Early Experience with Inhaled Nitric Oxide for the Treatment of Infants and Children with Pulmonary Hypertension

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When nitric oxide (NO), an endogenous regulator of smooth muscle tone, is administered by inhalation, it acts as a selective pulmonary vasodilator. This report details the treatment with inhaled NO of the first 11 patients in Hawaii.

Introduction

This report describes the development of the inhaled nitric oxide (NO) program and our initial experience with NO for pulmonary hypertension at Kapiolani Medical Center for Women and Children (KMCWC). NO, a clear, colorless gas,[1] is a component of the air we breathe as measured in parts per billion (ppb).[2-3] It also is found in higher concentrations of parts per thousand (ppt) in cigarette smoke.[4] In higher concentrations, NO is toxic and capable of causing acute pulmonary injury and death.[5] Furthermore, in the presence of oxygen, NO combines to form nitrogen dioxide (NO_2), another toxic gas.[6] The Environmental Protection Agency set the upper limit of exposure to NO and NO_2 at 25 ppm and 5 ppm, respectively.[7]

Over the last few years, NO has been identified as the endothelium-derived relaxing factor (EDRF).[8] This factor facilitates smooth muscle relaxation[9] and is an endogenous regulator of smooth muscle tone.[10-11] In the vascular endothelium, NO is synthesized from the amino acid L-arginine,[10] and readily diffuses into adjacent smooth muscle cells where it activates guanylate cyclase to form cyclic guanosine monophosphate (cGMP).[10] cGMP mediates smooth muscle relaxation by complex intracellular mechanisms.

This understanding of the role of NO in smooth muscle relaxation led to its clinical use as a therapy for patients with pulmonary hypertension.[12-14] It was determined that inhaled NO could reduce pulmonary vasoconstriction and shunt fraction, thereby improving oxygenation in these patients.[11] It also was found that inhaled NO is a selective pulmonary vasodilator. As NO diffuses through the smooth muscle cell into the blood vessel, it rapidly combines with hemoglobin to form methemoglobin;[10,15] free NO does not circulate in, and therefore does not affect, the systemic circulation.[12]

As of 1994, it has been estimated that more than 1,000 patients have been treated with inhaled NO worldwide. Subsequently, the use of inhaled NO in infants and children with pulmonary hypertension has increased.[11,16,17]

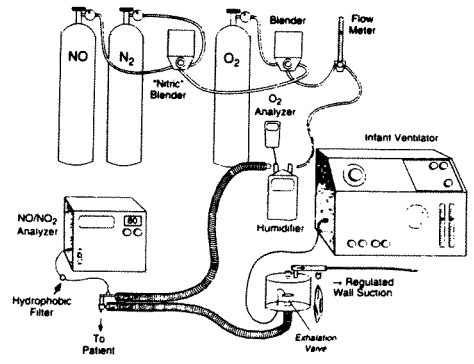
Methods

After review of the literature, consultation with national experts and personal experience at Massachusetts General Hospital by one of the authors (BO), the Department of Neonatology at KMCWC began the process of developing an NO therapy program for infants and children. The Food and Drug Administration approved our Investigational New Drug application for the rescue use of NO in infants and children with documented pulmonary hypertension and systemic hypoxemia. The protocol then was approved by our medical center's Institutional Review Board. In addition, separate animal studies were carried out to gain experience with NO administration before subjecting human infants to this new form of therapy. The following equipment and supplies were necessary (Fig 1).

Nitric oxide.—Nitric oxide is mixed with nitrogen (N_2) as an inert diluent at a concentration of 800 ppm.

Blender and connections.—Levels of NO concentration were adjusted using a blender connected with oxygen. The concentration of NO was measured by electrochemical analysis in parts per million.

Fig 1.—Basic nitric oxide (NO) delivery system using a double blender technique and NO analyzer, modified for a time-cycled, pressure-limited infant ventilator. Reprinted with permission.[21]



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Pulmonox electrochemical analyzer.—Electrochemical analysis was used for all NO and nitrogen dioxide measurements (Pulmonox II, Pulmonox Research and Development Corp, Alberta, Canada).

Exhalation scavenging device.—The exhalation block of the ventilator was enclosed by a custom-made plastic bottle connected to the wall vacuum set at -100 cmH_2O. NO_2 analysis verification was performed around this scavenging system with a Drager NO_2 chemical analyzer.

Ventilators.—NO was utilized only with conventional ventilators (Sechrist Infant Ventilator, Sechrist Industries, Anaheim, California; Servo 900C Ventilator, Siemens-Elema, Sweden).

Methemoglobin analyzer.—Methemoglobin levels were analyzed utilizing a co-oximeter (2500 Series, Ciba Corning, Medfield, Massachusetts) at 1, 2 and 4 hours after initiation of NO, then every 6 to 8 hours until stable while on ≥ 40 ppm. When NO was weaned to < 40 ppm, methemoglobin levels were followed every 12 hours.

Eligibility criteria.—To receive NO, patients were required to meet the following criteria: 1) ≥ 34 weeks of gestation for infants; 2) evidence of pulmonary hypertension by systemic hypoxemia ($AaDO_2 \geq 600$ torr or $PaO_2 \leq 70$ torr in FiO_2 1.0 on two arterial blood gases 30 minutes apart) with echocardiographic confirmation of pulmonary hypertension; 3) poor response to conventional or high frequency ventilation with mean airway pressure >12 cmH_2O; 4) increasing inotropic drug support; and 5) informed parental consent. We excluded infants with inoperable life-threatening anomalies. Common diagnostic categories included meconium aspiration syndrome, pneumonia and sepsis, diaphragmatic hernia, acute respiratory distress syndrome (ARDS), and postoperative patients with congenital heart disease.

Procedures.—Infants were placed on the conventional ventilator with the NO blender attached. We frequently attempted to use respiratory alkalosis therapy (pH ≥ 7.6 and $PaCO_2 \leq 20$ torr) to ensure adequate lung expansion and improve the chances for response to NO therapy during NO insufflation.

We used an initial dose of 40 ppm to 80 ppm. This dose allowed the clinician to immediately differentiate between responders and non-responders. Response was defined in an infant as a twofold increase in PaO_2. Failure to respond to NO therapy is an important determination and could be criteria to transfer the infant for extracorporeal membrane oxygenation (ECMO) therapy.

Determination of response to NO was usually made in the first 30 minutes after initiation. If the patient was a responder, small decreases in NO concentrations were made in proportion to the extent of the increase in PaO_2 >150 torr. The reductions were as small as 5 ppm to as great as 20 ppm at any one time. The goal was to lower the NO concentrations as quickly as possible to 5 to 6 ppm to reduce the risk of methemoglobin or NO_2 toxicity.[6,10,11] Accordingly, NO was preferentially weaned before attempting any reduction in oxygen or ventilator settings.

Non-ventilator conventional management continued during NO therapy and included minimal stimulation, medications such as fentanyl, Versed and pancuronium, pulmonary physiotherapy and suctioning. We maintained mean arterial pressures between 60 mmHg to 75 mmHg with varying combinations of dopamine, dobutamine, and amrinone and with fluid boluses.

Results

Of the 11 patients treated with NO to date, one was admitted to the pediatric intensive care unit; the others were neonates admitted to the neonatal intensive care unit. Two of these infants were transferred from other hospitals (Kaiser Medical Center, Tripler Army Medical Center) for NO therapy; two were transferred from other islands for treatment of congenital heart disease and diaphragmatic hernia; the remaining patients were born at KMCWC.

Seven of the 11 patients responded to NO therapy, with a mean increase in PaO_2 of 166 torr within 12 hours after NO was started. One infant, whose PaO_2 did not respond dramatically or consistently to NO, was considered a responder because his condition stabilized and he became easier to manage once NO was begun. NO was administered for an average of 105 hours (range 1 to 469 hours). The baseline methemoglobin level was < 2% in all but one infant, whose initial level after beginning NO at 60 ppm was 4.3. However, this level rapidly decreased to 1.1 within one hour after reducing the NO to 40 ppm. Otherwise, the maximum methemoglobin level recorded during therapy was 2.6. Platelet counts were normal or near normal.

Four patients did not respond to NO therapy. The first nonresponding infant had meconium aspiration syndrome and poor cardiac contractility, both factors known to decrease the success of NO therapy. This infant survived after transport to the Mainland for ECMO. Another nonresponding infant in retrospect was thought to have more pulmonary than pulmonary-vascular disease. The last nonresponding infant had congenital diaphragmatic hernia and died of that primary diagnosis. The only older child treated with NO was a three-year old who was critically ill with ARDS and pre-existing central nervous system disease. He was treated with NO for only one hour after not responding to conventional therapy. He did not respond to NO and died of his other diagnoses.

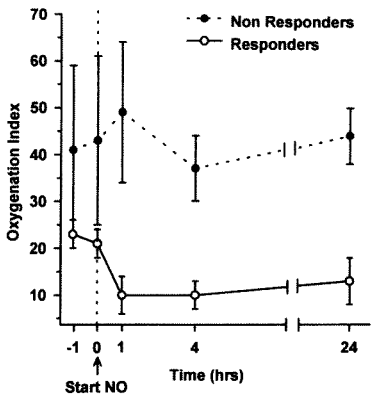
A summary of treatment and outcome information is shown in Table 1; the average oxygenation index (OI) is plotted before and after NO therapy in the responding and nonresponding infants in Figure 2.

Table 1.—Nitric Oxide Treatment and Outcome Data

Pt No	Birth Weight	Diagnoses	Treatment Duration	Maximum Dose	PaO_2 Pre/Post NO	Outcome
1	2840	MAS	2 hr	80	54/34	ECMO-survived
2	2650	MAS/pneumothorax	122 hr	40	73/297	survived-anatomic brain anomaly
3	3020	coarctation	469 hr	20	65/365	survived-seizure disorder
4	4600	pneumonia/DIC	76 hr	60	38/216	survived
5	3 yo	ARDS	1 hr	80	46/45	died
6	2790	MAS/pneumonia	112 hr	40	53/120	survived
7	3731	MAS/blood aspiration/ pneumonia	170 hr	52	90/270	survived
8	3365	MAS/pneumothorax/ pneumonia	72 hr	40	43/172	survived
9	3722	MAS/pneumonia	4 hr	60	82/84	survived
10	3099	CDH	14 hr	80	48/42	died
11	3610	MAS/pneumonia	114 hr	40	67/150	survived

NO, nitric oxide; MAS, meconium aspiration syndrome; ECMO, extracorporeal membrane oxygenation; DIC, disseminated intravascular coagulopathy; ARDS, acute respiratory distress syndrome; CDH, congenital diaphragmatic hernia.

Fig 2.—Oxygenation Index (OI) values in 7 responding and 4 nonresponding patients to inhaled nitric oxide. Values represent mean ± standard deviation. OI = (Mean airway pressure x FiO_2 x 100)/PaO_2.



Discussion

Although anecdotal, we are encouraged that NO contributed significantly to the survival and recovery of these critically ill infants who were not responding to conventional therapies. Randomized, controlled trials comparing NO to conventional therapy will be needed to definitively prove the value of NO therapy; such trials are currently being conducted in other centers. However, it is clear from anecdotal experience from other tertiary centers around the country that there is significant variability in response to NO therapy from center to center.

At this point in our experience, several observations suggest there are important factors enhancing the success of NO therapy. The four most important factors associated with a good response include: high systemic arterial pressures (means of > 60 mmHg); adequate lung volume as evaluated by frequent chest x-rays; normal cardiac contractility; and maintenance of respiratory alkalosis with pH ≥ 7.6 and $PaCO_2 \leq 20$ torr.

When the above factors were controlled, the lability in oxygenation was dramatically reduced, especially during attempts to wean the infant from ventilator support. Lability in oxygenation is of concern since it indicates the presence of pulmonary vasospasm which could lead to severe hypoxemia, acidosis, and death. Previously, systemic vasodilators such as tolazoline were used in an attempt to reduce this lability.[18] However, these drugs frequently dilated both pulmonary and systemic vascular beds resulting in systemic hypotension and further instability.[19] Because inhaled NO is inactivated by immediately combining with hemoglobin after diffusing into the systemic circulation,[10,15] it acts as a selective pulmonary vasodilator. Neither systemic hypotension nor lability of oxygenation was observed in infants responding to NO treatment. Thus, any deterioration during weaning attempts was easily reversed by returning to baseline conditions. Finally, this stability in oxygenation should promote future confidence in the treatment of these infants, knowing that the use of NO allows for more forgiving clinical management.

Until the benefits of this therapy are proved in randomized trials and adequate followup studies, we believe the most important consideration in the use of NO is safety.[10,11,20] NO should be used in the lowest concentration possible in order to avoid any potential toxic effects.[20]

In summary, we have presented the background knowledge and process that led to our use of this experimental therapeutic gas. Our initial experience with NO therapy has been encouraging, and we anticipate greater success with more experience. Furthermore, we speculate that future uses for inhaled NO therapy will be found other than those characterized strictly by pulmonary hypertension. These may include such conditions as bronchopulmonary dysplasia, chronic lung disease, viral and bacterial pneumonia, respiratory distress syndrome, and ARDS. Oxygenation in these disorders may improve from the reduction in shunt fraction seen with the use of this selective pulmonary vasodilator.[20]

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Addendum

Since submission of this paper, we have treated an additional 19 infants with NO. Thirteen of the last 15 treated infants responded to NO; the only infant who died had pulmonary hypertension complicated by diaphragmatic hernia. We believe that the improved response and survival were due to the beneficial effects of a learning curve. Furthermore, we credit the improvement in results to the liberal use of fluids to expand blood volume, pressors to maintain blood pressure, exogenous surfactant to reverse surfactant dysfunction, and diuretics after the initial period of stabilization to reduce pulmonary congestion. Finally, our current approach is to begin NO at 20 ppm and increase to 40 ppm only when necessary.

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