

# eNeonatal Review

Jointly Presented by The Johns Hopkins University School of Medicine and the Institute for Johns Hopkins Nursing

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## MAY 2006 VOLUME 3, NUMBER 9

### In this issue...

Inhaled nitric oxide (iNO) was approved for the treatment of near-term and term infants with hypoxemic respiratory failure and persistent pulmonary hypertension in December 1999. Now routinely used for the treatment of PPHN, there is increasing interest in the potential role of this therapy in the premature newborn at risk for bronchopulmonary dysplasia.

In this issue we discuss the rationale for the use of iNO in prematurity, and review the current literature reporting the results of laboratory studies in premature animal models with RDS and BPD, as well as the results of clinical trials of iNO in premature newborns.

**Editor's Note:** Important new studies are currently underway that will provide additional insights into the potential risks and benefits of iNO therapy in premature newborns. Preliminary data were reported at the Pediatric Academic Societies meeting in May 2006, and will form the basis of a future issue of eNeonatal Review.

### This Issue

- **COMMENTARY** Our guest editor opinion
- **EFFECTS OF iNO IN ANIMAL MODELS OF PREMATURETY AND RDS**
- **ANIMAL MODELS OF BPD HAVE DECREASED ENDOGENOUS eNOS**
- **iNO FAVORABLY MODULATES ANGIOGENESIS AND GROWTH IN THE IMMATURE LUNG**
- **CLINICAL TRIALS OF iNO THERAPY IN PREMATURE NEWBORNS WITH RESPIRATORY FAILURE**
- **ASK THE AUTHOR**

### Guest Editor of the Month

#### Program Information

##### CE Info

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##### Length of Activity

1.0 hours

##### Expiration Date

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#### **Guest Faculty Disclosure:**

Dr. Kinsella has acted as a consultant for INO Therapeutics, and INO Therapeutics has provided study gas and medical devices for some of Dr. Kinsella's clinical studies on iNO therapy in newborns.

#### **Unlabelled/Unapproved Uses:**

This presentation will include discussion of the role of nitric oxide in the premature newborn.

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### Learning Objectives

The Johns Hopkins University School of Medicine and The Institute for Johns Hopkins Nursing take responsibility for the content, quality, and scientific integrity of this CME/CE activity.

**At the conclusion of this activity, participants should be able to:**

- Describe the rationale for the use of inhaled nitric oxide in premature newborns
- Identify the possible risks and benefits of inhaled nitric oxide in this population
- Discuss the importance of the results of clinical trials of iNO in premature newborns as they may apply to current practice paradigms

### Commentary

It is now nearly a decade and a half since publication of the first descriptions of inhaled nitric oxide (iNO) therapy for the management of persistent pulmonary hypertension of the newborn (PPHN).<sup>1,2</sup> These early observations set the stage for subsequent randomized, controlled trials demonstrating that iNO therapy reduces the need for ECMO (extracorporeal membrane oxygenation) in near-term and term newborns with hypoxemic respiratory failure and PPHN, and is now used routinely in this population.<sup>3,4</sup> As a selective pulmonary vasodilator causing sustained effects without tachyphylaxis, iNO is uniquely suited as adjuvant treatment for PPHN. Moreover, clinical experience with this therapy has provided clinicians with both a therapeutic and diagnostic tool, as suboptimal responses have unmasked the critical role of both parenchymal lung disease and cardiac dysfunction in many cases of PPHN.<sup>5,6</sup>

There is also considerable interest in the potential role of iNO in premature newborns with hypoxemic respiratory failure. Although an important effect of iNO in such newborns is pulmonary vasodilation and a reduction in extra-pulmonary right-to-left shunting, other beneficial effects may include improvements in ventilation/perfusion matching, decreasing lung inflammation and oxidant stress, and favorably modulating angiogenesis and growth in the immature lung. As is discussed in this issue, there is also increasing evidence that endogenous NO may play a vital role in pulmonary vascular and parenchymal function and development in the immature lung, and that low-dose iNO may have beneficial effects on both the acute and chronic perturbations that are associated with the pathogenesis of BPD in the premature newborn.

To provide background and a fuller picture of the potential for iNO therapy, the results of laboratory studies in premature animal models with RDS and BPD are first reviewed, followed by the results of clinical trials of iNO in premature newborns, with particular emphasis on properly conducted randomized, controlled trials. These trials have yielded conflicting results to date, and the role of iNO therapy in this population remains controversial. For example: the Van Meurs trial, reviewed herein, suggests that low-dose iNO may be safe and effective in reducing the risk of death/BPD for a subset of premature newborns, in particular infants with birth

weights >1000 grams; however, the effects of iNO in the premature newborn may be dependent on the timing, dose, and duration of therapy, and the nature of the underlying disease. Further, interpretations of the findings among various trials are complicated by differences in the severity of illness of the study populations, the trial designs, and relevant outcome measures recorded. Persistent concerns about potential toxicity have appropriately limited the use of iNO in premature newborns pending the results of ongoing clinical trials.

The largest trials of iNO therapy in premature newborns have completed enrollment but have yet to be published, with preliminary results reported at the Pediatric Academic Societies meeting in May 2006. The results of these ongoing trials will provide additional insight into the potential risks and benefits of iNO therapy in the premature newborn, and help define the proper role of iNO in this population.

### References:

1. Kinsella JP, Neish SR, Shaffer E, Abman SH. [Low-dose inhalational nitric oxide in persistent pulmonary hypertension of the newborn.](#) Lancet 1992;340:819-820.
2. Roberts JD, Polaner DM, Lang P, et al. [Inhaled nitric oxide in persistent pulmonary hypertension of the newborn.](#) Lancet 1992;340:818-819.
3. Clark R.H., Kueser T.J., Walker M.W., et al: [Randomized, controlled trial of low-dose inhaled nitric oxide treatment of persistent pulmonary hypertension of the newborn.](#) N Engl J Med. 2000; 17;342(7):469-74.
4. Neonatal Inhaled Nitric Oxide Study Group. [Inhaled nitric oxide in full-term and nearly full-term infants with hypoxic respiratory failure.](#) NEJM 336:597-604,1997.
5. Kinsella J.P., Truog W.E., Walsh W.F., et al: [Randomized multicenter trial of inhaled nitric oxide and high frequency oscillatory ventilation in severe persistent pulmonary hypertension.](#) J Pediatrics, 131:55-62; 1997.
6. Kinsella J.P., Abman S.H.: [Clinical approach to inhaled nitric oxide therapy in the newborn.](#) J Pediatrics, 136:717-26; 2000.

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## EFFECTS OF iNO IN ANIMAL MODELS OF PREMATURETY AND RDS

Kinsella JP, Ivy DD, Abman SH. **Ontogeny of NO activity and response to inhaled NO in the developing ovine pulmonary circulation.** Am J Physiol 1994;267:H1955-H1961.

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Kinsella JP, Parker TA, Galan H, et al. **Effects of inhaled nitric oxide on pulmonary edema and lung neutrophil accumulation in severe experimental hyaline membrane disease.** Pediatr Res, 1997;41;457-63.

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Nelin LD, Welty SE, Morrisey JF, et al. **Nitric oxide increases the survival of rats with a high oxygen exposure.** Pediatr Res 1998;43:727-732.

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Storme L, Zerimech F, Riou Y, et al. **Inhaled nitric oxide neither alters oxidative stress parameters nor induces lung inflammation in premature lambs with moderate hyaline membrane disease.** Bio Neo 1998;73:172-181.

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Issa A, Lappalainen U, Kleinman M, et al. **Inhaled nitric oxide decreases hyperoxia-induced surfactant abnormality in preterm rabbits.** Pediatr Res,

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Unlike the pulmonary circulation in the term newborn, the premature pulmonary circulation was long viewed as a passive conduit, unresponsive to vasodilator and vasoconstrictor stimuli. In 1994, Kinsella et al showed that endogenous NO modulates pulmonary vascular tone very early in ovine gestation, and low-dose iNO (5 ppm) causes sustained improvements in gas exchange and reduces pulmonary vascular resistance in premature lambs with RDS.

In addition to its effects on pulmonary hemodynamics and gas exchange during inhalation, endogenous NO may regulate vascular permeability and neutrophil adhesion in the microcirculation. Additional studies by Kinsella, published in 1997, showed that low-dose iNO increased pulmonary blood flow and improved gas exchange without increasing pulmonary edema, and decreased lung neutrophil accumulation in premature lambs delivered at 78% of term. These effects of low-dose iNO on early neutrophil accumulation may have important clinical implications because the neutrophil plays an important role in the inflammatory cascade that contributes to lung injury and the evolution of the most important sequela of RDS, BPD. Sequestration of neutrophils in the lung is an early step in a complex inflammatory response mediated through the elaboration of oxyradicals, proteases, phospholipases, and lipid compounds. Therapies which reduce neutrophil accumulation in the lung in RDS could potentially modify the early inflammatory process which amplifies acute lung injury and contributes to the development of chronic lung disease.

Inhaled NO may also play a role in reducing oxidant stress in the premature newborn exposed to high inspired oxygen concentrations. Nelin et al studied the effects of iNO in rats exposed to 95% oxygen for 5 days. They demonstrated improved survival when 95% oxygen was combined with 100 ppm of iNO (21 of 30 vs. 2 of 24 exposed to 95% oxygen alone,  $p < 0.01$ ). Storme et al reported that lambs delivered at 130 days gestation and mechanically ventilated for 5 hours with iNO showed no evidence of lung oxidative stress injury (lung malondialdehyde, reduced glutathione, glutathione reductase) compared to controls. Moreover, Issa et al found that low doses of iNO preserved surfactant function in premature rabbits exposed to 98% oxygen for 20 hours. Addition of 14 ppm iNO prevented both increased minimal surface tension and reduced amounts of large aggregate surfactant and surfactant protein B in surfactant isolated from bronchoalveolar lavage of oxygen exposed animals.

Thus, NO may have multiple functions in protection from lung injury as well as hemodynamic effects in premature infants, providing a rationale for iNO therapy in premature infants with lung disease.

## ANIMAL MODELS OF BPD HAVE DECREASED ENDOGENOUS eNOS

MacRitchie AN, Albertine KH, Sun J, et al. **Reduced endothelial nitric oxide synthase in lungs of chronically ventilated preterm lambs.** *Am J Physiol Lung Cell Mol Physiol* 2001;281:L1011-1020.

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Afshar S, Gibson LL, Yuhanna IS, et al. **Pulmonary NO synthase expression is attenuated in a fetal baboon model of chronic lung disease.** *Am J Physiol Lung Cell Mol Physiol* 2003; 284:L749-758.

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Bland RD, Ling CY, Albertine KH, et al. **Pulmonary vascular dysfunction in preterm lambs with chronic lung disease.** *Am J Physiol* 285: L76-L85, 2003.

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In addition to the acute effects of iNO on pulmonary vasodilation, lung inflammation, and oxidant stress, there is increasing evidence that impaired endogenous NO production and signaling contributes to the pathogenesis of BPD. MacRitchie et al showed that chronic ventilation caused decreased lung eNOS expression in the

endothelium of small intrapulmonary arteries of preterm lambs that were mechanically ventilated for 3 weeks compared with control lambs born at term, suggesting that decreased eNOS in the pulmonary circulation of preterm lambs may contribute to the pathophysiology of chronic lung disease. Similarly, in a premature primate model of BPD, Afshar et al demonstrated that, in contrast to the normal increase in total NOS activity from 125 to 140 days gestation, there was a significant decline in animals with BPD related to marked diminutions in eNOS expression and enzymatic activity. Moreover, Bland et al found decreased soluble guanylate cyclase (sGC) in pulmonary arteries from lambs with BPD, suggesting that the loss of pulmonary vascular responsiveness to iNO in preterm lambs with BPD results from impaired signaling, possibly related to deficient or defective activation of sGC. These observed roles of endogenous NO in normal pulmonary development thus provide additional rationale for the use of iNO in premature infants at risk for BPD.

## INO FAVORABLY MODULATES ANGIOGENESIS AND GROWTH IN THE IMMATURE LUNG

Tang JR, Markham NE, Lin YJ, McMurtry IF, Maxey A, Kinsella JP, Abman SH. **Inhaled NO attenuates pulmonary hypertension and improves lung growth in infant rats after neonatal treatment with a VEGF receptor inhibitor.** *Am J Physiol. Lung Cell Mol Physiol.* 2004; 287:L344-51.

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Lin YJ, Markham NE, Balasubraminian V, et al. **Inhaled nitric oxide enhances distal lung growth after exposure to hyperoxia in neonatal rats.** *Pediatr Res.* 2005;58:22-9.

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McCurnin DC, Pierce RA, Chang LY, et al. **Inhaled NO improves early pulmonary function and modifies lung growth and elastin deposition in a baboon model of neonatal chronic lung disease.** *Am J Physiol - Lung* 2005;288:450-459.

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The potential for iNO to modulate the evolution of lung injury in animal models of BPD has been the focus of recent studies, providing further experimental rationale for the role of iNO in premature subjects. Tang et al tested the hypothesis that impaired signaling of Vascular Endothelial Growth Factor (VEGF) downregulates eNOS expression in the developing lung and that iNO improves lung growth after VEGF inhibition. Newborn rats were treated with a VEGF receptor inhibitor or control and their lung tissues examined microscopically and biochemically. Rats exposed to the inhibitor had reduced lung growth as determined by radial alveolar counts (RAC), increased right ventricular hypertrophy (RVH), reduced levels of endothelial Nitric Oxide Synthase (eNOS), and evidence of reduced NO production. As demonstrated by improved RAC despite pharmacologic VEGF inhibition, iNO therapy prevented the increase in RVH and improved lung growth.

Lin et al found that hyperoxic exposure of neonatal rats inhibited lung vascular growth and impaired alveolarization, and that treatment with iNO after neonatal hyperoxia enhanced late lung growth and improved alveolarization in this model of BPD. Newborn rats were exposed to 100% oxygen or room air for 6 days and then returned to room air with or without 10 ppm iNO for 2 weeks. Hyperoxia exposed rats had reduced body weight and lung growth as determined by morphometry, and decreased amounts of VEGF, VEGF receptor-2, and eNOS in their lung tissue. iNO treatment after hyperoxic exposure increased body weight and improved lung growth.

McCurnin et al studied the effects of iNO in a baboon model of BPD where the animals were delivered very prematurely (125 days vs. term gestation of 185 days) and had decreased pulmonary NO production. Treatment with 5 ppm of iNO improved early pulmonary function as determined by pressure-volume curves, increased lung DNA content and cell proliferation, and favorably altered lung growth in mechanically ventilated premature baboons with evolving BPD. Moreover, iNO treatment also improved extracellular matrix deposition, as it corrected the excessive elastin deposition observed in the animals with BPD, and stimulated secondary crest development.

Thus, there is increasing evidence that endogenous NO plays a vital role in pulmonary vascular and parenchymal function and development in the immature lung, and that low-dose iNO may have beneficial effects on both the acute and chronic perturbations that are associated with the pathogenesis of BPD in the premature newborn.

## CLINICAL TRIALS OF INO THERAPY IN PREMATURE NEWBORNS WITH REPIRATORY FAILURE

Subheddar NV, Ryan SW, Shaw NJ. **Open randomised controlled trial of inhaled nitric oxide and early dexamethasone in high risk preterm infants.** Arch Dis Child 1997;77:F185-190.

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Kinsella J.P., Walsh W.F., Bose C.L., et al. **Inhaled nitric oxide in premature neonates with severe hypoxaemic respiratory failure: a randomised controlled trial.** Lancet 1999;354:1061-5.

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The Franco-Belgium Collaborative NO Trial Group: **Early compared with delayed inhaled nitric oxide in moderately hypoxaemic neonates with respiratory failure: a randomised controlled trial.** Lancet. 1999;354:1066-71.

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Hascoet JM, Fresson J, Claris O, et al. **The safety and efficacy of nitric oxide therapy in premature infants.** J Pediatr 2005;146:318-23.

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Field D, Elbourne D, Truesdale A, et al. **Neonatal ventilation with inhaled nitric oxide versus ventilatory support without inhaled nitric oxide for preterm infants with severe respiratory failure: The INNOVO multicentre randomized controlled trial.** Pediatrics 2005;115:926-936.

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Schreiber MD, Gin-Mestan K, Marks JD, et al. **Inhaled nitric oxide in premature infants with the respiratory distress syndrome.** N Engl J Med 2003;349:2099-107.

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Van Meurs KP, Wright LL, Ehrenkranz RA, et al. **Inhaled nitric oxide for premature infants with severe respiratory failure.** N Engl J Med 2005;353:13-22.

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Mestan KK, Marks JD, Hecox K, et al. **Neurodevelopmental outcomes of premature infants treated with inhaled nitric oxide.** N Engl J Med 2005;353:23-32.

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Early case reports of iNO therapy in premature newborns demonstrated improvement in oxygenation, but also raised speculation about potential adverse effects, including intracranial hemorrhage (ICH). Such speculation was based, in part, on laboratory and clinical studies suggesting that high doses of iNO prolong bleeding. Although there is substantial evidence that low-dose iNO may protect the immature lung through various mechanisms described elsewhere in this issue, randomized, controlled trials have reported conflicting results on its safety and efficacy.

The results of 9 randomized trials of iNO in premature newborns have been reported and are summarized in the following Table:

	Year	N	Masked	CLD/Mortality	Gr 3-4 ICH/PVL
Subhedar	1997	42	No	No diff	No diff
Kinsella	1999	80	Yes	No diff	No diff
Franco-Belguim	1999	95	No	NA	NA
Schreiber	2003	207	Yes	↓ with iNo	↓ with iNo
Hascoet	2005	145	No	NA	NA
Field	2005	108	No	No diff	No diff
Van Meurs	2005	420	Yes	No diff	No diff
Ballard	2006	587	Yes	Pending	Pending
Kinsella	2006	793	Yes	Pending	Pending

However, the interpretation of the results of these studies is complicated by the diverse nature of the study populations and the timing, dose and duration of iNO therapy in the various trials.

In a small, unmasked, randomized trial of iNO (20 ppm) and dexamethasone treatment, Subhedar et al reported no differences in survival, chronic lung disease, or ICH between iNO treated infants and controls. However, in a randomized, masked, multicenter clinical trial by Kinsella et al of low dose iNO therapy (5 ppm) in severely ill premature newborns with RDS who had marked hypoxemia despite surfactant therapy (a/A O<sub>2</sub> ratio < 0.10), iNO acutely improved PaO<sub>2</sub>, but did not reduce mortality/BPD. Notably, there was no increase in the incidence or severity of ICH in this trial, and the incidence of the most severe ICH (grade 4) was 19% for the iNO group and 29% for the control group.

In 1999, the Franco-Belgium study group reported the results of an acute iNO response study (2 hour oxygenation endpoint); however, the brief duration of therapy and a high rate of crossover before the 2 hour trial endpoint compromised the interpretation of late outcome measures.

In 2005, Hascoet et al reported the results of an unmasked, randomized trial of iNO in 145 premature newborns with hypoxemic respiratory failure. They found no difference between the iNO and control groups in the primary outcome measure (intact survival at 28 days), and no differences in adverse events. As noted by Finer in an editorial accompanying publication of the results, interpretation of the findings is limited by a relatively high rate of "open-label" iNO use and the lack of important outcomes such as death before discharge and BPD incidence at 36 weeks.

Also in 2005, Field et al described the findings of the UK INNOVO trial. In this unblinded study, 108 premature infants with severe hypoxemic respiratory failure were randomized to receive or not receive iNO. There was no difference between the iNO and control group in the main outcome measure (death or severe disability at 1 year corrected age), and no difference in adverse events. Limitations of the study included an 8% crossover to iNO treatment, and treatment with other pulmonary vasodilators in 30% of the control group. Moreover, Field et al describe a lack of equipoise among investigators, demonstrated by the observation that 75 infants eligible for enrollment were treated with iNO outside of the trial, leaving only infants with very severe lung disease enrolled in the study.

The largest clinical trials of iNO therapy in premature newborns reported to date include the single center study of Schreiber et al, and the multicenter trial of Van Meurs et al. Both of these studies were randomized, controlled and masked. Schreiber et al randomized 207 infants to treatment with iNO or placebo, and found a reduction in the incidence of BPD and death by 24% in the iNO group. These benefits appeared to accrue

predominantly from the subset of newborns with relatively mild respiratory failure (OI<6.94). However, in addition to apparent pulmonary benefit caused by low-dose iNO, these authors also reported a 47% decrease in the incidence of severe ICH and periventricular leukomalacia (PVL). Moreover, in the subsequent report by Mestan et al, the same group showed that the early decrease in ICH/PVL associated with iNO treatment manifested in improved neurodevelopmental outcome on follow-up examinations of this population. In this followup study, 138 children (82% of survivors of the RCT) were evaluated for neurodevelopmental outcome at 2 years of age. In the group treated with iNO in the newborn period, 24% had abnormal outcomes (defined as cerebral palsy, blindness, hearing loss, or one score of less than 70 on the Bayley Scales of Infant Development II), in contrast to 46% in the control group.

Van Meurs et al enrolled 420 premature newborns (401-1500 grams birthweight) in a multicenter RCT. Overall, they found no difference in the incidence of death/BPD between the iNO and control groups. However, in post hoc analyses, infants with birthweight >1000 grams showed a reduction in death/BPD following treatment with iNO (50% iNO vs. 69% control). But a worrisome outcome was suggested in a post hoc analysis of newborns weighing <1000 grams, which showed an increased risk of ICH/PVL (43% iNO vs. 33% control). However, as noted by Martin and Walsh in the editorial that accompanied this article, baseline ultrasound examinations were not performed, and it cannot be determined whether these very severely ill infants had ICH before iNO was initiated.

Indeed, the severity of illness of infants in the Van Meurs trial was markedly different from the study of Schreiber et al. In the Van Meurs trial, the mean oxygenation index (OI) at enrollment for the iNO group was 23, compared to the median OI of 7.3 in the Schreiber study. This suggests that the degree of illness based upon the severity of respiratory failure may be related to iNO safety and efficacy in this population; however, an increased risk of ICH/PVL was not observed in a previous trial of iNO in premature newborns with severe hypoxemic respiratory failure. Other differences between these 2 trials may offer insights into the disparate outcomes, including the duration of iNO treatment (3 days vs. 7 days), birthweight (839 g vs. 992 g), and gestational age (26 weeks vs. 27.4 weeks). Thus, Van Meurs et al enrolled smaller, more immature infants with severe respiratory failure who were treated relatively briefly with iNO, making direct comparisons between these 2 trials problematic.

Referring again to the table, the two largest randomized, controlled and masked trials of iNO treatment in premature newborns have recently completed enrollment, but results have not yet been reported in peer-reviewed journals. Ballard et al randomized 587 premature newborns with birth weights of 500-1250 grams who required mechanical ventilation beyond the first week of life to treatment with iNO or placebo gas. In the second trial, Kinsella et al randomized 793 premature newborns with birth weights of 500-1250 grams, who required mechanical ventilation in the first 48 hours of life, to treatment with 5 ppm iNO or placebo gas, and treated for 21 days or until extubated. The results of these trials should help to clarify the role of iNO in premature newborns with respiratory failure.

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### LAST MONTH'S Q & A April 2006 - Volume 3 - Issue 8

Last issue we reviewed the increasing use of continuous (a)EEG monitoring in the NICU, with a particular focus on subclinical seizures, and discussed the effectiveness and risk/reward of anti-epileptic drugs in neonates.



Commentary & Reviews:  
**Mona C. Toet**

Neonatologist  
Wilhelmina Children's Hospital, UMCU,  
The Netherlands



Commentary & Reviews:  
**Linda de Vries**

Professor in Neonatal Neurology  
Wilhelmina Children's Hospital, UMCU,  
The Netherlands

## We received the following questions from one of our subscribers.



As described in the issue, phenobarbitone and phenytoin have been shown to be ineffective in controlling seizures. Which other anti-epileptics are recommended?



Benzodiazepine drugs such as midazolam and lorazepam are commonly used to control neonatal seizures. However, as there is a sedative effect with these agents that may mask subclinical seizure activity, the clinician should be aware that subclinical seizures may continue in spite of absence of clinical seizures.

Reference:

1. Boylan G.B, Rennie J.M, Chorley G et al. [Second-line anticonvulsant treatment of neonatal seizures](#). Neurology 2004; 62 (3):486-8.



Is there a role for lignocaine (lidocaine) in controlling neonatal seizures?



We and others have also used lignocaine, which, in our experience, appears to be more effective than the benzodiazepines in controlling seizures. However, the drug should only be used in an intensive care setting, as it presents a risk (although a low one) for cardiac arrhythmias. In addition, as both phenytoin and lignocaine have a proarrhythmic effect, it is not recommended to use lignocaine following administration of phenytoin.

References:

1. Hellström-Westas L, Svenningsen NW, Westgren U, Rosen I, Lagerstrom PO. [Lidocaine for treatment of severe seizures in newborn infants. II. Blood concentrations of lidocaine and metabolites during intravenous infusion](#). Acta Paediatr 1992; 81(10):35-9.

2. Malingre M et al. Development of an optimal lidocaine infusion strategy in neonatal seizures: In press: Eur J Pediatr

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This activity has been developed for Neonatologists, NICU Nurses and Respiratory Therapists working with Neonatal patients. There are no fees or prerequisites for this activity.

**Learning Objectives · [back to top](#)**

At the conclusion of this activity, participants should be able to:

- Describe the rationale for the use of inhaled nitric oxide in premature newborns
- Identify the possible risks and benefits of inhaled nitric oxide in this population
- Discuss the importance of the results of clinical trials of iNO in premature newborns as they may apply to current practice paradigms

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- Dr. Noguee has indicated a financial relationship of grant/research support with Forest Laboratories and has received an honorarium from Forest Laboratories.
- Dr. Lawson has indicated a financial relationship of grant/research support from the NIH. He also receives financial/material support from Nature Publishing Group as the Editor of the Journal of Perinatology.
- Dr. Lehmann has indicated a financial relationship with the Eclipsys Corporation.

All other faculty have indicated that they have not received financial support for consultation, research, or evaluation, nor have financial interests relevant to this e-Newsletter.

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No faculty member has indicated that their presentation will include information on off label products.

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