Nitric Oxide *Fuels* Clinicians' Interest

by Ray Ritz, BA, RRT

Interest in nitric oxide has been intense. More than 14,300 papers related to it have been published since 1966. The journal *Science* named nitric oxide the "Molecule of the Year" in 1992; and in 1998, Furchgott, Ignarro and Murad received the Nobel Prize in Medicine and Physiology for their discoveries concerning nitric oxide as a signaling molecule in the cardiovascular system.

To end more than a decade of intense research on the physiology and effects of nitric oxide, the U.S. Food and Drug Administration (FDA) issued final approval on Dec. 23, 1999, to INO Therapeutics, Inc. (Clinton, NJ) for the release of the drug nitric oxide (NO) as a treatment for hypoxic respiratory failure associated with pulmonary hypertension in the term or near-term (more than 34 weeks gestation) neonate.

NO occurs normally in virtually every organ in the human body and acts as a neurochemical transmitter. It also occurs naturally in the atmosphere in concentrations of 10 to 100 parts per billion (ppb) and in cigarette smoke at levels of 400 to 1,000 parts per million (ppm). One of its most studied effects in humans is its ability to function as an endothelial-dependent relaxing factor. Nitric oxide activates guanalyte cyclase, which converts into cGMP. The presence of cGMP at the smooth muscle causes relaxation. When this occurs in the pulmonary vasculature, the result is a reduced pulmonary vascular resistance, redistribution of pulmonary circulation, and a reduction in right heart work.

When NO is inhaled, this redistribution of pulmonary circulation is directed to the areas of the lung where ventilation is effective; and the improved matching of ventilation and perfusion can result in improved oxygenation. Once NO enters the circulation, it almost instantly combines with hemoglobin and forms methemoglobin, preventing any systemic effect making it a selective pulmonary vasodilator.

Administration issues

In the early years of NO use, each institution built its own delivery systems. The goal was to design a system that controlled the dosing for a variety of ventilators and other gas delivery systems, and stand-alone NO/NO_2 monitors were used but were notoriously difficult to calibrate and maintain. The commercial release of NO has been unique in that a request for the drug automatically includes an INOvent delivery system (Datex-Ohmeda, Madison WI). This delivery system is specifically designed to adapt to most mechanical ventilators currently in use. The INOvent maintains a constant concentration of NO throughout the respiratory cycle, monitors for NO, nitrogen dioxide (NO_2), and oxygen continuously, and provides a manual (non-electrical) backup

ventilation system for emergencies. Other delivery systems may be approved by the FDA in the future that are more convenient for both inter- and intra-hospital transport, but currently this system meets most institutional needs.

Dosing

Early NO trials utilized concentrations of between 1 and 80 ppm; but as study data was analyzed, it became clear that dosing at levels above 20 ppm did not offer significant benefit. In fact, levels between 5 and 20 ppm resulted in slightly better oxygenation than did higher doses. The risk of methemoglobin anemia was significantly increased between 40 and 80 ppm, as was the risk of inadvertent exposure to NO_2. These hazards offset the small additional reduction in pulmonary artery (PA) pressures at 80 ppm seen in some patients, compared to 20 ppm. The Neonatal Inhaled Nitric Oxide Study (NINOS) clearly demonstrated that newborns who responded to 20-ppm dosing did not increase their response at 80 ppm. In that same study, non-responders to 20 ppm did not respond when treated with 80 ppm. This leaves us with the generally accepted strategy of starting all NO at 20 ppm; and if the patient responds, the NO can usually be reduced to as low as 5 ppm within the next four hours. Non-responders at 20 ppm have not been shown in any study to subsequently respond to either a higher or lower concentration.

This being the case — if no response is detected either by an improvement in oxygenation or a reduction in PA pressures or right heart work — discontinuation should be strongly considered within the first hour of the trial. Quick discontinuance when there is no measurable response is critical. If therapy continues beyond one to two hours, the patient will adapt to the inhaled concentration of NO; and any interruption of therapy will cause sudden and significant desaturation and increased pulmonary hypertension. This phenomenon is termed "rebound."

The suggested method of minimizing the effect of rebound is to wait for the patient's lung function to improve, as is evidenced by a reduced need for oxygen and PEEP, and then decrease the NO to 1 ppm for one to two hours. After the period of 1 ppm, the fraction of inspired oxygen (FIO_2) is increased 20 to 30 percent and the NO is discontinued.

Monitoring

When assessing the efficacy of a NO trial, the clinician is left with a limited number of physiologic variables to evaluate. Conventional indicators of response include a 20 percent increase in oxygenation (as measured by either arterial blood gas or arterial oxygen saturation) and/or a 20 percent reduction in PA pressure. PA pressure changes may be assessed by direct monitoring via PA catheter or by echocardiography. The response to NO can be measured within 30 minutes after the initial dose; and if there is no improvement in either oxygenation or pulmonary pressures, the therapy should be rapidly discontinued. If therapy is continued, the patient should be assessed periodically for the development of methemoglobin anemia. The formation of methemoglobin is one of the undesired side effects of NO therapy and can be avoided by limiting NO exposure to 20 ppm or less.

Institutions need to develop an effective system that carefully screens patients in a way that utilizes nitric oxide with appropriate compassion and methodology.

"On label" versus "off label" uses

The recent FDA approval of NO for the newborn who is more than 34 weeks gestation and exhibits clinical signs of pulmonary hypertension and hypoxia was based on four multicenter randomized placebo-controlled trials that demonstrated NO's ability to reduce the need for extracorporeal membrane oxygenation and to decrease the development of chronic lung disease in survivors. The "On Label" indication is narrow and creates a challenging issue for clinicians — specifically, when to go "off-label."

Many physicians believe that NO is an appropriate therapy for adult respiratory distress syndrome (ARDS), right heart failure, acute rejection following lung transplan-

tation, and acute exacerbations of pulmonary hypertension. Compassionate use of NO for these and other indications is commonplace throughout the United States and Europe. "Off-label" does not mean illegal but simply that the FDA does not consider there is compelling data to justify advocating its use for other indications. There are numerous other drugs that are used outside of their "approved" indications; and all institutions wrestle with providing aggressive, effective levels of care that are balanced against using therapies that lack sufficient data to demonstrate clear benefit.

The use of "off-label" NO must be continually assessed in each institution in order to limit its potentially significant financial impact as well as to avoid using therapies that have no demonstrated benefit or where there has been insufficient research to justify its use. We must all realize any unplanned costs of NO will be paid for by removing monies from the budgets of hospital infrastructures such as dietary, environmental services, building maintenance, security, and staffing.

Before considering NO for an indication that is "off-label," conventional therapies that improve oxygenation and reduce PA pressures should be adequately applied first. To improve oxygenation, these therapies include lung recruitment maneuvers, a trial of PEEP 15, and prone positioning.

Summary

Frivolous and unrestricted use of NO is both fiscally irresponsible and inappropriate for those patients where there has been no benefit demonstrated or where insufficient clinical trials have been completed. On the other hand, many physicians believe that NO offers either long- or short-term benefit to those patients with right ventricular failure, transplant rejection, acute exacerbations of pulmonary hypertension, and hypoxemia associated with ARDS. Institutions need to develop an effective system that carefully screens patients in a way that utilizes nitric oxide with appropriate compassion and methodology.

additionalreading

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FINANCIAL DISCLOSURE

The author is the assistant director of respiratory care at Massachusetts General Hospital and also receives compensation as a non-employee paid consultant for INO Therapeutics, Inc., of Clinton, NJ.