Use of Inhaled Nitric Oxide in Infants Treated in Neonatal Units in England

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NDAU

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MOLECULE OF THE YEAR

NO News Is Good News

A startlingly simple molecule unites neuroscience, physiology, and immunology and revises scientists' understanding of how cells communicate and defend themselves

A decade ago, nitric oxide (NO) was just another toxic molecule, one of a lengthy list of environmental pollutants found in unsavory haunts such as cigarette smoke and smog. Destroyer of ozone, suspected ca sor of acid rain, this ga

But over the past 5 years, diverse lines of evidence have converged to show that this sometime poison is a fundamental player in

lar physiology, and carcinogenesis—suddenly realized they were studying the same molecule. Like a squirt of some powerful perfume, a puff of nitric oxide spurs different cells into an array of different activities, from communication to defense to regulation.

A thousand times NO. In 1992, scientists

istry of nitric oxide manufacture. Cells rely on various forms of an unusual enzyme called NO synthase (NOS) to do the job, and a

ing out how the enzyme works.

NO cure for heartache. This year, clin cal applications of NO knowledge bloome in several directions at once, but much effo focused on nitric oxide's role as the body own blood pressure police. In blood vessel NO is released by endothelial cells on th migrates to nearb hem. This dilat the vessel and lowers blood pressure.

Understanding this process opens the do to a host of new drugs. Indeed, faults in th

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SHORT REPORTS

Inhaled nitric oxide in persistent pulmonary hypertension of the newborn

JESSE D. ROBERTS, DAVID M. POLANER
PETER LANG WARREN M. ZAPOL

Nitric oxide (NO) has vasodilatory effects on the pulmonary vasculature in adults and animals. We examined the effects on systemic oxygenation and blood pressure of inhaling up to 80 parts per million by volume of NO at F_iO_2 0·9 for up to 30 minutes by 6 infants with persistent pulmonary hypertension of the newborn (PPHN). In all infants this treatment rapidly and significantly increased preductal oxygen saturation (SpO_2); in 5 infants postductal SpO_2 and oxygen tensions also increased. Inhalation of NO did not cause systemic hypotension or raise methaemoglobin. These data suggest that low levels of inhaled NO have an important role in the reversal of hypoxaemia due to PPHN.

Lancet 1992; **340**: 818–19.

Low-dose inhalational nitric oxide in persistent pulmonary hypertension of the newborn

JOHN P. KINSELLA STEVEN R. NEISH
ELIZABETH SHAFFER STEVEN H. ABMAN

We studied the effects of inhaled nitric oxide (NO) in 9 newborn infants with severe persistent pulmonary hypertension (PPHN) who were candidates for extracorporeal membrane oxygenation treatment. With low doses of NO (10–20 ppm) all showed rapid improvement in oxygenation without reduction of systemic blood pressure. In 6 infants treated with inhaled NO for 24 h, clinical improvement was sustained at 6 ppm.

Lancet 1992; **340**: 819–20.

In persistent pulmonary hypertension of the newborn (PPHN)—a syndrome that can be idiopathic or associated with various neonatal cardiorespiratory diseases, including meconium aspiration and group B streptococcal sepsis—increased pulmonary vascular resistance results in right-to-left shunting of blood across the patent ductus arteriosus and

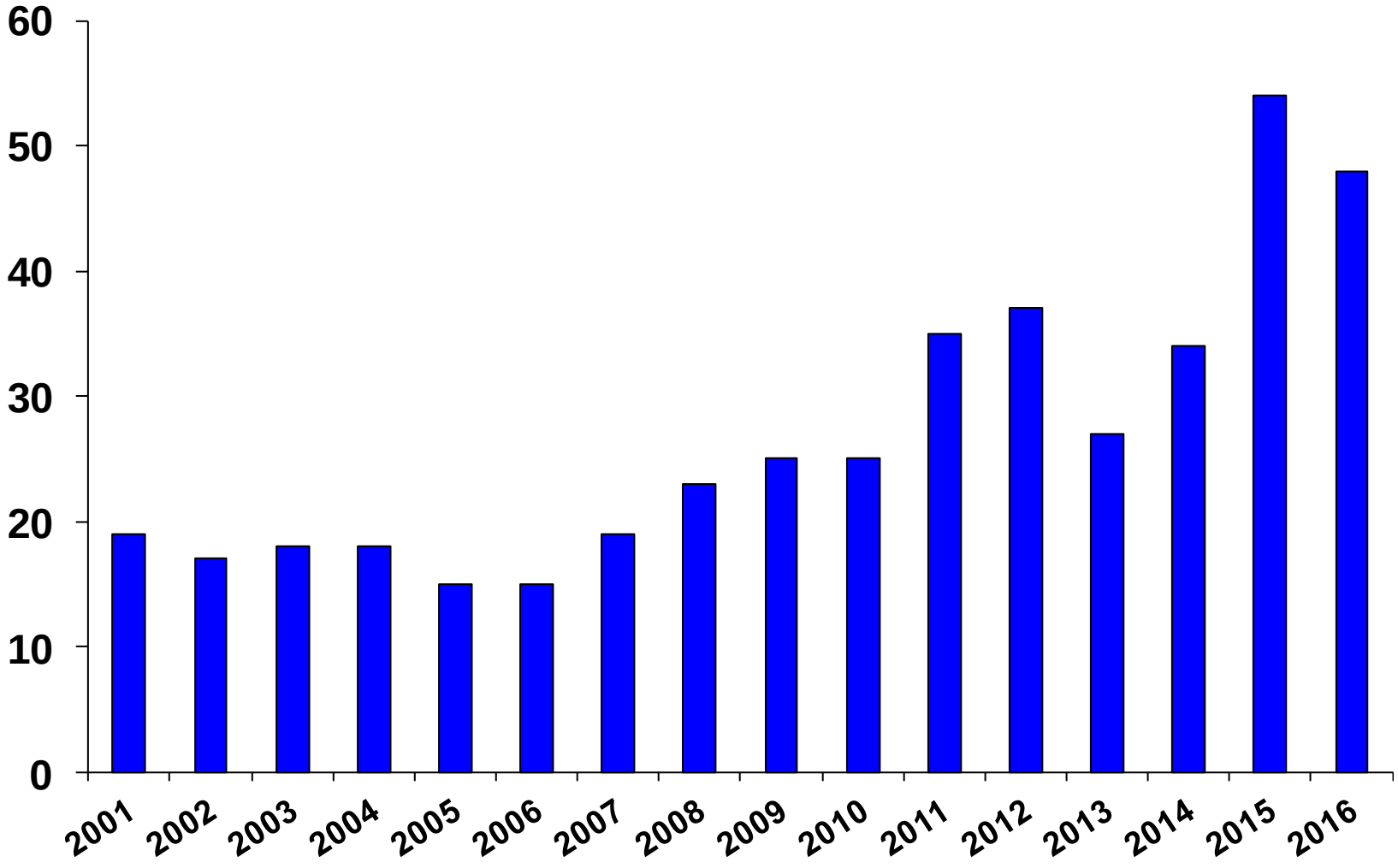
Inhaled Nitric Oxide: Product Licence

[EMEA 2001]

Licensed for the treatment of newborn infants ≥ 34 weeks gestation with hypoxic respiratory failure associated with clinical or echocardiographic evidence of pulmonary hypertension, in order to improve oxygenation and to reduce the need for extracorporeal membrane oxygenation

LWH – Nitric Oxide

Number of treatment episodes



Using data submitted from Badgernet platform into the NNRD database:

1. To investigate trends in iNO usage in neonates in a geographically defined population

2. To define the extent of unlicensed (off-label) use of iNO in neonates.

3. To describe variation in iNO use between neonatal units

- Retrospective cohort study of iNO use in neonates
- Badgernet – NNRD data download (2010-2015)
- English neonatal units (n~165)
- 6-year period, 3 epochs (2010-11, 2012-13, 2014-15)
- 3 gestation bands, <29w, 29-33w, >=34w
- Baby-level and unit-level analyses

	2010-2011	2012-2013	2014-2015
Neonatal admissions [babies receiving ≥ 1 day of IC]	37885	43160	48838
Infants treated with iNO	1296 (3.4%)	1941 (4.5%)	3112 (6.4%)*

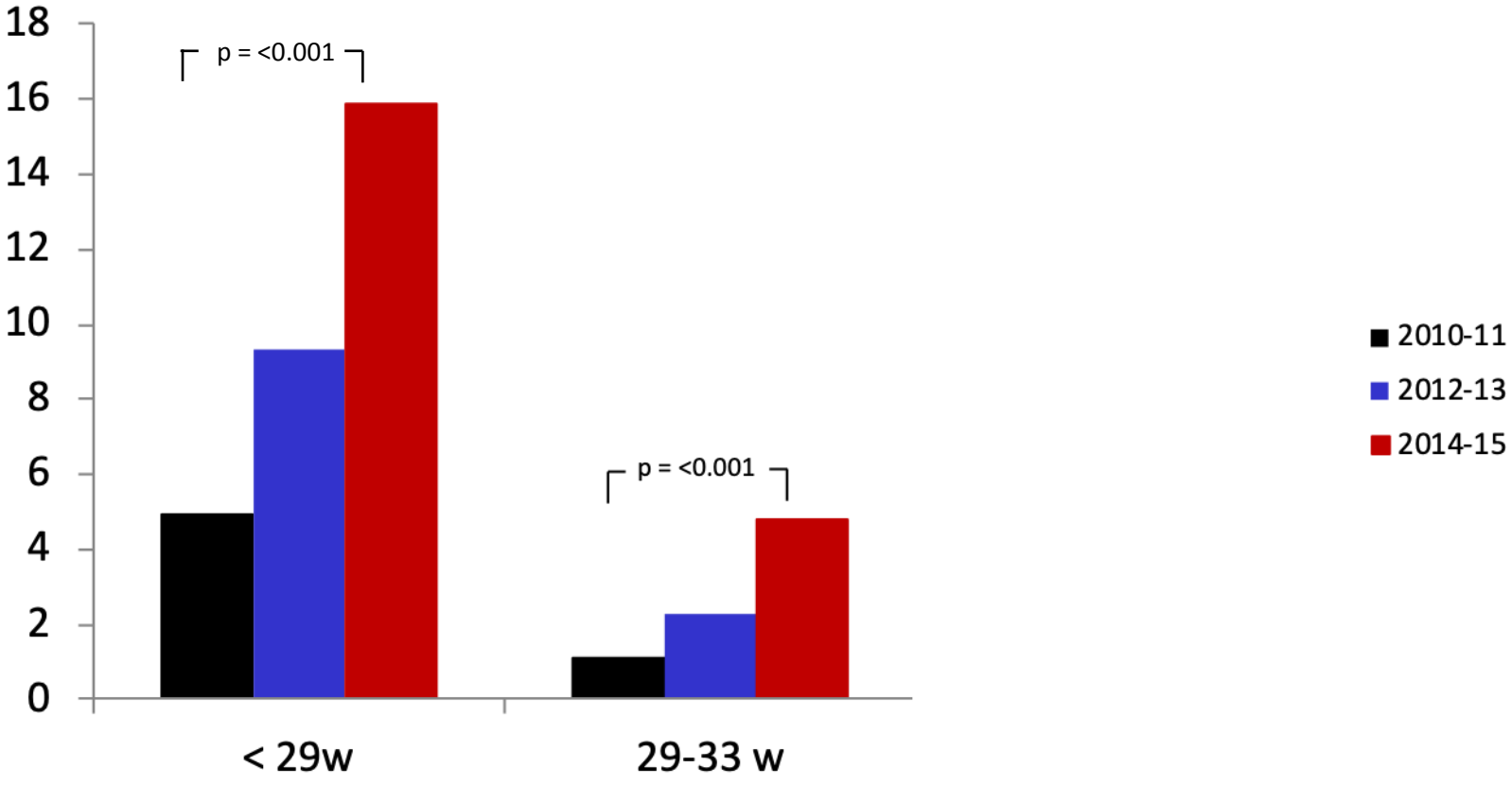
* $p < 0.001$ [2010-2011 compared with 2014-2015]

iNO use by Gestation

% of babies receiving > 1 day IC

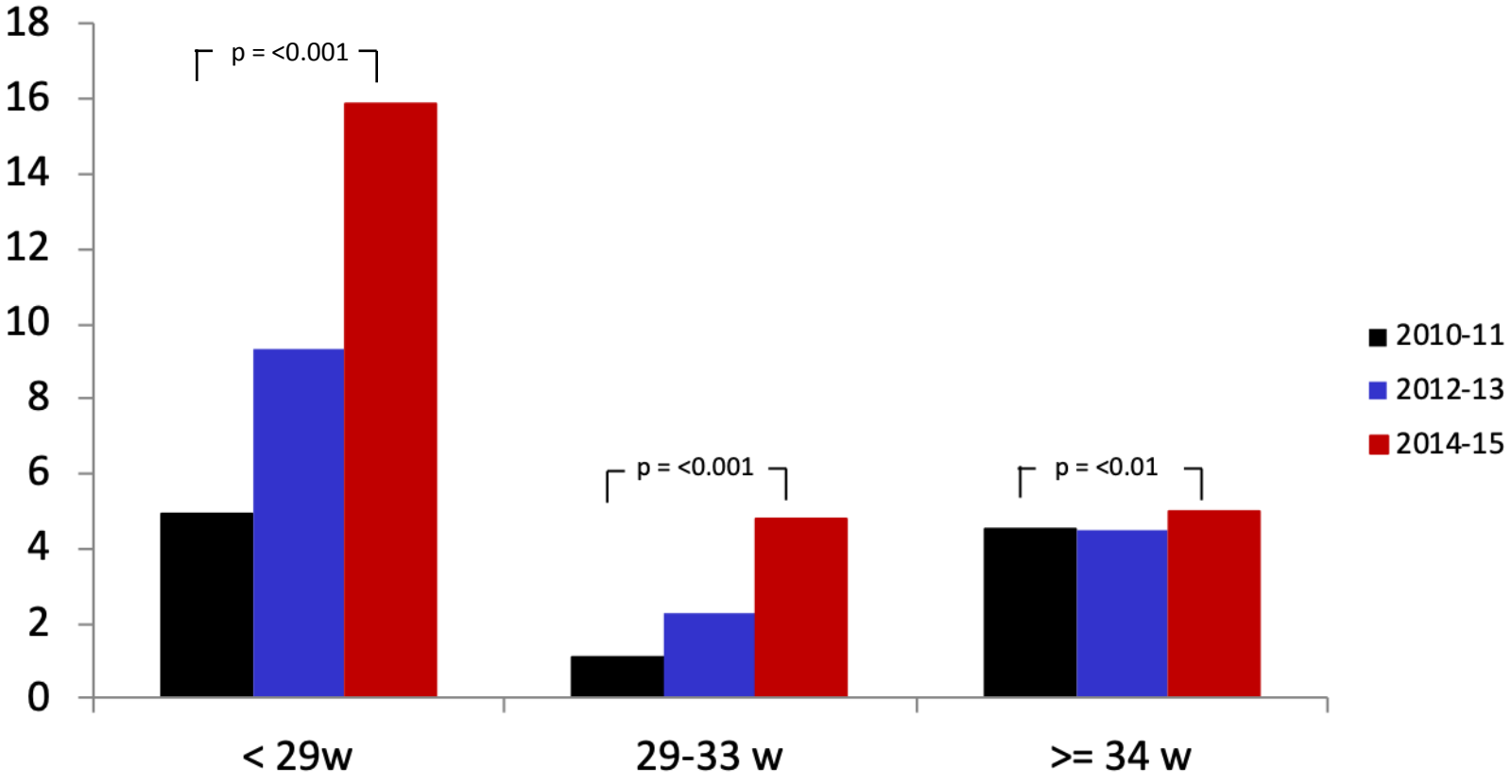
iNO use by Gestation

% of babies receiving > 1 day IC



iNO use by Gestation

% of babies receiving > 1 day IC



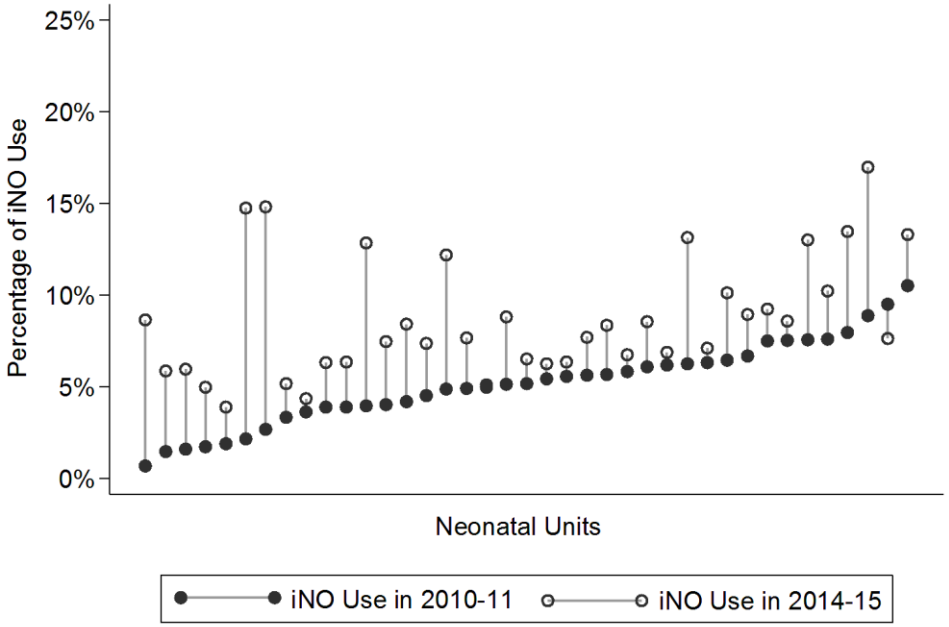
	2010-2011	2012-2013	2014-2015
Preterm infants < 34 weeks' gestation treated with iNO	772 (48%)	926 (48%)	1712 (55%)**

** p < 0.0001 [2010-2011 compared with 2014-2015]

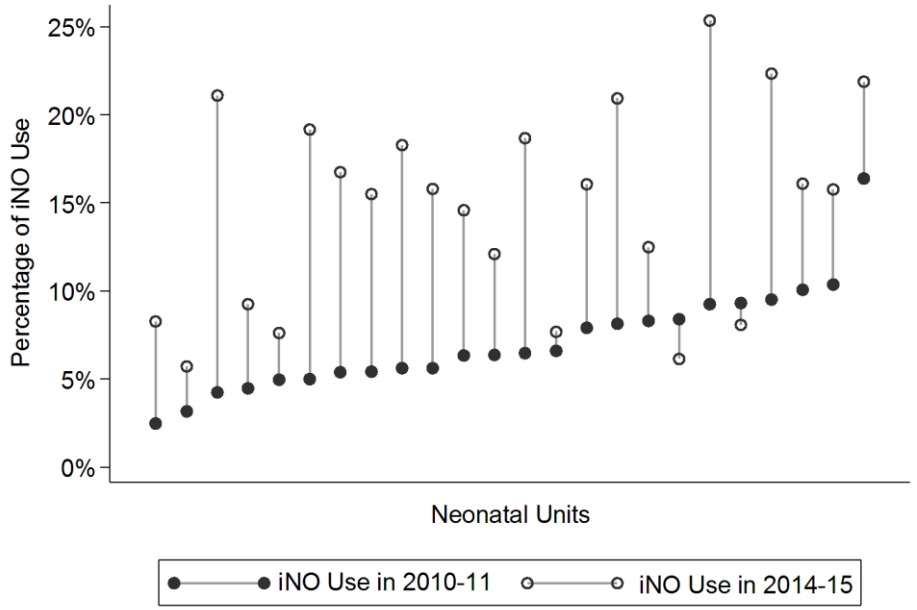
iNO use by Unit

% of babies receiving > 1 day IC treated with iNO

All babies



< 29 weeks



[Excludes units treating fewer than 5 babies]

Summary

1. The use of iNO increased significantly in English neonatal units between 2010 and 2015 with ~900 more babies treated/year.

2. 55% of all infants treated with iNO are preterm < 34 weeks' gestation in whom iNO is used outside its licensed indication.

3. The largest proportional increase was in preterm infants (3-4 fold increase).

4. There is wide variation in iNO usage between English neonatal units, especially in extreme preterm infants.

Why has the use of iNO increased?

- Increased familiarity with the drug, no reports of significant adverse safety signals in term infants
- Absence of other proven treatments in preterm hypoxaemic respiratory failure +/- PPHN physiology
- Emerging evidence of promise in specific disease conditions – expert consensus statements (eg. in PPHN/PPROM)
- No national guidelines/no financial restrictions on off-label use of iNO in preterm infants