Reassessment of inhaled nitric oxide in acute lung injury

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Inhaled nitric oxide (iNO) has now been used clinically since 1991, or twelve years. The acute aims of therapy have mainly been improvement of oxygenation and reduction of lung vasoconstriction. This is true also for the use in ALI (acute lung injury) of various degrees of severity including ARDS (acute respiratory distress syndrome).

EFFICACY OF A DRUG–HOW TO DEFINE IT?

Endpoints such as acute pressure reduction or oxygenation change are purely physiological, and cannot easily be put forward as credible rationale for clinical use, at least not with the drug regulatory agencies of USA and the European Union (EU). Efficacy would have to be expressed and proved in other ways, less controversial and with more obvious benefit for the patient and society. Examples of more solid endpoints are improved long-term survival, less morbidity after initial insult, and shorter time on mechanical ventilation. Mortality can be criticized as being the end result of a complicated decision process in the ICU, involving procedures for establishing DNR (do-not-resuscitate) criteria in "obviously" futile clinical situations and influences from ethical discussions involving family members and wishes expressed prior to insult by the patient. Other examples of endpoints for larger studies can be discussed, such as less need of expensive resources or painful/scarce/complicated procedures with a preserved acceptable outcome. The NINOS study[1] used a combined endpoint of death at 120 days OR use of ECMO (extracorporeal membrane oxygenation) as a primary endpoint. This was subsequently accepted on both sides of the Atlantic Ocean as added evidence of efficacy coupled with acutely improved oxygenation in the treatment arm. Here it is important to add, that adverse events in the NINOS study could be reported as similar in both arms. Upon such data iNO therapy was accepted as a drug, after another independent study could confirm these observations in newborn term or near-term babies with hypoxemic respiratory failure[2].

EFFICACY OF iNO IN RELATION TO ALI

The situation when using iNO in adult patients with severe ALI differs in many aspects from that found in the newborns. Several multicentre studies have failed to demonstrate improved survival or other signs of altered outcome from the use of iNO, although evidence of a significantly acute improvement in oxygenation is present[3-5]. ALI is a syndrome resulting from a diverse set of disease processes. Patients can have anything from single organ failure (lung) to multi-organ failure with a much worse prognosis. Age has a strong influence on prognosis independent of other factors. However outcome is surprisingly little influenced by the degree of gas exchange abnormality at the time of diagnosis (ref Luhr). As a matter of fact, we recently found ICU patients in Scandinavia had the similar 90-day mortality of around 40 % regardless whether they had ARDS or only a milder form of acute respiratory failure[6].

Does the above facts make it clear that we shall never use iNO in ALI or ARDS? The recent report from use of iNO in Beijing during 2003 by Dr CHEN *et al* (Prof HEDENSTIERNA, personal communication) in patients with SARS (severe acute respiratory syndrome) could be seen as an example of how use of iNO in better defined subgroups of patients could be studied. The SARS patients have a well-defined etiology (SARS virus) and the correct stage of therapy start might be easier to define (early during start of respiratory symptoms, still single organ failure). If this proves to be the fruitful way to work, we should no longer accept to group ***all*** ARDS or ALI patients of various timing and etiology together in coming studies. Another important report recently came from the Berlin

group, in which the correct dose of iNO to use in ALI was re-examined[7].

OFF-LABLE USE OF iNO

A more deplorable situation would be to accept on-going use of iNO as therapy for ALI without ever establishing proof of efficacy, as is the fact in some centres. This use is often justified on data from anecdotes, small case series, and personal belief in the importance of acute physiological alterations from using iNO. We may take use of iNO in postoperative cardiac surgery as a problematic example: some clinicians (mainly surgeons) intuitively understand what constitutes a failing heart. Such a heart results in a bed-ridden often dyspnoeic patient with a poor 3-month prognosis. Avoiding such crises=benefit. Consequently they are reluctant to randomize their patients to placebo in the presence of iNO therapy, as some studies give evidence of less hypertensive crises postoperatively when using iNO[8]. How may we now make progress and establish an evidence-based approach to use of iNO in these patients?

FUTURE PERSPECTIVES

So where does iNO therapy stand in 2003? It is clear that an expansion from strictly neonatal clinical use to additional indications like ALI would need a consensus on what exactly constitutes a clinically meaningful ***benefit*** from iNO therapy which can be expected to mainly influence pulmonary events. A pharmacoeconomic endpoint would be: more patients treated to the same result (survival, adverse effects, morbidity) with equal resource allocation. This points to studies directed towards time in the ICU, time on therapy like mechanical ventilation or other types of support; as well as follow-up of adverse effects. Reduction in morbidity such as intracranial haemorrhage, neurological deficit, could be other examples of possible primary or secondary endpoints to study. A clearly undesired result from using iNO would be longer short term (weeks) survival in the ICU, without more patients discharged alive from such a unit. Careful consideration of correct dose for chosen endpoint should be made. It could also be discussed at what stage of disease to start therapy. Use of iNO early during CPAP before intubation might be a way to go but first necessitates development of new delivery systems for iNO[9]. With these types of deliberations done, additional meaningful studies on the use of iNO (and other therapies) in the ICU could be launched. Without these considerations cleared up at the outset, planning of clinical studies cannot be carried out rationally. Assumed acceptance of efficacy is simply too risky and expensive today, when a single multicentre GCP (good clinical practice) – type study may cost >5 million dollars. This author argues that new studies, should only be initiated on use of iNO after an interactive process involving clinicians, people involved in health economics, the public and regulatory opinion has been concluded. When we can agree what endpoints give solid evidence of efficacy, a clinical study testing that endpoint(s) can be designed.

The author wishes to disclose a conflict of interest in that he has participated in patent applications on the clinical use of inhaled nitric oxide. In addition, he has acted as a consultant to industry regarding the clinical use of inhaled NO.

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