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Nitric Oxide II: Therapeutic Uses and Clinical Applications

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Abstract: Nitric oxide is a biological mediator in human organisms which plays important roles in tissue and organ hemostasis. Recent advances in the therapeutic uses of inhaled nitric oxide in lung diseases and other pathologic states urges the efficient and appropriate use of nitric oxide in hospitals. This study is a literature search based on a keyword search and the abstracts in English in Medline. The therapeutic indications for inhaled nitric oxide and various clinical applications are summarized. Subsequently, adverse effects and toxicity for inhaled nitric oxide and contraindications for its use are discussed.

Key Words: inhaled nitric oxide, nitric oxide's adverse effects

Introduction

Nitric oxide (NO) is an endogenous messenger molecule that is extensively involved in the physiologic regulation of different tissues in the human body (1, 2). Basic biological research on different tissues and organs to understand its important roles in human body continues (3,4). Nitric oxide has been shown to have therapeutic potential as a drug (5,6). The major medical use of nitric oxide has been the administration of inhaled nitric oxide. This gas is administered by special instruments developed using different techniques. For precise and safe delivery, the monitoring of the levels of nitric oxide and nitrogen dioxide is essential (7). Clinical studies show the potential benefits of the use of inhaled nitric oxide in various diseases. This review will emphasize its therapeutic roles in health and disease states.

Materials and Methods

The Medline database was searched by using the PubMed-National Library of Medicine (U.S.A.) medical database web site. The keywords were searched for the period of January 1, 1990, to May 30, 2001. The restrictions were "English Language" and "English Abstracted Articles". The abstracted articles on the therapeutic uses and the adverse effects and toxicity of nitric oxide were then summarized.

Indications of Nitric Oxide and Various Clinical Applications

1) Pulmonary Indications of Inhaled Nitric Oxide Therapy

a) Pulmonary Hypertension: Inhaled nitric oxide provides selective pulmonary vasodilatation with maintanance of systemic blood pressure and coronary perfusion pressure. In the presence of right ventricle failure with increased pulmonary vascular resistance, inhaled nitric oxide in the range of 2-40 ppm is effective in reducing elevated pulmonary vascular resistance and does not increase cardiac output. Lindberg et al. (8) have demonstrated in post-coronary artery bypass graft patients a full hemodynamic response at 2 ppm. Mean pulmonary artery pressure and pulmonary vascular resistance decreased by 11% and 22% respectively. Systemic hemodynamics did not change.

The effects of inhaled nitric oxide on myocardial function have been investigated in a recent study (9). Inhaled nitric oxide in patients with chronic pulmonary hypertension lowered pulmonary artery pressure and RVEDP (right ventricular diastolic pressure) and improved stroke volume caused by a decrease in right ventricle afterload. These effects have been compared with the effects of intravenous nitroprusside and sublingual nifedipine. Nitroprusside caused a similar degree of pulmonary vasodilation, although it caused increased heart rate and contractility, but overall systemic

hypotension was observed. Sublingual nifedipine did not cause pulmonary vasodilation, but RVEDP increased and right ventricle contractility decreased.

The decrease in the expression of eNOS (endothelial nitric oxide synthase) observed in pulmonary hypertension contributes to the pulmonary vasoconstriction and the excessive growth of the tunica media (10). Inhaled nitric oxide therapy shows beneficial results in various clinical situations where pulmonary hypertension is pertinent. The following are these typical clinical situations: hypoxemia (11,12), chronic obstructive pulmonary disease (COPD) (13), interstitial pulmonary fibrosis (14), acute respiratory distress sydrome (ARDS) (15-17), persistent pulmonary hypertension in the newborn (18), primary pulmonary hypertension (19) and cardiac surgery (5).

The vascular reactivity to inhaled nitric oxide in pulmonary hypertension varies widely. Chronic pulmonary hypertension leads to various degrees of vascular remodeling and medial hypertrophy in the musculature of small pulmonary arteries. The disease states that chronic pulmonary hypertension is a common feature of can be divided into four groups: (1) Diseases affecting the pulmonary vasculature: thromboembolic, primary pulmonary hypertension, and vasculitis; (2) Diseases affecting the parenchyma: fibrosis, and COPD; (3) Cardiac diseases: congenital heart disease, mitral stenosis, and cardiomyopaties; and (4) Abnormal ventilation: sleep apnea, obesity-hypoventilation syndrome.

Hypoxemia due to pulmonary disease states causes a low ventilation/perfusion ratio, and right-to-left shunting of blood through pulmonary routes. Inhaled nitric oxide dilates only the vessels adjacent to the alveolar units being ventilated. Therefore, in patients with intrapulmonary shunt, inhaled nitric oxide can increase oxygenation by improving V/Q (ventilation/perfusion) matching, with redistribution of blood flow from unventilated shunted areas to ventilated but underperfused areas (steal phenomenon) (16,20). These effects are helpful in acute respiratory distress patients where right-to-left intrapulmonary shunting is a hallmark. The data reviewed in the literature shows that different inhaled nitric oxide doses were used: <1ppm or 1.25 to 80 ppm (16,17,21).

The reduction of pulmonary vascular resistance and improved oxygenation leading to decreased Fi02 (fraction of inspired oxygen) and airway pressures were recorded in the studies searched. However, retrospective studies with matched controls showed no difference in survival, time spent on mechanical ventilator, or intensive care unit stay between acute respiratory disease syndrome patients treated with inhaled nitric oxide and control groups (22,23).

In COPD patients, reports of worsening oxygenation with inhaled nitric oxide shows broad V/Q heterogeneity and the presence of low V/Q areas (24).

Persistent pulmonary hypertension of the newborn, is a disease of decreased pulmonary blood flow with a persistent fetal circulation. Inhaled nitric oxide has been used successfully to decrease pulmonary vasoconstriction and to increase Pa02. In the Neonatal Inhaled Nitric Oxide Study Trial, the effects of 20 ppm inhaled nitric oxide were investigated in more than 200 full-term and nearly full-term infants with hypoxic respiratory failure (25). A significant improvement in oxygenation and reduced need for extracorporeal membrane oxygenation (39% nitric oxide group v 54% control group) was seen. There was no apparent effect on mortality. However, by avoiding the invasiveness of extracorporeal membrane oxygenation and systemic anticoagulation, nitric oxide is likely, although unproven, to reduce morbidity.

Respiratory distress syndrome (RDS) usually occurs in premature babies with gestation < 30 weeks. Lecithin to sphingomyelin ratio is < 2:1 (26). The complications of RDS includes pulmonary hypertension, intrapulmonary shunting with severe hypoxemia, and myocardial dysfunction. Nitric oxide is supposed to work by improving gas exchange through ventilation-perfusion matching and reducing pulmonary vascular resistance. Its exact mechanism of action in RDS is not completely understood. Skimming et al. (27) documented improved oxygenation in 23 premature neonates at doses of 5-20 ppm. This effect was dose-independent.

In newborns with congenital diaphragmatic hernia, inhaled nitric oxide did not appear to be of significant benefit (28).

b) Heart and Lung Surgery: Inhaled nitric oxide is the medication of choice for treatment of pulmonary hypertension and hypoxemia following cardiopulmonary bypass (29) or the use of a ventricular assist device (30), for mitral valve replacement (31), coronary artery by-pass graft (32), heart or lung transplantation (33,34), and pulmonary embolism.

In pediatric surgery, inhaled nitric oxide has been used for preoperative assessment of pulmonary vascular resistance reactivity, diagnosis of anatomic obstructions leading to pulmonary hypertension (35), treatment of pulmonary hypertension when weaning from cardiopulmonary bypass, and postoperatively.

Schulze-Neick et al. (36) reported beneficial effects of 50 ppm inhaled nitric oxide in children after surgical correction of ventricular and atrioventricular septal defects. A 43% decrease in pulmonary vascular resistance and an approximate 30% increase in cardiac index and right ventricular ejection fraction were observed. Pulmonary vascular resistance is a unique determinant of systemic cardiac output in a setting of "passive" pulmonary blood flow (Fontan-type anatomy). Inhalation of 1.5 to 10 ppm nitric oxide in patients undergoing Fontan-type procedures was shown to significantly improve hemodynamics (37). Central venous pressure and transpulmonary gradient decreased by 15% and 42%, respectively, while increasing left atrial pressure and mean arterial pressure by 28% and 12% respectively.

The use of inhaled nitric oxide to relieve pulmonary hypertension in patients after heart and lung transplantation is well described (38,39).

c) Asthma and Bronchospastic Diseases: Expired nitric oxide has been suggested as a marker of severity and therapeutic response in asthmatics. Exhaled nitric oxide has been shown to increase proportionally to airway inflammation in several studies (40,41). The data on inhaled nitric oxide therapy in asthma patients are contradictory.

d) One-lung Ventilation: Inhaled nitric oxide reduces pulmonary vascular resistance in the ventilated lung, increases pulmonary blood flow and enhances the effects of hypoxic pulmonary vasoconstriction in the non-ventilated lung. Results of studies are contradictory; the results vary from beneficial to no effect (42,43).

e) Sickle Cell Disease: Improving blood flow is a critical aspect in treating the painful and potentially deadly complications associated with sickle cell anemia. When nitric oxide is inhaled, it binds to hemoglobin. Once attached, the gas hitches a ride through the blood stream, and may dilate vessels as it passes through. In sickle cell anemia, hemoglobin molecules cluster into rigid spikes as oxygen is lost. The result is misshapen blood cells that slow blood flow and can block vessels entirely. When blood flow is disrupted, oxygen can not be delivered to the body, causing painful and potentially deadly damage to organs and tissues. Stamler et al. (44,45) found that hemoglobin in red blood cells – not the vessel wall – actually plays the major role in regulating blood flow. It does so by changing shape and releasing a souped-up molecule of nitric oxide called s-nitrosothiol (SNO), which it carries along with oxygen, through the blood stream. Thus, hemoglobin simultaneously releases SNO to dilate blood vessels and delivers oxygen to nourish tissue. When oxygen levels are high, hemoglobin scavenges excess oxygen and nitric oxide, constricting blood vessels and reducing blood flow. Each hemoglobin molecule carries four oxygen molecules when it leaves the lung. In the tissue, hemoglobin changes shape, allowing it to release the oxygen. But, on average, it returns to the lung still carrying three oxygen molecules. Thus, hemoglobin did not seem to be efficiently releasing oxygen. It has always been a mystery why most of the oxygen is lost in flow controlling arteries and is shunted back to the lung before hemoglobin completes its trip through the tissues. The loss of oxygen is a switch that releases nitric oxide in the arteries to dilate blood vessels and increase blood flow so that the remaining oxygen can be delivered to tissue. Then, on the return trip to the lungs, the oxygen that was lost in the arteries is recaptured in the veins, giving the appearance of inefficient oxygen delivery. In test tube experiments, hemoglobin scavenges nitric oxide and constricts blood vessels. Yet in the body, hemoglobin does not have this effect under normal conditions. This tendency to constrict blood vessels seems to oppose hemoglobin's job of delivering oxygen. Hemoglobin releases nitric oxide in the arteries to counteract the nitric oxide it scavenges. Findings showed for the first time that nitric oxide, combined with hemoglobin, is a major regulator of gas exchange in the circulatory system. These findings may be useful in the care of stroke patients and in ischemic/perfusion related injury management (46,47).

Adverse Effects and Toxicity of Inhaled Nitric Oxide: Threshold limit values have been set by Occupational Safety and Health Administrations for permissible exposure limits for workers in different countries (48). Nitric oxide exposure for an 8 hour time-weighted average period must not exceed 25 ppm, and not exceed 5 ppm during any part of the working day.

Nitrogen dioxide maximum exposure must not exceed 5 ppm or 3 ppm. Although there is concensus concerning nitric oxide exposures limits in different countries, nitrogen dioxide limits are still controversial (49). Nitric oxide in the presence of oxygen will, in most instances, combine to become nitrogen dioxide. Nitrogen dioxide can result in increased airway reactivity and parenchymal lung injury. The determinants of nitrogen dioxide production are nitric oxide concentration, the FiO2, and the time nitric oxide is in contact with oxygen. OONO- formed from nitric oxide and O2- has a variety of toxic effects related to lipid peroxidation and intracellular alterations (50).

Nitric oxide has been found to have an affinity for hemoglobin that is 280 times faster than carbon monoxide, therefore, continuous monitoring is essential. High levels of methemoglobin can potentially interfere with tissue oxygen delivery and result in hypoxia. At some hospitals, methemoglobin levels < 4% are considered acceptable. If at any time the level rises above that point, then the concentration of inhaled nitric oxide should be reduced or discontinued completely (49). Significant methemoglobinemia has not been observed with inhaled nitric oxide doses below 20 ppm. It can easily be detected by careful monitoring of blood methemoglobin levels and can be treated with methylene blue or N-acetyl-L-cysteine (51).

One other potential complication that should be mentioned is the possible effect on coagulation caused by decreased platelet aggregation. In an acute respiratory distress syndrome population, Samama et al. (52) noted dose-independent decreases in platelet aggregation and agglutination without a change in bleeding time. Inhaled nitric oxide inhibits platelet aggregation and prolongs bleeding time in adults. The clinical significance of this effect is unclear. Premature neonates are at high risk for bleeding disturbances, especially intraventricular hemorrhage (53).

In patients with left ventricular dysfunction, inhaled nitric oxide has been associated with pulmonary edema (54).

A number of investigators have reported severe rebound hypoxemia and pulmonary hypertension on inhaled nitric oxide withdrawal (55). The suppression of endogenous nitric oxide synthase activity or downregulation of guanyl cyclase have been investigated. Several methods have been described for weaning inhaled nitric oxide. The easiest method is to withdraw inhaled nitric oxide after the patient is significantly improved and to increase FiO2 before discontinuation of inhaled nitric oxide (15). Gradual weaning is also suggested in order to avoid adverse rebound effects (56).

Conclusion

Nitric oxide is a selective pulmonary vasodilator with minimal adverse effects . Discoveries involving the extrapulmonary effects of inhaled nitric oxide are expanding. Large trials are needed to demonstrate the beneficial effects of inhaled nitric oxide in various clinical applications. Specific patient groups, their ages, and characteristics need to be defined and the optimal concentration and duration of therapy must be established. The importance of inhaled nitric oxide in neonatal and pediatric intensive care units is becoming more evident with new clinical trials. Exhaled nitric oxide may become a useful marker of asthma. As nitric oxide gains wider use in hospitals, clinicians must be familiar with its pharmacophysiology, monitoring and delivery systems, its various clinical applications and side effects to ensure safe and effective therapy.

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