Addition of inhaled nitric oxide to the treatment options available to an acute neonatal transport service

Licensed for use with term and near-term neonates suffering acute hypoxic respiratory failure, the pulmonary vasodilator inhaled nitric oxide (iNO) is used to reduce pulmonary hypertension and improve oxygenation. It is administered in the form of a gas added to ventilator circuits. Patients receiving iNO can suffer severe rebound effects if it is stopped and therefore it needs to be continued in transit when patients receiving it are moved between hospitals. This article discusses the issues involved with using iNO in transit and describes the setting up of mobile iNO capability for the transport service of a neonatal network.

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Key points

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1. Use of inhaled nitric oxide raises health and safety issues for both staff and patients.
2. Patients receiving this therapy should not have it stopped if they are transferred between hospitals.
3. With adequate planning and training, and with use of appropriate equipment, nitric oxide administration can be safely continued during transport.
4. Transport nitric oxide capability can be successfully added to the options available to a neonatal transport service.

The clinical use of inhaled nitric oxide (iNO) began in the early 1990s[1]. When administered to term or near-term babies with acute hypoxic respiratory failure it has been shown to improve oxygenation and reduce the number of babies who go on to require support with extra corporeal membrane oxygenation (ECMO)[2] and it is for this use that iNO is officially licensed. Though it does not appear to benefit acutely hypoxic infants born below thirty four weeks' gestation there is some evidence that iNO reduces the incidence of chronic lung disease in some groups of premature infants[3, 4]. This potential application of iNO is currently being studied by large randomised trials in both North America and Europe.

The reorganisation of neonatal services in the UK into clinical networks[5] has led to an increase in the centralisation of intensive care provision for very sick and/or premature babies. This centralisation will potentially lead to an increase in the inter-hospital transport of such babies. To cater for these organisational changes and ensure the availability of effective transport within their areas of responsibility, three neonatal networks jointly established a stand alone transport service in 2003. Based at Addenbrookes Hospital in Cambridge the East of England Acute Neonatal Transport Service (ANTS) is responsible for neonatal transfers throughout the Norfolk, Suffolk and Cambridgeshire; the Bedfordshire and Hertfordshire; and the Essex neonatal networks. This service covers eighteen hospitals in an area stretching from north Norfolk to the M25. ANTS provides a road transport service but does not carry out air transports. The transport by air of patients receiving iNO, which is subject to specific regulations, is therefore not covered in this article.

Only a small number of patients per year within the ANTS area require administration of iNO. These babies require very intensive medical and nursing input and are usually cared for in the lead centres that provide the bulk of network intensive care services. This allows the staff of the lead centre units to build up expertise and experience of a treatment that is potentially dangerous for both patients and staff. However it is not usually possible to predict the occurrence of acute hypoxic respiratory failure antenatally and consequently babies who may potentially benefit from iNO could be born at any of the network hospitals. The establishment of transport iNO capability for the ANTS team allows iNO to be tried whilst patients are still on their referring unit. This has the potential both to improve patient stability during transports and to minimise the transport of such patients.

After arrival at a referring unit the ANTS team can now initiate iNO if required. The response of a baby to iNO can help inform decisions about further treatment options. For example a baby failing to respond to iNO at a referral unit could, if appropriate, be referred to an ECMO centre and transferred directly there without first being moved to a network lead centre for a trial of iNO. Babies who do respond to

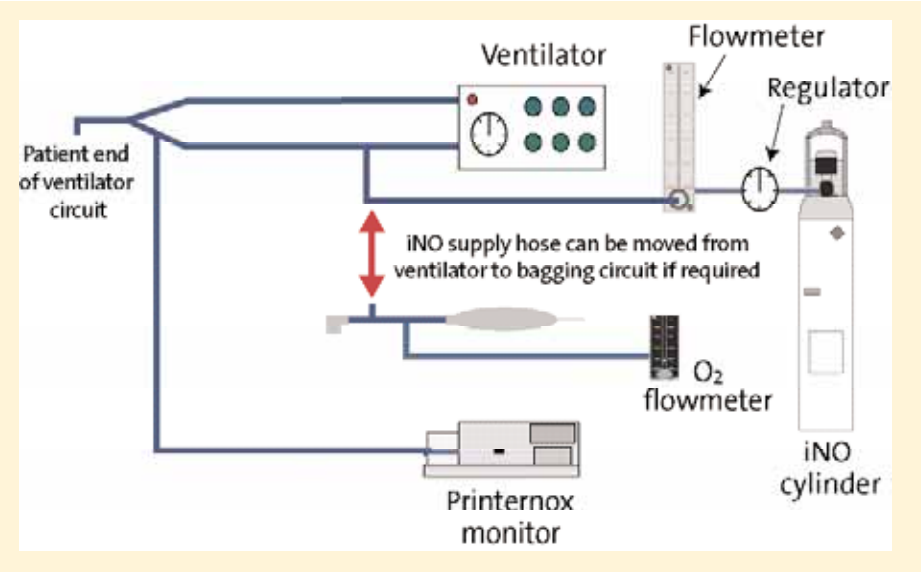

FIGURE 1 Schematic diagram of typical transport iNO circuit.

iNO may be more stable during transfer to the lead centre than they would be if moved before iNO can be started. European guidelines[6] recommend that arrangements are in place for transferring babies receiving iNO without interruption of therapy. The ANTS team can now either start or continue iNO on any unit they are collecting a patient from, whether within or outside of their networks.

Evidence/experience base

Practical and ethical issues would make a formal randomised comparison of using or not using transport iNO very difficult, if not impossible. There is however a growing base of experience and a number of case series reports have now been published. In the UK all four of the supra-regional ECMO centres have been using transport iNO for some time. The Leicester Neonatal Service has an established transport iNO capability, as have some other UK neonatal services. A survey of ECMO centres in the United States (US)[7] found that of the 44 (from a total of 85) centres who responded, 19 had transport iNO capability and a further 12 were developing it.

Two large US case series[7,8] reported use of iNO during transport of 25 and 78 patients respectively. In the UK Westrope et al[9] report a series of 55 patients safely transferred to an ECMO centre whilst receiving iNO. These recent series all reported safe and successful use of iNO whilst transporting sick patients. Earlier smaller series from Australia[10], the UK[11] and the US[12] also reported successful use of this therapy.

Equipment issues

Whilst iNO gas itself (marketed in the UK as INOmax® by INO Therapeutics®) is available in small cylinders designed for transport use, there is no equipment available in the UK specifically designed for using iNO during transport. The Inovent® delivery/monitoring system from Datex Ohmeda® (now GE Healthcare) is used for transport by some teams in the US but its weight makes compliance with European transport regulations a problem and its size creates practical problems with transport incubators. The AeroNOx® from PulmoNOx® is a small, compact, lightweight delivery/monitoring system designed specifically for transport[13] but is not currently approved or available for use in Europe. Availability of this device may in the future solve many of the technical problems that have traditionally been associated with setting up transport iNO systems. The lack of commercially available purpose built iNO delivery equipment has required UK transport teams to work with hospital technical staff to develop systems in-house, modifying available equipment and components as necessary. In most cases a battery powered Printernox® iNO/Nitrogen Dioxide (NO_2) monitor is used and iNO is administered from a small transport cylinder into the patient ventilator circuit via a suitable regulator and flow meter (**FIGURE 1**).

Safety issues

As with any equipment used for patient transfer, the equipment used for iNO must be securely fixed to the transport incubator to minimise the risk of injury in the case of a road accident. Because iNO is potentially hazardous, ambulance services must be informed when it is being carried and any carrier specific protocols or policies must be adhered to. The use of iNO in transit raises several specific safety issues that have implications for both patients and staff and therefore need to be considered.

Exposure to a very large concentration of iNO can have severe respiratory effects[14]. For this reason staff must ensure constant monitoring of the dose being received by a baby. They must also monitor for signs of gas leaking from equipment into a transport vehicle. In practice even a serious leak from a cylinder or regulator is unlikely to pose a hazard to staff because discharge of a full transport cylinder should not release enough iNO to raise environmental levels within the vehicle near to or above the recommended exposure limits[15]. The use of environmental monitors can potentially warn staff of leaks but there is anecdotal evidence that they may give false alarms in an ambulance environment and any monitors used must be checked for suitability and accuracy. Scavenging filters can be used to remove iNO and NO_2 from the expiratory tubing of the ventilator but in practice this can be difficult with transport equipment and should not be necessary if there is reasonable environmental air flow[16].

The mixing of iNO with oxygen in ventilator circuits results in the formation of nitrogen dioxide (NO_2), which can have toxic pulmonary effects at high concentrations[17], particularly at levels over ten parts per million[13]. Consequently NO_2 levels in the inspiratory limb of ventilator circuits are monitored continuously. When the iNO system is readied for use it must be purged of old gas to remove any NO_2 buildup and the NO_2 level must be known before connection to the patient. iNO binds readily to and is inactivated by haemoglobin. This process results in the formation of methaemaglobin, high levels of which may affect the oxygen carrying capacity of the blood. This is not usually a problem with the doses of iNO used clinically[18] but must be considered and blood levels checked if possible.

Stopping iNO therapy may cause rebound pulmonary hypertension and severe hypoxia, sometimes even in babies who have not shown a positive response[19]. Sudden cessation of treatment during transport, for instance caused by running

out of gas, could therefore be potentially catastrophic. For this reason transport staff must ensure that they have adequate supplies for any journey undertaken, particularly as there are many hospitals that do not use iNO and obtaining extra cylinders away from base may be very difficult or impossible.

Whilst the very small environmental levels of iNO and NO_2 produced by iNO administration are not believed to pose any risk to pregnant staff there is no official information available about iNO and pregnancy[19] and many units give pregnant staff a choice about whether or not they work with patients receiving this therapy.

Setting up the service

Once a firm decision had been made to add transport iNO capability to the ANTS service, and funding had been identified, a plan was devised to ensure that the introduction of iNO would be safe and effective. Four main topics needed to be addressed. These were equipment, clinical guidelines, documentation and training.

Equipment

The use of iNO during transport requires the addition of a gas cylinder, administration equipment and a monitoring device to the transport incubator setup. To meet legal requirements, and to ensure both safety and effectiveness, equipment must be user friendly, as light as possible and securely attached. Both UK[20] and European[21,22] recommendations and directives related to transport incubators must be adhered to for safety and insurance purposes.

To overcome the lack of specifically designed equipment the ANTS team worked closely with the Addenbrookes medical physics and clinical engineering departments to identify and fit suitable delivery and monitoring equipment. Ventilator circuits, pre-fitted with appropriate connections and tubing for iNO delivery and monitoring, were purchased and the transport incubator (**FIGURES 2 AND 3**) was modified to allow secure mounting of a transport iNO cylinder together with a regulator, flowmeter and a Printernox® iNO/Nitrogen Dioxide (NO_2) monitor. If a baby receiving iNO requires hand ventilation at any time, iNO administration can be continued by moving the iNO delivery tubing from the ventilator circuit to the hand ventilation circuit. It was decided that the ANTS team would be responsible for maintenance of all iNO equipment and a maintenance guide was drawn up[23] to help ensure that this would be carried out correctly and on time (**FIGURE 4**).

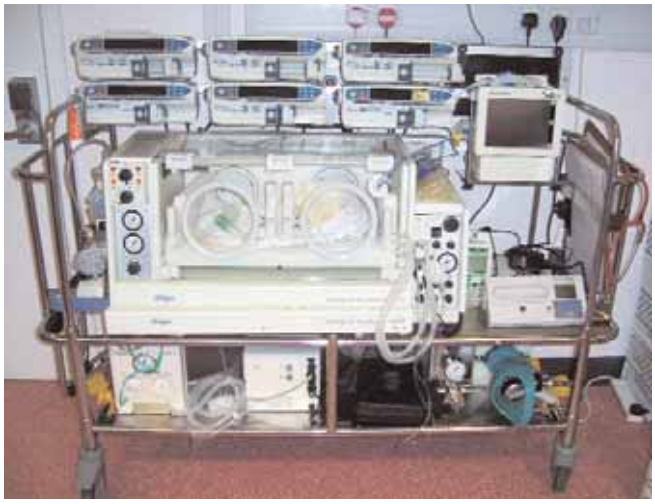

FIGURE 2 The ANTS transport incubator with iNO delivery and monitoring equipment mounted.

FIGURE 3 Close up of the iNO cylinder, regulator and flowmeter.

Clinical guidelines

To ensure that iNO is used safely and appropriately by the ANTS team two guideline documents were drawn up. The first[24] covers patient eligibility, dosing, monitoring, complications and system set-up. The second[25] covers set-up and use of the ANTS iNO system. The aim of these documents is to provide medical and nursing staff with guidance about when to consider iNO use and give them practical reminders and information about equipment use. The guidelines are aimed at backing up information given during formal training sessions.

Documentation

Good record keeping aids communication and contributes towards high standards of care[26]. On all transfers ANTS team members regularly record patient observations such as heart and respiratory rate, blood pressure and oxygen saturation. During iNO use these routine observations are added to by careful recording of the iNO dose and the effect of any dose changes upon oxygenation status. NO_2 levels are also recorded and, if a baby receives iNO for two hours or more, the methaemaglobin level is checked and documented if possible. Recording of clinical observations is supplemented by narrative notes that clearly record both the overall course of a transfer and what has happened in relation to iNO use.

Clinical use of iNO is usually charged for on an hourly fee basis but at present iNO used during transport is provided free of charge. Despite this the ANTS team keep accurate records of when, for whom and for how long iNO is used by completing an iNO usage form. There is specific paperwork to be completed when used cylinders are returned to pharmacy. Accurate recording of iNO use aids the clinical audit process and may in the future be required to cross-reference any costs incurred by using iNO during patient transfers. A series of monthly checks and calibrations is required to maintain the iNO equipment. To ensure these are carried out, and thus prevent equipment becoming inaccurate, monthly maintenance is clearly documented (**FIGURE 4**).

Training

The introduction of any new treatment and/or equipment requires appropriate education to ensure competence and thus safe, effective practice. To adhere to their code of conduct[27] nursing staff must be satisfied with their own competence for any role they agree to take on. The responsibility for training is jointly held by staff and employers and should involve both practice and education staff[28]. As part of the initial training an iNO study day was organised for the ANTS team. A combination of internal and external speakers covered topics that included the physiology of iNO, suitable and non-suitable patients, advantages and disadvantages, side effects, monitoring and general practical issues related to

Monthly checks on nitric equipment			
Date:			
• Calibrate printernox cells			
• Connect cylinder to regulator/flowmeter • Leak check			
• Run system at 10ppm and ensure there is no NO_2 build up			
• Check bag contents			

FIGURE 4 Checklist for monthly maintenance of iNO equipment (above).

Statement of competency for using nitric oxide on transport			
Name:	Date	Signature of nurse	Signature of assessor
Pre-use checks • Calibrating cells • Connecting cylinder to regulator/flowmeter • Leak checks			
• Using printernox • Menu functions			
• Connecting nitric to ventilator circuit			
• Head ventilation			
• Documentation			
• Basic troubleshooting • Safety			

FIGURE 5 Staff competency document (right).

using iNO during transport.

This study day was backed up by providing one-to-one practical training, if required, and by encouraging staff to practice set-up and use of the system using the written guidelines. When staff had been through this process and were happy with the use of iNO they were asked to undertake a formal assessment of competence (**FIGURE 5**). It is intended that this assessment of competence becomes an annual requirement for ANTS team nursing staff. Once assessed as competent, ANTS staff are able to use the transport iNO system should the need arise.

Discussion

The benefits, advantages and use of iNO during the transport of critically ill neonates have been documented by authors from several countries. If appropriate guidelines, adequate training and suitable equipment are available this potentially dangerous but beneficial treatment can be administered safely and effectively in many different environments. The ANTS team decided to introduce transport iNO capability in order to increase their capability and improve the service being offered to neonatal units, and patients, across three networks. Since introduction of iNO capability the ANTS team have used the system successfully and it is now an integral part of the service that they provide.

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