Clinical experience in the use of inhaled nitric oxide in infants with pulmonary hypertension

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Inhaled nitric oxide (iNO) is a potent local vasodilator. Numerous case reports describe its efficacy in treating persistent pulmonary hypertension of the newborn (PPHN). This report describes experience at the authors' institution with iNO therapy in 10 consecutive infants with PPHN of a number of etiologies. Infants received iNO at doses of 0.2 to 80 ppm for 1 to 481 h. Five infants were classified as responders (20 torr or greater rise in PaO_2) and one as a partial responder (PaO_2 rise of 10 to 19 torr). The remaining four did not respond. Overall observed mortality was three of 10, with two of four of nonresponders and the only partial responder dying. Survivors required ventilation for 18 ± 18 days and oxygen for 29 ± 30 days, and they remained in hospital 40 ± 30 days (mean $\pm$ SD). Although improvement in oxygenation with iNO was primarily due to reduction in pulmonary pressure, in selective patients, changes in ventilation-perfusion relationships could account for some of the increase in oxygenation. The presence of significant methemoglobinemia in two patients (7% and

4.5%) when the infants' iNO dose was increased to 80 ppm highlights the importance of careful monitoring for toxicity. Further studies are needed to define the best dosage and duration of iNO. While iNO shows great promise in the treatment of PPHN, randomized controlled trials are needed to delineate in which infants iNO use is indicated.

Key Words: *Inhaled nitric oxide, Newborn, Persistent pulmonary hypertension*

Expérience clinique relative à l'utilisation d'oxyde nitrique en inhalation chez les nourrissons atteints d'hypertension pulmonaire

RÉSUMÉ : L'oxyde nitrique en inhalation est un vasodilatateur local puissant. De nombreuses études de cas décrivent son efficacité dans le traitement de l'hypertension pulmonaire persistante du nouveau-né (HPPN). Le présent article décrit l'expérience de l'établissement où pratique l'auteur en ce qui concerne l'utilisation d'oxyde nitrique en inhalation pour traiter une série de 10 nouveau-nés souffrant d'HPPN d'étiologies variées. Les nouveau-nés ont reçu de l'oxyde nitrique en inhalation à des doses de 0,2 à 80 parties/million pendant 1 à 481 heures. Cinq nourris-

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sons ont été classifiés comme « répondeurs » (augmentation de la PaO₂ égale ou supérieure à 20 torr) et un nourrisson comme « répondeur partiel » (augmentation de la PaO₂ de 10 à 19 torr). Les quatre autres nourrissons n'ont pas répondu au traitement. La mortalité globale observée était de trois sur 10 nourrissons, dont deux des quatre nourrissons n'ayant pas répondu au traitement ainsi que le seul nourrisson ayant répondu partiellement. Les survivants ont reçu une ventilation artificielle pendant 18±18 jours et de l'oxygène pendant 29±30 jours; ils sont restés hospitalisés pendant 40±30 jours (moyenne ± écart-type). Bien qu'une amélioration dans l'oxygénation avec de l'oxyde nitrique en inhalation était principalement attribuable à une réduction de la pression de l'artère pulmonaire, chez certains patients, les changements observés dans le

rapport ventilation-perfusion pourraient expliquer une partie de l'augmentation de l'oxygénation. La présence d'une méthémoglobinémie significative chez deux nourrissons (7 % et 4,5 %) quand la dose d'oxyde nitrique en inhalation administrée atteignait 80 parties/million démontre l'importance d'un monitoring rigoureux pour prévenir la toxicité. Il est nécessaire de mener d'autres études pour définir un dosage et une période d'administration optimaux de l'oxyde nitrique en inhalation. Si l'oxyde nitrique en inhalation apparaît comme un traitement prometteur dans l'HPPN, il est indispensable de mener d'autres essais comparatifs randomisés pour préciser chez quels nourrissons l'utilisation de l'oxyde nitrique en inhalation est indiquée.

Nitric oxide is a potent cellular messenger that plays a critical role in the modulation of vascular tone throughout the body (1). An important clinical application of this action is in the treatment of persistent pulmonary hypertension of the newborn (PPHN) (2-9). In this paper we describe all neonates treated at our institution from the time of introduction of nitric oxide as an investigational treatment modality up to the start of our involvement in a large multicentre trial of inhaled nitric oxide (iNO) for PPHN. Our experience thus far raises some interesting points with regard to iNO dosage and treatment duration, measures of response and its potential role in the treatment of many types of neonatal lung disease. Ultimately, the need for multicentre, randomized trials to assess iNO is apparent.

PATIENTS AND METHODS

Ten infants admitted to the neonatal intensive care unit, Winnipeg Children's Hospital, Winnipeg, Manitoba between September 1993 and March 1994 received iNO. All had clinical evidence of primary or secondary pulmonary hypertension as demonstrated by hypoxemia and a significant difference between pre- and postductal oxygen saturations. All patients were intubated and mechanically ventilated with oxygen requirements in excess of 80% for at least 8 h despite

Figure 1) Circuit used to deliver nitric oxide to patients

conventional therapy, consisting of assisted ventilation, bicarbonate administration (to maintain pH above 7.50), paralysis (pancuronium) and sedation (fentanyl or morphine),

TABLE 1
Patient characteristics, with infants grouped based on response to iNO

Patient #	Diagnosis	Birth weight (g)	Gestation (weeks)	Sex	IPPV (days)	Oxygen (days)	Hospital days
Responders							
1	CDH	3300	39	F	57	89	95
2	CDH	2700	36	M	24	45	53
3	Hypoxia	4000	41	M	5	9	20
4	CDH	3200	38	M	21	28	32
5	PPHN	4500	39	M	3	6	14
Partial responder							
6	RDS	930	27	M	9	9	9
Nonresponders							
7	PPHN	3800	41	M	7	8	30
8	MAS	3900	41	F	11	15	28
9	RDS	1000	26	M	1	1	1
10	MAS	3900	38	M	1	1	1

CDH Congenital diaphragmatic hernia; iNO Inhaled nitric oxide; IPPV Intermittent positive pressure ventilation; MAS Meconium aspiration syndrome; PPHN Persistent pulmonary hypertension of the newborn; RDS Respiratory distress syndrome

TABLE 2
Characteristics of iNO treatment, with infants listed by decreasing postductal PaO₂ rise with iNO initiation

Patient #	PDA on echocardiography		Onset (h)	iNO		Max methHb (%)	Max NO ₂ (ppm)	Postductal PaO ₂ increase (torr)	Survival
	Before	After		Duration (h)	Dose range (ppm)				
Responders									
1	R→L	R↔L	45	481	80–0.2	7	0.4	149	Yes
2	R↔L	L→R	23	33	20–8	1.7	0.3	68	Yes
3	CL	CL	32	35	20–2.5	1.6	0.2	61	Yes
4	R↔L	R↔L	19	213	20–1.5	1.8	0.3	31	Yes
5	R↔L	L→R	14	32	20–10	1.5	0.2	30	Yes
Partial responder									
6	R↔L	R↔L	20	60	5–0.2	1.2	0.1	13	No
Nonresponders									
7	CL	CL	35	88	80–2	2.9	0.1	9	Yes
8	L→R	L→R	11	21	80–20	4.5	0.3	8	Yes
9	L→R	L→R	16	1	5	0.7	0	6	No
10	R↔L	n/a	14	1	80–20	0.8	0.1	2	No

Extrapulmonary shunting via patent ductus arteriosus (PDA): R↔L, bidirectional; L→R, systemic to pulmonary; R→L, pulmonary to systemic. CL Ductus closed; iNO Inhaled nitric oxide; methHb Methemoglobin; n/a Patient died before echocardiography

and inotropic support (dopamine, dobutamine and/or norepinephrine). Surfactant was used at the discretion of the attending neonatologist. One infant with diaphragmatic hernia was treated with high frequency jet ventilation (Bunnell Life Pulse, Bunnell Inc, Utah). Patient characteristics are detailed in Table 1. Patients with nontreatable, life-threatening malformations were excluded.

Infants with any increase in PaO₂ were permitted to remain on iNO to allow for possible late response. Patients were weaned from iNO as soon as they were clinically stable. Dose was sequentially reduced as long as ventilator rate, pressures or oxygen concentration did not increase more than 25% to compensate for any deterioration in oxygenation (ie, saturations below 90%).

Infants had postductal arterial lines in place and underwent detailed echocardiographic examinations before starting iNO to assess cardiac performance and confirm normal cardiac anatomy and the presence, magnitude and direction of continuous or intermittent shunting via a patent ductus arteriosus. In addition to serial arterial blood gases, pre- and post ductal oxygen saturations were continually measured to assess the degree of shunting at the level of the ductus as well as the response to iNO. Infants were classified as responders when the PaO₂ rose by 20 torr or more and as partial responders if the PaO₂ rose 10 to 19 torr within half an hour of initiation of iNO. To quantify further the longer term response, the oxygenation index (OI) was also measured. The OI ($\text{OI} = [\text{mean airway pressure} \times \text{fraction of inspired oxygen} \times 100] / \text{PaO}_2$) corrects for changes in ventilation over time. For term infants, treatment was initiated at a concentration of 20 ppm for 30 mins, and was increased to 80 ppm for an additional 30 mins if the patient did not experience an improvement in PaO₂ of at least 20 torr above baseline on the same ventilator settings and fraction of inspired oxygen, and as long as there were no side effects (eg, hypotension). Premature infants were started on 5 ppm and were not increased fur-

ther because of concern of altered platelet function and the potential effect on intraventricular hemorrhage.

The administration of iNO was accomplished by the setup shown in Figure 1. Gas from a tank of nitric oxide (1000 ppm) in balance with nitrogen (Matheson Gas Products Canada) was delivered via a flow meter (# 603, Matheson Gas Products) into the inspiratory limb of a pressure-limited, time-cycled infant ventilator (100B, Sechrist Industries Inc, California) 60 cm proximal to the humidifier and 210 cm proximal to the patient's endotracheal tube connector. The concentration of iNO was measured by a chemiluminescent nitrogen oxides analyzer (Model 8940, Monitor Labs, Lear Siegler Measurement Corp, Colorado) from gas sampled just proximal to the humidifier. Exhaust gases were scavenged from the expiratory limb to prevent environmental contamination.

Potential toxicity from iNO was monitored by regular measurement of blood levels of methemoglobin (methHb) with a co-oximeter (Radiometer, Copenhagen, Denmark) and measures of nitrogen dioxide in expired air by an electrochemical sensor (4584 NO₂ Analyzer, Exidyne Instrument Technologies, Pennsylvania). Parental informed consent was obtained before administration of iNO, and the protocol was approved by the Human Ethics Committee of The University of Manitoba.

RESULTS

Patient results are detailed in Table 2. Before the initiation of iNO, patients had a pre- to postductal saturation difference of $34 \pm 14\%$. Infants received iNO of 0.2 to 80 ppm for between 1 and 481 h. Administration of iNO led to increases in PaO₂ of greater than 20 torr in five of 10 patients (responders), an increase of 10 to 19 torr in one patient (partial responder) and a rise of less than 10 torr in four patients (nonresponders) within the first hour of initiating iNO. Responders tended to have a lower initial OI (23 ± 17 versus

Figure 2) Changes in oxygenation index (OI, defined as mean airway pressure $\times$ fraction of inspired oxygen $\times$ 100)/ PaO_2) for responders (left) and partial and nonresponders (right) during initial 24 h of inhaled nitric oxide (iNO) administration. Only two responders showed a progressive reduction in OI (Patients #3 and #4). Two other responders manifested transient increases in OI between 2 and 8 h after starting iNO (Patients #2 and #5). In patients #9 and #10, large changes in OIs corresponded to small changes in PaO_2 despite constant ventilator settings

63 $\pm$ 53) and had iNO initiated later in life than partial and nonresponders (27 $\pm$ 11 h versus 19 $\pm$ 8 h, mean $\pm$ SD), suggesting that partial and nonresponders had a more severe disease process. Further examination of OI data for the initial 24 h of iNO revealed two responders who had some deterioration between 2 and 8 h postonset of iNO (Figure 2). Only two infants, both responders, showed progressive improvement in OIs in the first 24 h.

The maximum concentration of nitrogen dioxide detected in any patient was 0.4 ppm. Eight patients had maximum measured metHb below 2.9%. In the remaining two cases, metHb rose to 7% and 4.5% when the infants' iNO dose was increased to 80 ppm. It rapidly returned to 2.8% and 2.6% when their respective doses were reduced to 30 and 20 ppm. Only one patient (#10) suffered deterioration in systemic blood pressure with initiation of iNO. However, this is likely to have been coincidental because this infant was extremely unstable hemodynamically for his entire hospital course until death, soon after iNO was discontinued.

Among the 10 patients, three died, of whom two were nonresponders and one a partial responder. Four patients received surfactant: two with meconium aspiration and two premature infants with respiratory distress syndrome. Survivors required ventilation for 18 $\pm$ 18 days, oxygen for 29 $\pm$ 30 days and remained in hospital 40 $\pm$ 30 days.

DISCUSSION

Nitric oxide is a potent smooth muscle relaxant produced endogenously in endothelial cells, and because of rapid metabolism exerts its action locally in the pulmonary bed only (1). This selectivity differs greatly from that of other vasodilator agents previously used to treat PPHN (10). To date, published case reports have addressed treatment success in selected patients treated with iNO, while the overall experience of individual centres remains largely unknown (2-9). Although we have treated only a small number of newborns

with iNO, our experience thus far raises some interesting points with regard to iNO use in the therapy of PPHN.

Echocardiography has been widely used to assess iNO's effect on ductal shunting, an indicator of the presence and degree of pulmonary hypertension (5). In our 10 patients, neither the direction of ductal shunting on initial echocardiography nor the change in shunting after initiating iNO was correlated with, and therefore predictive of, the degree of improvement in oxygenation. This may be a reflection of the limitations of echocardiography in estimating actual pulmonary artery pressure (11) and its ability to provide only a 'snapshot' of the continually changing relationship between pulmonary and systemic arterial pressures. Conversely, the poor correlation between echocardiographic findings and changes in oxygenation due to iNO may reflect the presence of concomitant altered ventilation-perfusion (V/Q) relationships. Indeed, nitric oxide is known to have important effects on V/Q mismatching (12,13), which can be quantified clinically by comparing the increases in pre- and postductal PaO_2 with initiation of iNO. In two of our patients (#1 and #4) where both arterial lines were placed, larger improvements in PaO_2 were seen preductally (190 and 63 torr) than postductally (149 and 31 torr), indicating that improved V/Q relationships were partially responsible for the response with iNO. Consequently, the response to iNO in any patient must be related to overall clinical improvement in hypoxemia and not just to isolated echocardiographically determined alterations in shunting.

However, the expression of clinical improvement in oxygenation is also susceptible to misinterpretation. Although only five infants were classified as responders due to changes in PaO_2 , nine of 10 patients showed some improvement in the OI within the 24 h following iNO administration. Because OI reflects changes in both oxygenation and the patients' ventilator settings, one must be careful in attributing a patient's improvement to iNO alone when examining OI data. Indeed, depending on the 'window' of time one wishes

to examine, an improvement in the OI while on iNO is seen in all of our patients, despite overall mortality of 30%. The determination of cause and effect is especially difficult in any infant classified as a 'late responder' where improvement may have little to do with iNO. More important, large changes in OI may correspond to clinically insignificant improvements in PaO_2 when infants are profoundly hypoxic. For example, although our ninth patient's OI dropped by 43 within 1 h of institution of iNO (Figure 2), PaO_2 increased by only 6 torr. Thus, there is a need for a randomized controlled trial to truly delineate infants who will benefit from iNO.

We note that all three of our congenital diaphragmatic hernia (CDH) patients were successfully treated for their PPHN with iNO, which was administered continuously during their operative repairs, usually a period of instability (14). As a group, infants with CDH have one of the poorest outcomes in the neonatal extracorporeal membrane oxygenation (ECMO) registry, despite this extremely aggressive form of therapy (15). There is no reliable means of predicting which infants with CDH will survive before treatment is initiated (16-19). We speculate that only infants with CDH who have lesser degrees of pulmonary hypoplasia will respond to iNO, and that the remainder will continue to require ECMO. Thus, iNO should reduce the overall need for ECMO in CDH patients.

An important, and largely unanswered, issue is the potential long and short term toxicity of iNO. Nitric oxide reacts with hemoglobin and is then oxidized to methHb (10). Although it normally constitutes less than 3% of the total hemoglobin present (20), methHb is significantly elevated by increasing doses of iNO, which may produce hypoxia. Similarly, iNO in the presence of oxygen reacts directly to produce higher oxides of nitrogen, which are toxic in high concentrations (21). Because the formation of methHb and higher oxides of nitrogen is dose-dependent, reducing iNO to the lowest possible efficacious levels should reduce potential toxicity (22). Case reports have described using iNO at 2 ppm in children with pulmonary hypertension after cardiac surgery (23) and 0.1 ppm for adults with adult respiratory distress syndrome (ARDS) (24). We observed responses to iNO as low as 0.2 ppm in two of our patients with CDH, which we believe are the lowest doses thus far reported in neonates. Although such doses are small, they are 100 times higher than the concentration of nitric oxide exhaled by healthy humans (25).

In general, the duration of iNO administration has been restricted to less than 72 h (2-7). Although there is a report of its use at 20 ppm for 23 days, this patient ultimately died while still on iNO (8). Rossaint et al (13) described administration of iNO for 53 days in patients with ARDS. In two of our patients with CDH, iNO was given for nine and 20 days before successful discontinuation. We believe these to be the longest iNO administrations with successful outcome reported in the neonatal literature. The need for prolonged administration of iNO highlights the refractory nature of PPHN and the propensity for continued V/Q mismatching in some patients. Surprisingly, one of our previously mentioned patients with CDH manifested the largest initial increases in PaO_2 of all

our patients, suggesting that the magnitude of the initial response is independent of the duration of therapy required.

Although experience in the use of iNO in infants with PPHN is limited, the potential value of iNO in the therapy of this condition is readily apparent. Our small patient number limits our ability to discern which patients will respond to iNO. Indeed, many questions remain concerning the use of iNO, including possible long term toxicity and optimal dosage level and duration of therapy. The ultimate clarification of iNO's future therapeutic role awaits the results of multicentre controlled trials, to which we have now concentrated our efforts.

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