Letter

Extrapulmonary effects of nitric oxide inhalation therapy: time to consider new dosing regimes?

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Published: 11 February 2008
This article is online at http://ccforum.com/content/12/1/406

Critical Care 2008, **12:**406 (doi:10.1186/cc6775)

Studies with nitric oxide (NO) inhalation suggest transformation of NO in the lung into a more long-lived bioactive NO species that also has distal effects [1,2]. The exact nature of these species has not been pinpointed, but probable candidates include circulating nitrite anions and/or *S*-nitrosothiols [3]. When using inhaled NO therapeutically for pulmonary disorders, the dose is typically expressed as the concentration of NO without adjustments for body size. When inhaling 10 ppm NO, the concentration of NO that reaches the lungs with every breath is the same whether it in a mouse, a premature infant or an adult. The minute ventilation in relation to body weight, however, is about three to four times higher in a premature infant compared with an adult, so the resulting accumulation of bioactive NO metabolites in blood is much greater. This greater accumulation suggests that the dose of inhaled NO should be adjusted in relation to body weight, and also calls for some caution when extrapolating results from animal data to humans. A concentration of inhaled NO that is effective in a small animal may therefore not be sufficient in humans. Conversely, a concentration that is effective and safe in adults may cause unwanted toxic effects in premature infants.

Several factors will affect the metabolism of inhaled NO into bioactive circulating NO species. The vast majority of inhaled NO eventually ends up as nitrate, which is considered biologically inert. In awake subjects, however, nitrate undergoes enterosalivary circulation and is reduced to nitrite in the oral cavity [4]. Swallowed nitrite then reenters the circulation, where it can be further reduced to bioactive NO [5]. In intubated sedated patients the enterosalivary nitrate/nitrite cycle is disrupted, and consequently less nitrite is generated. The levels of circulating NO species will also depend on NO oxidation in blood into nitrite, on renal excretion and on the activity of the reductive systems that ultimately catalyse NO formation from the circulating NO metabolites [3].

In summary, it is clear that inhaled NO has distal effects outside the lungs that may be harnessed therapeutically in the future; for example, in the prevention of ischemia-reperfusion injury. Although the precise nature of the NO metabolite(s) responsible for these effects remains to be pinpointed, there are indications that the nitrite anion plays an active role. In experimental settings and in future clinical trials we should consider adjusting the dose of inhaled NO in relation to body size and should consider other factors that may affect the transduction of NO bioactivity to the target organ. Finally, the possibility of delivering the active NO metabolites directly instead of via NO inhalation should also be considered.

Competing interests

The authors declare that they have no competing interests.

References

1. Fox-Robichaud A, Payne D, Hasan SU, Ostrovsky L, Fairhead T, Reinhardt P, Kubes P: **Inhaled NO as a viable antiadhesive therapy for ischemia/reperfusion injury of distal microvascular beds.** *J Clin Invest* 1998, **101:**2497-2505.
2. Cannon RO 3rd, Schechter AN, Panza JA, Ognibene FP, Pease-Fye ME, Waclawiw MA, Shelhamer JH, Gladwin MT: **Effects of inhaled nitric oxide on regional blood flow are consistent with intravascular nitric oxide delivery.** *J Clin Invest* 2001, **108:**279-287.
3. Lundberg JO, Weitzberg E, Gladwin MT: **The nitrate–nitrite–nitric oxide pathway in physiology and therapeutics.** *Nat Rev Drug Discov* 2008, **7:**156-167.
4. Lundberg JO, Weitzberg E, Cole JA, Benjamin N: **Nitrate, bacteria and human health.** *Nat Rev Microbiol* 2004, **2:**593-602.
5. Lundberg JO, Govoni M: **Inorganic nitrate is a possible source for systemic generation of nitric oxide.** *Free Radic Biol Med* 2004, **37:**395-400.

NO = nitric oxide.