 8 hours or 0.25 mg/kg enterally every 8 hours. Four infants were able to discontinue iNO within 48 hours of sildenafil initiation, 1 patient discontinued iNO within 5 days, and 1 patient within 10 days of sildenafil initiation. One patient experienced weaning failure from iNO despite initiation of sildenafil. No adverse events, such as hypotension or deaths, were reported in any of the 7 infants.

CONCLUSIONS Sildenafil facilitated weaning off iNO in most preterm neonates evaluated without adverse side effects.

ABBREVIATIONS BPD, bronchopulmonary dysplasia; cGMP, cyclic guanosine monophosphate; FDA, US Food and Drug Administration; iNO, inhaled nitric oxide; IV, intravenously; NICU, neonatal intensive care unit; PAH, pulmonary arterial hypertension; PPHN, persistent pulmonary hypertension of the newborn; ppm, parts per million

KEYWORDS inhaled nitric oxide; neonate; persistent pulmonary hypertension; phosphodiesterase type 5; premature neonate; prematurity; sildenafil

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Introduction

As survival rates of preterm and even extremely preterm neonates increase, so does the prevalence of bronchopulmonary dysplasia (BPD).[1] Significant BPD can lead to pulmonary arterial hypertension (PAH), which is a distinct form of pulmonary hypertension thought to be caused by pulmonary vascular remodeling and altered pulmonary capillary beds.[2] In addition, preterm neonates are at higher risk for developing chronic PAH associated with fetal growth restriction or pulmonary hypoplasia.

Inhaled nitric oxide (iNO), a selective pulmonary vasodilator, increases intracellular cyclic guanosine monophosphate (cGMP), promoting smooth muscle relaxation. Inhaled NO decreases pulmonary vascular resistance in adults with pulmonary hypertension, decreases pulmonary vascular disease and inflammation, as well as increases pulmonary blood flow in animal models.[3]

Following multiple pivotal trials in the 1990s, the US Food and Drug Administration (FDA) approved the use of iNO for the treatment of hypoxic respiratory failure associated with clinical or echocardiographic evidence of pulmonary hypertension in term and near-term (greater than 34 weeks' gestational age) neonates.[4–7] Since then, it has been a mainstay of treatment for infants with persistent pulmonary hypertension of the newborn (PPHN) in neonatal intensive care units (NICUs) globally. However, the use of iNO in preterm neonates, remains controversial, with

recommendations from major organizations varying greatly.[8–10]

While the use of iNO in the preterm population remains a subject of debate, its use in this population has exponentially increased over time.[11,12] Some studies demonstrate promise in the preterm population, including a potential reduction in chronic lung disease.[13,14] Although the current incidence of iNO use in the preterm population is unknown, past literature has indicated that up to 26.2% of infants less than 34 weeks' gestation, admitted to the NICU in the United States, are treated with iNO[15] and that treatment varies with gestational age (13.9% of neonates at 23 to 24 weeks' gestation versus 0.6% of 33 weeks' gestation).[12] What remains a constant, however, is that iNO is one of the most expensive therapies in the NICU. While costs vary by contract, the cost per hour nationwide in recent years was $140 per hour.[16] Based on this and with its increased use in the NICU, judicious weaning is needed.[16]

The abrupt discontinuation of iNO can cause rapid depletion of cGMP, leading to rebound pulmonary hypertension and prolonged courses of iNO. A selective inhibitor of phosphodiesterase-5, such as sildenafil, can potentially ameliorate the effects of abrupt discontinuation of iNO.[17] While sildenafil has been studied for the treatment of PPHN, there is minimal literature on its use for facilitating the weaning of iNO in neonates specifically. This includes one case study of 3 infants of unknown gestational age, weighing 3.1 to 4.1 kg, who each received a 1-time dose of sildenafil 0.26 to 0.32 mg/kg as a bridge therapy to successfully wean off iNO.[17] This was the first time in neonatal literature that sildenafil was used for this specific purpose.

Use of sildenafil to facilitate weaning off iNO, to our knowledge, has not been specifically described in the preterm neonatal population. In this analysis, we describe multiple cases where sildenafil was implemented safely as a bridging therapy for preterm neonates receiving iNO treatment.

Methods

In this retrospective chart review, we evaluated neonates admitted to the NICU at the University of Chicago Medicine Comer Children's Hospital between 2017 and 2021. Neonates were included if they met the following criteria: gestational age less than 34 weeks, receiving iNO for a diagnosis of pulmonary hypertension, and subsequent initiation of sildenafil specifically to facilitate weaning from or discontinuation of iNO. Patients were excluded if they had major congenital anomalies, including congenital heart disease or congenital diaphragmatic hernia.

Results

We identified 7 neonates with a gestational age range of 22 5/7 weeks to 31 0/7 weeks and birth weight range of 545 to 910 g. The postnatal age at the time of initiation of iNO ranged from 3 to 66 days. All neonates had experienced 1 to 3 prior failed attempts at weaning from iNO before sildenafil initiation. The dose of iNO when sildenafil was initiated varied greatly between 4 parts per million (ppm) to 10 ppm. The most common starting dose for sildenafil was 0.125 mg/kg intravenously (IV) every 8 hours (3 patients) and 0.25 mg/kg enterally every 8 hours (3 patients), which are equivalent doses when using an IV to oral formulation ratio of 1:2. Six of 7 infants successfully weaned off iNO following initiation of sildenafil. Four infants discontinued iNO within 48 hours after sildenafil initiation, 1 patient discontinued iNO 5 days after sildenafil initiation, and 1 patient discontinued iNO 10 days after sildenafil initiation. One patient was discontinued from sildenafil at 5 days post initiation owing to failure to wean off iNO. The iNO was eventually weaned successfully 7 days after sildenafil discontinuation.

The weaning of sildenafil following discontinuation of iNO was variable between patients. Of the 4 infants who discontinued iNO within 48 hours of sildenafil initiation, weaning or stopping of sildenafil varied from immediately after discontinuing iNO, 24 hours after, 48 hours after, and almost 2 weeks later. In general, weaning steps typically occurred every 1 to 2 days and generally consisted of reducing the frequency from every 8 hours to every 12 hours (and sometimes then to every 24 hours) prior to discontinuation.

No adverse events attributable to sildenafil occurred in any of the 7 infants. Specifically, no patients developed hypotension or required initiation or escalation of vasopressors after sildenafil was started. Additional information for each patient can be found in the Table.

Discussion

In this retrospective chart review, sildenafil successfully and safely facilitated weaning off iNO in preterm neonates, with discontinuation of iNO reported within 48 hours in 4 of 7 infants evaluated. Infants 1, 2, and 3 were still 32 weeks' postmenstrual age or less when sildenafil was initiated, which suggests that this therapy may be safe for a limited duration in the premature population. Our review found that our most common starting dose for sildenafil was either 0.125 mg/kg IV every 8 hours or 0.25 mg/kg enterally every 8 hours, which are equivalent IV to oral doses.

A recent study at our institution showed that implementing an iNO weaning protocol decreased the total hours of iNO use by 60%.[16] The full iNO weaning protocol is available in this prior publication. It includes consideration for the addition of a 1-time dose of sildenafil 0.25 mg/kg enterally (or 0.125 mg/kg IV) prior to weaning off iNO if there is a failure to wean iNO alone. A dose escalation of sildenafil to 0.4 mg/kg enterally (0.2 mg/kg IV) for further failed attempts

Table. Demographic Characteristics and Clinical Features of the 7 Premature Neonates Receiving Sildenafil as Bridge Therapy for Inhaled Nitric Oxide

	Demographics (GA, birthweight, race, sex)	PMA at initiation of iNO	Dose of iNO at initiation	PMA at initiation of sildenafil	Dose of iNO at initiation of sildenafil	History of iNO prior to sildenafil initiation	Duration of iNO after sildenafil initiation	Sildenafil Dose	Duration of sildenafil therapy
Infant 1	24 3/7 weeks 660 g Black Male	24 6/7 weeks	20 ppm	26 2/7 weeks	10 ppm	On iNO 10 days prior Failed 2 prior wean attempts Lowest dose 4 ppm	1 day	0.125 mg/kg IV q8h then weaned	6 days
Infant 2	22 5/7 weeks 545 g Black Male	28 0/7 weeks	20 ppm	29 3/7 weeks	4 ppm	On iNO 10 days prior Failed 1 prior wean attempt Lowest dose 4 ppm	2 days	0.125 mg/kg IV q8h then weaned	5 days
Infant 3	24 4/7 weeks 686 g Black Male	27 3/7 weeks	10 ppm	32 0/7 weeks	10 ppm	On iNO 32 days prior Failed 3 prior wean attempts Lowest dose 5 ppm	12 days	0.25 mg/kg PO q6h	5 days
Infant 4	27 5/7 weeks 910 g Hispanic Female	35 6/7 weeks	20 ppm	37 6/7 weeks	5 ppm	On iNO 14 days prior Failed 2 prior wean attempts Lowest dose 1 ppm	5 days	0.25 mg/kg PO q8h → up to 0.5 mg/kg PO q8h then weaned	36 days
Infant 5	31 0/7 weeks 840 g Hispanic Male	38 6/7 weeks	20 ppm	39 5/7 weeks	5 ppm	On iNO 6 days prior Failed 2 prior wean attempts Lowest dose 0 ppm	1 day	0.125 mg/kg IV q8h → 0.25 mg/kg PO q8h	14 days
Infant 6	26 2/7 weeks 880 g Black Male	35 5/7 weeks	10 ppm	36 1/7 weeks	5 ppm	On iNO 3 days prior Failed 2 prior wean attempts Lowest dose 4 ppm	2 days	0.25 mg/kg PO q8h then weaned	3 days
Infant 7	24 3/7 weeks 630 g Black Male	27 2/7 weeks	10 ppm	34 2/7 weeks	5 ppm	On iNO 49 days prior Failed 3 prior wean attempts Lowest dose 2 ppm	10 days	0.25 mg/kg PO q8h → 0.5 mg/kg PO q8h then weaned	62 days

GA, Gestational age; iNO, inhaled nitric oxide; IV, intravenously; PO, by mouth; PMA, Postmenstrual age; PPM, parts per million

at weaning iNO is also included. The primary focus of our iNO weaning protocol was for term and near-term neonates with PPHN; however, premature neonates were not specifically excluded. After successful use in older neonates, use of the protocol increased in our premature neonates as well, as demonstrated in this analysis. However, the use of sildenafil was added as a scheduled medication in all the preterm neonates evaluated in this review rather than as a 1-time dose as described in our original protocol.[16]

The patient with failure to wean off iNO despite sildenafil treatment (infant 3) had 3 previous failed attempts at iNO weaning at a period prior to the implementation of this standardized iNO weaning protocol. It is possible that a lack of a standardized weaning approach may have been a contributing factor for the iNO weaning failure in this patient. Additionally, the patient who required 10 additional days of iNO after initiation of sildenafil (infant 7) had 3 previous failed attempts at iNO weaning and was on iNO for the longest duration at 49 days prior to initiation of sildenafil. The patient also remained on sildenafil for a total of 62 days, suggesting a more refractory form of PAH.

We do acknowledge that the use of sildenafil in this review is off-label because it is still not approved in this population by the FDA. More research is needed to better understand the safety of sildenafil in premature neonates. One of the major safety concerns with the use of sildenafil is systemic hypotension; however, no episodes of hypotension requiring the initiation or escalation of vasopressor support were observed. This may be attributed to the low starting dose strategy used for most infants at our institution. Only 2 of the 7 infants required dose escalation of their sildenafil, while 4 had no dose changes other than weaning sildenafil and 1 infant converted from an IV to an equivalent enteral dose of sildenafil.

One limitation of our study was that we did not have a control group identified for this retrospective review. Overall, our findings support a previous case series using sildenafil as a bridge to wean iNO in the full-term population.[17] The mechanism is likely explained by negative feedback inhibition by exogenous iNO, which hinders the production of endogenous nitric oxide via the inhibition of endothelial nitric oxide synthase.[18,19] A multicenter randomized control study would be of great benefit in analyzing the effectiveness and safety of sildenafil as a bridge therapy in this population for this indication in the future.

Conclusion

The use of sildenafil in premature neonates may facilitate weaning off iNO, including extremely preterm neonates. Monitoring for systemic hypotension after sildenafil initiation is warranted and use of a lower starting dose should be considered. No safety risks were identified in our analysis. However, this is an off-label use of sildenafil and further research is warranted regarding its use to facilitate weaning off iNO in premature neonates.

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