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BIBLIOGRAFIA

Tema: Oxido Nitrico: técnicas analíticas, farmacología, farmacocinética, casos clínicos, toxicidad

Fecha: 7.7.99

WinSPIRS 2.1

No.	Registros	Solicitud
1	981	nitric
2	5463	oxide
3	282	nitric oxide
4	45418	HPLC
5	29850	pharmaceutical
6	11443	products
7	0	#3 and HPLC and pharmaceutical products
8	14887	PY = "1990"
9	6	#3 and (PY = "1990")
10	981	nitric
11	5463	oxide
12	45418	hplc
13	14	nitric oxide and hplc
14	981	nitric
15	5463	oxide
16	29850	pharmaceutical
17	138565	analysis
* 18	6	nitric oxide and pharmaceutical and analysis

Registro 1 de 6 - Analytical Abstracts
TI: Real time measurement of nitric oxide released from cultured endothelial cells.
AU: Kurumantani,-H; Kikuchi,-K; Nagano,-T; Hirobe,-M; Yamazaki,-J; Nagao,-T
AD: Lab. Pharm. Toxicol., Univ. Tokyo, Tokyo 113-0033, Japan
CP: Japan
SO: Biol-Pharm-Bull. Dec 1998; 21(12): 1286-1289
JN: BIOLOGICAL-and-PHARMACEUTICAL-BULLETIN
IS: 0918-6158
CO: BPBLEO
PY: 1998
LA: English
PT: Journal
AB: Bradykinin (0.001-1micro M) and/or 10mM-L-NG-monomethyl-L-arginine were applied to a column containing beads covered with endothelial cells and perfused (2 ml/min) with Krebs-Henseleit buffer comprising 118mM-NaCl, 4.7mM-KCl, 2.5mM-CaCl2, 1.2mM-MgSO4, 1.2mM-KH2PO4, 25mM-NaHCO3 and 10mM-glucose. The column effluent was mixed with a solution (0.5 ml/min) of 33micro M-luminol, 350micro M-desferrioxamine, 15mM-H2O2 and 6mM-potassium carbonate. Chemiluminescence of NO released by cells was detected continuously. Results are presented and discussed.
IA: nitric-oxide-A: [10102-43-9]. detmn. of, in biological cells, by chemiluminescence
IM: biological-cells-M: detmn. of nitric oxide in, by chemiluminescence
IC: chemiluminescence-C
SC: F-Clinical-and-Biochemical-Analysis
SS: 10000
COP: Copyright: The Royal Society of Chemistry
AN: 6105F00032
UD: 6105

Registro 2 de 6 - Analytical Abstracts
TI: Improved nitric oxide detection using 2,3-diaminonaphthalene and its application to the evaluation of novel nitric oxide synthase inhibitors.
AU: Nakatsubo,-N; Kojima,-H; Sakurai,-K; Kikuchi,-K; Nagoshi,-H; Hirata,-Y; Akaike,-T; Maeda,-H; Urano,-Y; Higuchi,-T; Nagano,-T
AD: Graduate School Pharm. Sci., Univ. Tokyo, Tokyo 113-0033, Japan
CP: Japan
SO: Biol-Pharm-Bull. Dec 1998; 21(12): 1247-1250
JN: BIOLOGICAL-and-PHARMACEUTICAL-BULLETIN
IS: 0918-6158
CO: BPBLEO
PY: 1998
LA: English
PT: Journal
AB: A method was developed for the detection of NO in living cells and tissue cultures. Cytokines were incubated with cultured vascular smooth muscle cells. for 12 h. After washing, 100micro M-2,3-diaminonaphthalene and 2-phenyl-4,4,5,5-tetramethylimidazoline-3-oxide-1-oxyl, and 1mM-L-arginine in Kreb's-Ringer phosphate buffer of pH 7.2 (containing 120mM-NaCl, 4.8mM-KCl, 0.54mM-CaCl2, 1.2mM-MgSO4, 11mM-glucose and 15.9mM-sodium phosphate) were added and, after 2 h, NO was measured by fluorescence at 425 nm (excitation at 375 nm). Results are presented and discussed.
IA: nitric-oxide-A: [10102-43-9]. detmn. of, in biological cells, by fluorimetry
IM: biological-cells-M: detmn. of nitric oxide in, by fluorimetry
IC: fluorimetry-C
SC: F-Clinical-and-Biochemical-Analysis
SS: 10000
COP: Copyright: The Royal Society of Chemistry
AN: 6105F00031
UD: 6105

Registro 3 de 6 - Analytical Abstracts

TI: Analysis of lead compounds - key to drug development.
AU: Duffin,-S
AD: CSP, Hornchurch, Essex RM12 4EH, UK
CP: UK
SO: Lab-Update. Nov 1998; 10-11
JN: Laboratory-Update
CO: QQQQQQ
PY: 1998
LA: English
PT: Journal
AB: A chemiluminescence-based nitrogen-specific detector for use in HPLC is described. HPLC eluates are heated in oxygen, causing nitrogen to be released as nitric oxide. This is reacted with ozone to form nitric dioxide in an excited state. The nitric dioxide releases photons as it undergoes a transition to its ground state, which are detected by a photomultiplier tube. The detector has a true equimolar response to any N-containing compound, and does not rely on the presence of a chromophore, unlike other types of detectors. The detection limit is 0.3 ng (10 pmol) N per sample, and the detectors response is linear over four orders of magnitude (from very low to very high percentages of N). The use of the detector in drug discovery is discussed.
IA: nitrogen-A: [7727-37-9]. detmn. of, by HPLC, detectors for
IC: chromatography,-liquid,-high-performance-(HPLC)-C: detectors for, chemiluminescence, for nitrogen;
pharmaceutical-analysis-C: by HPLC, nitrogen detectors for, in drug discovery
SC: D-Inorganic-and-Organic-Analysis
SS: 25000
CR: B3; G001

AN: 6104D00090
UD: 6104

Registro 4 de 6 - Analytical Abstracts
TI: Novel detection method of nitric oxide using horseradish peroxidase.
AU: Kikuchi,-K; Nagano,-T; Hirobe,-M
AD: Univ. Tokyo, Fac. Pharm. Sci., Tokyo 113, Japan
CP: Japan
SO: Biol-Pharm-Bull. Apr 1996; 19(4): 649-651
JN: BIOLOGICAL-and-PHARMACEUTICAL-BULLETIN
IS: 0918-6158
CO: BPBLEO
PY: 1996
LA: English
PT: Journal
AB: The most common procedure for the detection of NO (a signal transmitter in various physiological and pathophysiological processes has been the oxyhemoglobin oxidation method (cf., Kelm et al., Cir. Res., 1990, 66, 1561) based on the oxidation of HbO2 to methaemoglobin by NO. This procedure, however, failed to provide constant amounts of HbO2 and differentiation of NO from its decomposed product. A method using horse radish peroxidase (I) which gave a sensitive and simple assay system is described. NO solution (2mM) was mixed with 1.5micro M-I and sodium phosphate buffer of pH 7.4. The Soret band shifted toward longer wavelength from 396.5-420 nm. I (a haem protein with ferric ion) formed a very stable NO-ferric complex without side reactions. Calibration graphs were linear in the studied NO-concentration range. The detection limit was 10nM-NO.
IA: nitric-oxide-A: [10102-43-9]. detection of, by spectrophotometry
IC: spectrophotometry,-absorption,-ultra-violet-visible-C: in biochemical analysis
SC: F-Clinical-and-Biochemical-Analysis
SS: 10000

AN: 5812F00029
UD: 5812

Registro 5 de 6 - Analytical Abstracts
TI: Formation of S-nitroso compounds from sodium nitroprusside, nitric oxide or nitrite and reduced thiols: analysis by capillary isotachophoresis.
AU: Tsikas,-D; Boeger,-RH; Bode-Boeger,-SM; Brunner,-G; Froelich,-JC
AD: Hannover Med. School, Inst. Clinical Pharmacol., 30623 Hannover, Germany
CP: Germany
SO: J-Chromatogr,-A. 5 May 1995; 699(1-2): 363-369
IS: 0021-9673
CO: JCRAEY
PY: 1995
LA: English
PT: Journal
AB: A method is described for the analysis in aqueous solution of sodium nitroprusside, some S-nitroso compounds derived from biological and pharmacological precursors and their final metabolites nitrite and nitrate. Isotachophoresis was carried out on a PTFE column (25 cm x 0.5 mm i.d.) with 10mM-HCl of pH 4/0.25% hydroxypropylmethylcellulose as leading electrolyte and 10mM-hexanoic acid as terminal electrolyte. A constant driving current of 25 micro A was applied, with zone detection at 254 nm and by conductivity. The method was applied to studies of the reaction of sodium nitroprusside with reduced thiols such as N-acetyl-L-cysteine, glutathione and N-acetyl-D,L-penicillamine at pH 7.4. The thiols reacted spontaneously to give the corresponding S-nitroso compounds, which may be responsible for the anti-aggregatory and vasodilating properties of sodium nitroprusside. A commercial drug preparation was also analysed.
IA: sodium-nitroprusside-A: [14402-89-2]. detmn. of, and its S-nitroso derivatives, by isotachophoresis
IC: isotachophoresis,-capillary-C: in pharmaceutical analysis

SC: G-Pharmaceutical-Analysis
SS: 10900

AN: 5710G00076
UD: 5710

Registro 6 de 6 - Analytical Abstracts

TI: Nitrogen-specific gas chromatography detection based on chemiluminescence.
AU: Courthaudon,-LO; Fujinari,-EM
AD: Antek Instruments GmbH, W-4000 Dusseldorf 31, Germany
CP: Germany
SO: LC-GC. Oct 1991; 9(10): 732-734
IS: 0888-9090
CO: LCGCE7
PY: 1991
LA: English
PT: Journal
AB: A GC method that uses nitrogen-specific detection based on chemiluminescence is described and used for the analysis of nitrosamines, pesticide residues, food flavourings, pharmaceuticals and petroleum light cycle oil. The method was capable of detecting as little as 12 pg of N and the nitric oxide calibration curve showed a linear detector response. Nitrogen-specific detection simplified the analysis of complex samples and often reduced analysis time by examining only the N-containing components.
IM: nitrosamines-M: analysis of, by GC with nitrogen-specific detection based on chemiluminescence;
pharmaceutical-preparations-M: analysis of, by GC with nitrogen-specific detection based on chemiluminescence;
pesticides-M: analysis of, by GC with nitrogen-specific detection based on chemiluminescence;
flavourings-M: analysis of food, by GC with nitrogen-specific detection based on chemiluminescence;
petroleum-products-M: analysis of light cycle oil, by GC with nitrogen-specific detection based on chemiluminescence
IC: chromatography,-gas-C: nitrogen-specific detection based on chemiluminescence in
SC: B-Chromatography-and-Electrophoresis
SS: 10000
CR: H8; H5; G0; E4; D3

AN: 5504B00016
UD: 5504

WinSPIRS 2.1

No.	Registros	Solicitud
1	981	nitric
2	5463	oxide
3	282	nitric oxide
4	45418	HPLC
5	29850	pharmaceutical
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7	0	#3 and HPLC and pharmaceutical products
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9	6	#3 and (PY = "1990")
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11	5463	oxide
12	45418	hplc
13	14	nitric oxide and hplc
14	981	nitric
15	5463	oxide
16	29850	pharmaceutical
17	138565	analysis
18	6	nitric oxide and pharmaceutical and analysis
19	981	nitric
20	5463	oxide
21	45418	hplc
* 22	14	nitric oxide and hplc

Registro 1 de 2 - Analytical Abstracts

TI: A simple and selective monitoring method for nitric oxide capturing ability by HPLC fluorescence detection with 2,3-`diaminonaphthalene as a fluorogenic reagent.
AU: Wada,-M; Ikehata,-T; Yoshida,-Y; Kuroda,-N; Nakashima,-K
AD: School Pharm. Sci., Nagasaki Univ., Nagasaki 852-8521, Japan
CP: Japan
SO: Anal-Sci. Dec 1998; 14(6): 1177-1179
JN: Analytical-Sciences
IS: 0910-6340
CO: ANSCEN
PY: 1998
LA: English
PT: Journal
AB: Portions (200 micro l) of 250micro M-2,3-diaminonaphthalene (DAN) in 10mM-Tris hydrochloride buffer of pH 7 containing 10% DMSO were added to S-nitro-N-acetylpenicillamine (SNAP) in 200 micro l 10mM-Tris buffer containing 0.1% Triton X-100. The mixture was incubated at 37degreeC for 30 min and a 20 micro l portion was analysed by HPLC on a 5 micro m Shimpack CLC C8 column (15 cm x 4.6 mm i.d.). 1(H)-Naphthotriazole (NT), formed by the in situ reaction of NO with DAN, was eluted with 50% acetonitrile with fluorescence detection at 425 nm (excitation at 375 nm). The calibration graphs were linear for 0.5-100micro M-SNAP, with a detection limit (signal-to-noise 3) of 0.3micro M (2 pmol/injection). The RSD (n = 5) of 8.8% for 100micro M-SNAP. The NO capture abilities of a number of haemoglobins (listed) were investigated with the procedure.
IA: nitric-oxide-A: [10102-43-9]. detmn. of, by HPLC, reagents for
IC: chromatography,-liquid,-high-performance-(HPLC)-C: reagents for, fluorescence, 2,3-diaminonaphthalene as, in detmn. of nitric oxide
SC: D-Inorganic-and-Organic-Analysis
SS: 25000
CR: C3

AN: 6106D00094
UD: 6106

Registro 2 de 2 - Analytical Abstracts

TI: Electrochemical determination of S-nitrosothiols with a Clark-type nitric oxide electrode.
AU: Pfeiffer,-S; Schrammel,-A; Schmidt,-K; Mayer,-B
AD: Karl-Franzens-Univ. Graz, Inst. Pharmakol. und Toxikol., 8010 Graz, Austria
CP: Austria
SO: Anal-Biochem. 10 Apr 1998; 258(1): 68-73
JN: Analytical-Biochemistry
IS: 0003-2697
CO: ANBCA2
PY: 1998
LA: English
PT: Journal
AB: The method was based on the Cu+-catalysed cleavage of S-nitrosothiols and detection of the NO released using a Clark-type electrode at 0.6 Hz. Sample (0.5 ml) was incubated at 37degreeC in 50mM-K2HPO4/H3PO4 of pH 7.4 and NO release was effected with 5 micro l 1M-copper nitrate solution in the presence of 1mM-glutathione or 4mM-L-cysteine. Calibration graphs were linear for 50nM- (detection limit) to 5micro M-S-nitrosoglutathione, -S-nitroso-N-acetyl-penicillamine or S-nitroso-BSA. The method was >=10-fold more sensitive than the Saville assay or HPLC. No RSD are given. No dependence on pH was observed in the range 7-9 and the method was selective for S-nitrosated compounds. NO release was inhibited by neocuproine.

IA: thiols,-nitroso-A: detmn. of, by electrochemical analysis
SC: F-Clinical-and-Biochemical-Analysis
SS: 90000

AN: 6010F00257
UD: 6010

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Chem Res Toxicol 1998 Dec;11(12):1393-7

Published erratum appears in Chem Res Toxicol 1998 Dec;11(12):1608

NO release from NO donors and nitrovasodilators: comparisons between oxyhemoglobin and potentiometric assays.

Artz JD, Thatcher GRJ

Department of Chemistry, Queen's University, Kingston, Ontario K7L 3N6, Canada.

Unraveling the biology, pharmacology, and toxicology of NO depends on accurate NO assays, two of the more common being the oxyHb (oxyhemoglobin) assay and potentiometric detection using a Clark-type NO-selective electrode. Comparison of the specificity and sensitivity of the oxyHb and potentiometric methods was carried out using a broad series of nitrovasodilators, including organic nitrates, nitrites, thionitrates, nitrosothiols, and diazenium diolates. Only with the more labile diazenium diolates was a linear relationship observed between the rates of NO release measured potentiometrically and the rate of oxyHb oxidation from the oxyHb assay. The nonlinear plots indicate that N,O-species other than NO itself are capable of oxidizing oxyHb.

Can J Anaesth 1997 Sep;44(9):973-88

Inhaled nitric oxide: clinical applications, indications, and toxicology.

Troncy E, Francoeur M, Blaise G

Department of Anaesthesia, Centre Hospitalier de l'Universite de Montreal-Pavillon Notre-Dame, Quebec, Canada.

PURPOSE: Although the analogy of nitric oxide (NO) to Endothelium-derived Relaxing Factor remains controversial, medical use of exogenous NO gas by inhalation has grown exponentially. This review presents the

mechanisms of
action of inhaled NO in pulmonary hypertension, hypoxaemia, inflammation and oedema, as well as its therapeutic and
diagnostic indications with emphasis on acute respiratory distress syndrome (ARDS) and toxicology. SOURCE: Two
medical databases (Current Contents, Medline) were searched for citations containing the above-mentioned key words
to December 1996. Moreover, many presentations in congresses such as 4th International Meeting of Biology of Nitric
Oxide, 52nd and 53rd Annual Meeting of Canadian Anaesthetists' Society or 10th Annual Meeting of European
Association of Cardiothoracic Anaesthesiologists were used. PRINCIPAL FINDINGS: Inhaled NO is now
recognized as an invaluable tool in neonatal and paediatric critical care, and for heart/lung surgery. Other clinical
applications in adults, such as chronic obstructive pulmonary disease and ARDS, require a cautious approach. The
inhaled NO therapy is fairly inexpensive, but it would seem that it is not indicated for everybody with regards to the
paradigm of its efficiency and potential toxicity. The recent discovery of its anti-inflammatory and extrapulmonary
effects open new horizons for future applications. CONCLUSION: Clinical use of inhaled NO was mostly reported in
case series, properly designed clinical trials must now be performed to establish its real therapeutic role. These trials
would permit adequate selection of the cardiopulmonary disorders, and subsequently the patients that would maximally
benefit from inhaled NO therapy. Publication Types: Review

Cancer Res 1997 May 15;57(10):1823-8

Nitrotyrosine formation, apoptosis, and oxidative damage:
relationships to nitric oxide production in SJL mice bearing the RcsX
tumor.

Gal A, Tamir S, Kennedy LJ, Tannenbaum SR, Wogan GN

Department of Chemistry, Massachusetts Institute of Technology, Cambridge 02139, USA.

In SJL mice, growth of RcsX lymphoma cells results in activation of macrophages in the spleen and lymph nodes to
produce high levels of NO radical (NO.). We used this experimental model system to study the toxicology of NO. in
vivo. To characterize spatial relationships between sites of NO. production and tissue damage, immunohistochemical
techniques were developed for simultaneous detection of inducible NO. synthase (iNOS), 3-nitrotyrosine, and
apoptosis in spleen and lymph nodes of tumor-bearing animals. Elevated expression of iNOS, presumed to reflect
increased NO. production, was associated with a significant increase in frequency of apoptotic nuclei. Both apoptotic
nuclei and 3-nitrotyrosine staining were found in cells juxtaposed to iNOS-expressing (ie., NO.-producing)

macrophages and also within the macrophages themselves. To assess the extent of DNA damage associated with the
response, 8-oxoguanine levels were quantified in DNA extracted from spleens of tumor-bearing mice. No increase in
levels of this marker of oxidative DNA damage was found in tissues in which apoptosis and 3-nitrotyrosine levels were
highly elevated within specific subsets of cells. Collectively, our results indicate that under the pathophysiological
conditions existing in the RcsX tumor-bearing SJL mouse, cellular damage caused by NO. and/or other reactive
species produced by activated macrophages is highly localized within cells in close proximity to the activated macrophages.

Early Hum Dev 1997 Feb 20;47(3):247-62

Current status of inhaled nitric oxide therapy in the perinatal period.

Mupanemunda RH

Department of Paediatrics and Neonatal Medicine, Royal Postgraduate Medical School, Hammersmith Hospital,
London, UK.

The recent discovery of nitric oxide (NO) and the elucidation of its biological roles has been accompanied by significant
advances in our understanding of several physiological and pathological processes. Impaired NO synthesis and/or
release may underlie the pathophysiology of several cardiopulmonary disorders characterised by hypoxemia and
pulmonary hypertension. Inhaled NO produces selective pulmonary vasodilation and appears to be an effective new
therapy for infants with pulmonary vasospasm or hypoxemia associated with ventilation-perfusion imbalance. Although
formal reports from current randomised and controlled clinical trials of inhaled NO therapy are awaited, preliminary
results suggest an improved outcome. NO is, however, still an investigational drug. The limitations of this therapy and its
toxicology are reviewed. Publication Types: Review

Proc Natl Acad Sci U S A 1996 Dec 24;93(26):15102-7

Mutagenesis associated with nitric oxide production in transgenic
SJL mice.

Gal A, Wogan GN

Department of Chemistry, Massachusetts Institute of Technology, Cambridge 02139, USA.

We recently reported development of an experimental model for the study of nitric oxide (NO.) toxicology in vivo. SJL
mice were injected with superantigen-bearing RcsX (pre-B-cell lymphoma) cells, which migrated to the spleen and
lymph nodes, where their rapid growth induced activation of macrophages to produce large amounts

of NO. over a
period of several weeks. In the experiments described here, we used this model to investigate mutagenesis in
splenocytes exposed to NO. during RcsX cell growth. Transgenic mice were produced by crossbreeding animals of
the pUR288 transgenic C57BL/6 and SJL strains. RcsX cells were injected into F1 mice and NO. production was
confirmed by quantification of urinary nitrate, the ultimate metabolite of NO. Mutant frequency in the lacZ gene of the
pUR288 plasmid was determined in DNA isolated from spleen (target) and kidney (nontarget) tissues. A significant
elevation in mutant frequency was found in the spleen, but not in the kidney, of tumor-bearing mice. Furthermore,
increases in mutant frequency in the spleen as well as NO. production were abrogated by administration of
N-methylarginine, a NO. inhibitor, to mice following injection of RcsX cells. These results indicate that NO. had
mutagenic activity in RcsX tumor-bearing mice and thus support a possible role for its involvement in the carcinogenic process.

Chem Res Toxicol 1996 Jul-Aug;9(5):809-20

Nitric oxide regulation of tissue free radical injury.

Rubbo H, Darley-Usmar V, Freeman BA

Department of Anesthesiology, University of Alabama at Birmingham 35233, USA.

We have presented evidence from a broad range of chemical, cell biological, and in vivo studies showing that .NO can
mediate tissue-protective reactions during oxidant stress, as well as toxic and tissue prooxidant effects. One
predominant factor that has been identified which influences .NO being protective versus toxic is the relative rates of
production and concentrations of .NO and the more "traditional" family of reactive oxygen species, including O2.-,
H2O2, .OH, LO., LOO., and high valency complexes of iron. Also, since so many anti-neutrophil actions of .NO have
been described, it is likely that .NO will serve a protective role in acute inflammatory reactions. One issue is
certain--many new truths remain to be revealed, as we continue to develop our understanding of the toxicology of
reactive oxygen- and nitrogen-containing species. Publication Types: Review

Eur Respir J 1995 Jun;8(6):976-95

Respiratory effects of air pollutants: experimental studies in humans.

Sandstrom T

Dept of Pulmonary Medicine and Allergology, University Hospital of Northern Sweden, Umea.

Epidemiological and environmental chamber studies in man, and toxicological studies in animals,

have provided valuable
insights into the biological effects, the mechanisms of action, and the dose-response characteristics of some major air
pollutants. This review describes the information currently available on air pollutant effects in man, as the result of
experimental studies. There are certain advantages, as well as some limitations, in human chamber exposure studies, but
if carefully designed and based upon relevant background data they may give information that is valuable for
understanding the effects of air pollutants in man. Reversible effects on the airway mechanics, the responsiveness of the
airways to methacholine and allergen have been shown to be caused by air pollutants. Furthermore, significant changes
have been demonstrated in airway permeability, bronchoalveolar lavage, nasal lavage, and peripheral blood cells and
inflammatory markers. Currently, human toxicology to air pollutants is a progressive research area.
Publication Types: Review

Toxicology 1995 May 5;99(1-2):77-88

On the effects of paraquat on isolated mitochondria. Evidence that paraquat causes opening of the cyclosporin A-sensitive permeability transition pore synergistically with nitric oxide.

Costantini P, Petronilli V, Colonna R, Bernardi P

Consiglio Nazionale delle Ricerche, University of Padova Medical School, Italy.

This paper reports an investigation on the effects of the bipyridylium herbicide, paraquat, on rat liver mitochondria in
vitro. We show that paraquat induces a Ca(2+)-dependent permeability increase of the inner mitochondrial membrane
leading to membrane depolarization, uncoupling and matrix swelling. The permeability increase is not observed in the
absence of Ca2+ accumulation, and is not due to a direct effect of paraquat on the membrane energy level, as assessed
by measurements of membrane potential, respiration and mitochondrial permeability to solutes at high concentrations of
paraquat in the presence of excess ethylene-bis(oxoethylenenitrilo)tetraacetic acid (EGTA), a Ca2+ chelator. The
Ca(2+)-dependent permeability increase is due to inappropriate opening of the endogenous permeability transition pore
(MTP), a regulated, voltage-dependent channel of the inner mitochondrial membrane. The pore is primarily affected by
paraquat through a shift of the gating potential to more negative values, allowing pore opening at physiological
membrane potential. This effect apparently involves oxidation of a critical dithiol in the pore voltage sensor, while other
regulatory aspects of the MTP (matrix pH and Ca2+) are unaffected by paraquat, which is not transported inside the
mitochondrial matrix. The effects of paraquat on MTP opening depend on inhibition of electron transfer at Site I by
rotenone, or by respiratory chain inhibition by nitric oxide, one of the proposed endogenous

mediators of paraquat
toxicity to the lung (Berisha, H.I., Hedayatollah, P., Absood, A., and Said, S.I. (1994) Proc. Natl. Acad. Sci. USA
91, 7445-7449). Taken together, these data provide an additional biochemical mechanism by which paraquat may
affect cell function, and support the idea that mitochondrial damage is an important determinant in paraquat toxicity
(Hirai, K.-I., Ikeda, K., and Wang, G.-Y. (1992) Toxicology 72, 1-16).

Adv Pharmacol 1995;34:1-15

Chemistry of nitric oxide: biologically relevant aspects.

Fukuto JM

Department of Pharmacology, UCLA School of Medicine, Center for the Health Sciences 90095, USA.

This discussion of NO chemistry has addressed only certain aspects that may be of biological relevance. It is not meant
to be a comprehensive in-depth treatment of general NO chemistry. For more information regarding the chemistry of
NO and related nitrogen oxides, the reader is referred to a number of reviews (Ragsdale, 1973; Schwartz and White,
1983; Vosper, 1975; McCleverty, 1979; Gilbert and Thomas, 1972; Bonner and Hughes, 1988). Hopefully, it has
become evident that an appreciation and knowledge of the chemistry of NO are key to understanding its physiological
utility as well as its toxicology. It appears that Nature exploits a variety of the unique chemical aspects of NO in order
to attain the needed physiological specificity. For example, the specific activation of guanylate cyclase by NO is most
likely due to its unique binding properties to iron hemes. Also, the inherent lack of reactivity of NO makes it a fairly
innocuous species unless it is coupled with other radical species, such as O2-. This chemical property thus allows NO
to be utilized as a physiological messenger molecule and, under certain conditions, as a cytotoxic effector molecule as well. Publication Types: Review

J Toxicol Clin Toxicol 1995;33(5):427-38

The pharmacology and toxicology of three new biologic agents used in
pulmonary medicine.

Albertson TE, Walby WF, Allen RP, Tharratt RS

University of California, Davis, USA.

Biological agents have played an important role in the evolution of modern medical therapeutics. Recent advances in
biologicals have in part been stimulated by the biotechnology revolution seen over the last several years. Toxicologists
need to be aware of the proposed mechanisms and approved and experimental uses of these new

biologic agents.
Further, controversies about their use, efficacy, cost issues and potential toxicities should be known. Often these drugs
are designed for small patient populations thus limiting the availability of human toxicological data bases. This paper
reviews the pharmacology and toxicology of three new biologics (recombinant human DNase I, alpha 1-protease
inhibitor, and nitric oxide). These agents appear to have important roles in treating specific diseases or disease states
seen in pulmonary medicine. Publication Types: Review

Circulation 1998 Jul 21;98(3):211-6

Increased bioavailability of nitric oxide after lipid-lowering therapy in hypercholesterolemic patients: a randomized, placebo-controlled, double-blind study.

John S, Schlaich M, Langenfeld M, Weihprecht H, Schmitz G, Weidinger G, Schmieder RE

Department of Medicine IV, University of Erlangen-Nurnberg, Klinikum Nurnberg-Sud, Germany.

BACKGROUND: Impaired endothelium-dependent vasodilation is an early sign of atherosclerosis in
hypercholesterolemic patients. We hypothesized that lipid-lowering therapy can improve endothelial function and that
this effect is mainly mediated by increased bioavailability of nitric oxide (NO). METHODS AND RESULTS: In a
randomized, double-blind, placebo-controlled trial, we studied 29 patients (age, 50+/-12 years) with hypercholesterolemia (LDL cholesterol > or = 160 mg/dL) randomly assigned to receive either fluvastatin (40 mg twice
daily; 17 patients) or placebo (12 patients). Forearm blood flow was measured by plethysmography before and after
24 weeks of treatment. Endothelium-dependent vasodilation was assessed by intra-arterial infusion of acetylcholine
(ACh; 3, 12, 24, and 48 microg/min) and basal NO synthesis rate by intra-arterial infusion of NG-monomethyl-L-arginine (L-NMMA; 1, 2, and 4 micromol/min). Simultaneous intra-arterial infusion of L-NMMA
(4 micromol/min) and ACh (12, 24, and 48 microg/min) was used to test whether any increase in endothelium-dependent vasodilation after lipid-lowering therapy could be blocked by this NO synthase inhibitor.
Endothelium-dependent vasodilation improved significantly after 24 weeks of lipid-lowering therapy compared with
before therapy (ACh 24 microg/min: 240+/-34% before versus 347+/-50% after therapy; P< or =0.01) and placebo
(changes between after and before therapy with ACh 24 microg/min: 108+/-39% for fluvastatin versus -26+/-32% for
placebo; P< or =0.05). This improvement in endothelium-dependent vasodilation could be blocked by simultaneous
administration of L-NMMA (ACh 24 microg/min plus L-NMMA 4 micromol/min: 170+/-69% before versus
219+/-47% after treatment; P=NS). CONCLUSIONS: Lipid-lowering therapy with fluvastatin can improve disturbed
endothelial function in hypercholesterolemic patients compared with placebo. This improvement is

mediated by
increased bioavailability of NO. Publication Types: Clinical trial

Clin Pharmacokinet 1998 Jun;34(6):457-82

Clinical pharmacokinetics of vasodilators. Part I.

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Understanding the mechanism of action and the pharmacokinetic properties of vasodilatory drugs facilitates optimal use
in clinical practice. It should be kept in mind that a drug belongs to a class but is a distinct entity, sometimes derived
from a prototype to achieve a specific effect. The most common pharmacokinetic drug improvement is the
development of a drug with a half-life sufficiently long to allow an adequate once-daily dosage. Developing a controlled
release preparation can increase the apparent half-life of a drug. Altering the molecular structure may also increase the
half-life of a prototype drug. Another desirable improvement is increasing the specificity of a drug, which may result in
fewer adverse effects, or more efficacy at the target site. This is especially important for vasodilatory drugs which may
be administered over decades for the treatment of hypertension, which usually does not interfere with subjective
well-being. Compliance is greatly increased with once-daily dosing. Vasodilatory agents cause relaxation by either a
decrease in cytoplasmic calcium, an increase in nitric oxide (NO) or by inhibiting myosin light chain kinase. They are
divided into 9 classes: calcium antagonists, potassium channel openers, ACE inhibitors, angiotensin-II receptor
antagonists, alpha-adrenergic and imidazole receptor antagonists, beta 1-adrenergic agonist, phosphodiesterase
inhibitors, eicosanoids and NO donors. Despite chemical differences, the pharmacokinetic properties of calcium
antagonists are similar. Absorption from the gastrointestinal tract is high, with all substances undergoing considerable
first-pass metabolism by the liver, resulting in low bioavailability and pronounced individual variation in
pharmacokinetics. Renal impairment has little effect on pharmacokinetics since renal elimination of these agents is
minimal. Except for the newer drugs of the dihydropyridine type, amlodipine, felodipine, isradipine, nilvadipine,
nisoldipine and nitrendipine, the half-life of calcium antagonists is short. Maintaining an effective drug concentration for
the remainder of these agents requires multiple daily dosing, in some cases even with controlled release formulations.
However, a coat-core preparation of nifedipine has been developed to allow once-daily administration. Adverse
effects are directly correlated to the potency of the individual calcium antagonists. Treatment with the potassium channel

opener minoxidil is reserved for patients with moderately severe to severe hypertension which is refractory to other
treatment. Diazoxide and hydralazine are chiefly used to treat severe hypertensive emergencies, primary pulmonary and
malignant hypertension and in severe preeclampsia. ACE inhibitors prevent conversion of angiotensin-I to
angiotensin-II and are most effective when renin production is increased. Since ACE is identical to kininase-II, which
inactivates the potent endogenous vasodilator bradykinin, ACE inhibition causes a reduction in bradykinin degradation.
ACE inhibitors exert cardioprotective and cardioreparative effects by preventing and reversing cardiac fibrosis and
ventricular hypertrophy in animal models. The predominant elimination pathway of most ACE inhibitors is via renal
excretion. Therefore, renal impairment is associated with reduced elimination and a dosage reduction of 25 to 50% is
recommended in patients with moderate to severe renal impairment. Separating angiotensin-II inhibition from
bradykinin potentiation has been the goal in developing angiotensin-II receptor antagonists. The incidence of adverse
effects of such an agent, losartan, is comparable to that encountered with placebo treatment, and the troublesome
cough associated with ACE inhibitors is absent. Publication Types: Review

J Med Chem 1998 Apr 23;41(9):1361-6

2-Iminohomopiperidinium salts as selective inhibitors of inducible
nitric oxide synthase (iNOS).

Hansen DW Jr, Peterson KB, Trivedi M, Kramer SW, Webber RK, Tjoeng FS, Moore WM, Jerome GM,
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An attractive approach to the treatment of inflammatory conditions such as osteo- and rheumatoid arthritis,
inflammatory bowel disease, and sepsis is through the selective inhibition of human inducible nitric oxide synthase
(hiNOS) since localized excess nitric oxide (NO) release has been implicated in the pathology of these diseases. A
series of monosubstituted iminohomopiperidinium salts possessing lipophilic functionality at ring positions 3, 5, 6, and 7
has been synthesized, and series members have demonstrated the ability to inhibit the hiNOS isoform with an IC50 as
low as 160 nM (7). Compounds were found that selectively inhibit hiNOS over the human endothelial constitutive
enzyme (heNOS) with a heNOS/hiNOS IC50 ratio in excess of 100 and as high as 314 (9). Potencies for inhibition of
hiNOS and the human neuronal constitutive enzyme (hnNOS) are comparable. Substitution in the 3 and 7 positions

provides compounds that exhibit the greatest degree of selectivity for hiNOS and hnNOS over heNOS.
Submicromolar potencies for 6 and 7 in a mouse RAW cell assay demonstrated the ability of these compounds to
inhibit iNOS in a cellular environment. These latter compounds were also found to be orally bioavailable and efficacious
due to their ability to inhibit the increase in plasma nitrite/nitrate levels in a rat LPS model.

Herz 1998 Mar;23(2):97-105

[The role of endothelial function for ischemic manifestations of
coronary atherosclerosis].

[Article in German]

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The vascular endothelium controls vasomotor tone by releasing a number of substances like nitric oxide (NO). NO has
been shown to play a very important role, because it mediates vasodilation and furthermore inhibits platelet aggregation,
expression of adhesion molecules for monocytes and adhesion of neutrophils and it impairs growth of vascular smooth
muscle cells. An increased oxidative stress, decreasing the bioavailability of NO, is mainly responsible for a blunted
endothelium dependent vasoreactivity. Risk factors for endothelial dysfunction are coronary artery disease,
hypertension, hypercholesterolemia, smoking, and aging. Endothelial dysfunction in the presence of these risk factors
might contribute to the occurrence of myocardial ischemia, aggravate acute coronary syndromes and accelerate
progression of coronary artery disease. Amelioration of blunted endothelial function appears to be a major
therapeutical goal to reduce ischemia and clinical events and might even retard progression of coronary artery disease. Publication Types: Review

Am J Physiol 1997 Nov;273(5 Pt 1):G1007-13

Role of nitric oxide in gut ischemia-reperfusion-induced hepatic
microvascular dysfunction.

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The overall objective of this study was to assess the contribution of an altered bioavailability of nitric oxide (NO) to the
leukocyte adhesion and hypoxic stress elicited in the liver by gut ischemia-reperfusion (I/R). The

accumulation of
leukocytes, number of nonperfused sinusoids (NPS), and NADH autofluorescence were monitored (by intravital
microscopy) in mouse liver after 15 min of superior mesenteric artery occlusion and 60 min of reperfusion. Leukostasis,
NPS, and NADH autofluorescence (indicating hypoxia) were all increased in the liver at 60 min after gut I/R. The NO
synthase inhibitor NG-monomethyl-L-arginine (L-NMMA) exaggerated the liver leukostasis elicited by gut I/R,
responses that were prevented by coadministration of L-arginine. The NO donor diethylenetriamine-NO (DETA-NO)
and L-arginine were both effective in attenuating the gut I/R-induced leukostasis and increased NADH
autofluorescence, whereas neither DETA nor D-arginine exerted a protective action. These findings indicate that NO is
an important determinant of the liver leukostasis, impaired sinusoidal perfusion, and tissue hypoxia elicited by gut I/R.

J Biol Chem 1997 Jul 4;272(27):17012-7

Homocyst(e)ine decreases bioavailable nitric oxide by a mechanism
involving glutathione peroxidase.

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Hyperhomocyst(e)inemia is believed to injure endothelial cells in vivo through a number of mechanisms, including the
generation of hydrogen peroxide (H2O2). Earlier in vitro studies demonstrated that homocyst(e)ine (Hcy) decreases
the biological activity of endothelium-derived relaxing factor and that this decrease can be reversed by preventing the
generation of hydrogen peroxide. Here we show that Hcy treatment of bovine aortic endothelial cells leads to a
dose-dependent decrease in NOx ($p = 0.001$ by one-way analysis of variance) independent of endothelial nitric-oxide
synthase activity or protein levels and nos3 transcription, suggesting that Hcy affects the bioavailability of NO, not its
production. We hypothesized that, in addition to increasing the generation of H2O2, Hcy decreases the cell's ability to
detoxify H2O2 by impairing intracellular antioxidant enzymes, specifically the intracellular isoform of glutathione
peroxidase (GPx). To test this hypothesis, confluent bovine aortic endothelial cells were treated with a range of
concentrations of Hcy, and intracellular GPx activity was determined. Compared with control cells, cells treated with
Hcy showed a significant reduction in GPx activity (up to 81% at 250 microM Hcy). In parallel with the decrease in
GPx activity, steady-state GPx mRNA levels were also significantly decreased compared with control levels after

exposure to Hcy, which appeared not to be a consequence of message destabilization. These data suggest a novel
mechanism by which Hcy, in addition to increasing the generation of hydrogen peroxide, may selectively impair the
endothelial cell's ability to detoxify H2O2, thus rendering NO more susceptible to oxidative inactivation.

Lab Invest 1996 Nov;75(5):617-36

Extracellular superoxide dismutase: a regulator of nitric oxide bioavailability.

Oury TD, Day BJ, Crapo JD

Clin Pharmacokinet 1996 May;30(5):372-84

Clinical pharmacokinetics of molsidomine.

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Molsidomine is a prodrug for the formation of nitric oxide (NO). Its pharmacokinetics are characterised by rapid
absorption and hydrolysis, taking a short time to achieve maximal systemic concentrations of both the parent compound
and its active metabolite, SIN-1. The time to peak plasma drug concentration (tmax) is 1 to 2 hours. The bioavailability
of the parent compound after oral administration in tablet form is 44 to 59%, but further metabolism to release NO and
form polar metabolites is rapid; the half-life (t-1/2) of SIN-1 is 1 to 2 hours. Urinary excretion accounts for more than
90% of the part of the administered dose of molsidomine which is not excreted unchanged. Protein binding of the
parent compound is very low (3 to 11%) and its volume of distribution (Vd) corresponds to the range of bodyweight.
Single-dose studies (1, 2 and 4 mg) have revealed linear pharmacokinetics, and multiple dose studies in healthy
individuals (2 mg 3 times daily for 7 days) and coronary artery disease (CAD) patients (4 mg 4 times daily for 4
weeks) do not show any accumulation of the drug. A study in young and elderly individuals indicated that the first-pass
effect is decreased and t-1/2 prolonged with age, resulting in an increased area under the concentration-time curve
(AUC) of molsidomine and SIN-1. In patients with liver disease and congestive heart failure similar changes were
observed, but much less so in patients with CAD. Clearance was also impaired in patients with liver disease, but the
pharmacokinetics of molsidomine were not markedly altered by impaired renal function. In general, due to a large
therapeutic dose range, dosage adjustments are not required on the basis of clinical experience. In certain patients a
lower starting dose may be recommended, such as in those with impaired liver or kidney function,

in congestive heart
failure or in the presence of concomitant treatment with other vasoactive compounds. A linear dose-effect relationship
is observed with counterclockwise hysteresis, i.e. a greater effect associated with the decrease of plasma
concentrations than during their increase, which may be at least partly due to the metabolic delay in the formation of
NO from SIN-1. Accordingly, the duration of action of molsidomine is longer than would be expected on the basis of
the elimination half-life. The pharmacokinetics of molsidomine support the recommended dosages for use in angina pectoris.

Cancer Treat Rev 1995 Mar;21(2):159-81

Nitric oxide and anti-cancer therapy.

Sagar SM, Singh G, Hodson DI, Whitton AC

Hamilton Regional Cancer Centre, Ontario, Canada.

Publication Types: Review

Mayo Clin Proc 1995 Mar;70(3):247-55

Inhaled nitric oxide therapy.

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OBJECTIVE: To review the basic science, physiology, toxicity, and delivery of inhaled nitric oxide (NO). DESIGN: A
literature review of inhaled NO is presented, and a brief discussion of current clinical applications is included.
RESULTS: Inhaled NO is a new investigational drug used for selective vasodilation of the pulmonary vasculature. It
mimics the effects of endogenously produced endothelium-derived relaxing factor. In addition to selective pulmonary
vasodilation, inhaled NO can improve hypoxemia by improving ventilation-perfusion relationships within the lung. The
doses of inhaled NO that produce improvements in oxygenation are lower than those needed to produce maximal
vasodilation. Inhaled NO is being used in the intensive-care unit to treat critically ill patients with pulmonary
hypertension or hypoxemia associated with ventilation-perfusion imbalance. It is also being used in the cardiac
catheterization laboratory as a diagnostic tool. Few adverse effects have been associated with the use of inhaled NO.
CONCLUSION: Despite a lack of randomized, controlled studies that show improved outcome in comparison with
traditional treatments, inhaled NO seems to be an effective new therapy for patients with pulmonary vasospasm or
hypoxemia associated with ventilation-perfusion imbalance. It may also prove to be a valuable

diagnostic tool in the
cardiac catheterization laboratory. Publication Types: Review

Eur J Pharmacol 1999 Jun 30;375(1-3):157-76

Antiatherosclerotic activity of drugs in relation to nitric oxide function.

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Many studies have shown that loss of endothelium-derived nitric oxide is a major factor of ischemic episodes in
patients with coronary artery disease and there is increasing evidence to suggest that nitric oxide might exert
antiatherosclerotic actions. Based on these concepts, the results of animal studies on the effects of lipid lowering drugs,
antioxidants, angiotensin converting enzyme inhibitors, Ca2+ channel blockers, estrogens and agents which modulate
nitric oxide bioavailability are presented and compared to the results of patient studies and clinical trials. In spite of
encouraging results obtained with antioxidants in animals, clinical trials could only show a clear positive effect of vitamin
E treatment on the outcome of cardiovascular disease. Angiotensin converting enzyme inhibitors can ameliorate
endothelial dysfunction in coronary heart disease, but their impact on disease progression remains unclear. There is
evidence that estrogen replacement therapy in post-menopausal women may increase the bioavailability of nitric oxide.
Finally, improved endothelial function and plaque stability clearly contribute to the clinical benefits of lipid lowering
interventions, statins in particular. Taken together, these studies lend support to the concept that improving endothelial
function and nitric oxide release might serve as valuable elements in the prevention or therapy of cardiovascular disease.

Curr Opin Pediatr 1999 Jun;11(3):241-8

Advances in ventilatory support of the pediatric surgical patient.

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Severe respiratory failure in newborn and pediatric patients is associated with significant morbidity and mortality. Basic
science laboratory investigation has led to advances both in our understanding of ventilator-induced lung injury and in
optimizing the supportive use of conventional ventilation strategies. Over the past few years, progress has been made in
alternative therapies for ventilating both children and adults with severe respiratory failure. This

review focuses on
recent laboratory and clinical data detailing the techniques of permissive hypercapnia, high frequency oscillatory
ventilation, inhaled nitric oxide, intratracheal pulmonary ventilation, and liquid ventilation. Some of these modalities are
becoming commonplace, and others may have much to offer the clinician if their benefit is clearly demonstrated in future clinical trials.

Curr Opin Pediatr 1999 Jun;11(3):223-8

Hypoxic-ischemic brain injury: advancements in the understanding
of mechanisms and potential avenues for therapy.

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Hypoxic-ischemic brain injury occurs frequently in infancy and childhood. Events such as perinatal asphyxia, near
drowning, respiratory arrest, and near sudden infant death syndrome cause significant mortality and morbidity. Despite
current critical care practices, the outcomes from such injuries may be life-long neurologic deficits. This review
discusses findings from laboratory investigations into such injuries--in particular the roles of excitotoxic amino acids,
proteolytic enzymes, free radicals, nitric oxide, and leukocytes. Understanding of the two distinct forms of neuronal
death, necrosis and apoptosis, provides additional insights into mechanisms of injury. The development of new
therapies for hypoxic-ischemic brain injury depends on such understanding. To date, the results of preclinical
therapeutic trials have not demonstrated a "magic bullet." Nevertheless, the understanding of injury mechanisms has
uncovered potential avenues for new therapies, particularly combination therapies or single interventions that have
multiple effects. Clinical trials, using these strategies, are planned or have been recently begun and offer hope for advancements in treatment.

Ann Acad Med Singapore 1998 May;27(3):414-21

Nitric oxide in septic shock: directions for future therapy?

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Septic shock is a major cause of death among patients in intensive care units. It has a mortality rate of 20% to 80%.
The clinical syndrome of septic shock is characterised by hypotension, hyporesponsiveness to vasoconstrictors and
volume depletion which will then lead to multiorgan dysfunction and death. Except for surgical and supportive care, no

specific therapy is known. Recently interest has been focused on the role of nitric oxide (NO) in septic shock. Large
amounts of NO released by the endothelium and vascular smooth muscle cells lead to profound vasodilation and
hyporesponsiveness to vasoconstrictors. The cytotoxic effect of NO could also cause tissue injury and organ failure.
Inhibition of NO synthase, the enzyme responsible for NO production, has been proposed as a new therapy for septic
shock. However, experimental reports have provided conflicting results, demonstrating both beneficial and detrimental
effects. A brief review of the role of NO in septic shock and the possible use of NO synthase inhibitors as potential therapeutic agents is presented here.

Croat Med J 1998 Jun;39(2):165-70

Which interventions for neonatal respiratory failure are effective?

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AIM: To review the evidence from clinical trials of various interventions to treat and prevent respiratory failure in the
neonate and to determine which interventions are effective and which require further study.
METHODS: Randomized
controlled trials and/or meta-analyses of trials of interventions for neonatal respiratory failure were sought from
databases including the Cochrane Collaboration. The results were synthesized as typical relative risks and typical risk
differences, with 95% confidence intervals (CI). RESULTS: The following interventions were effective: conventional
mechanical ventilation (absolute reduction in mortality 12%, 95% CI 4-21%), continuous positive airway pressure
(absolute reduction in mortality 15%, 95% CI 1-28%), surfactant therapy (absolute reduction in mortality 4 to 9%,
95% CI 1-13%), and extracorporeal membrane oxygenation (absolute reduction in mortality 29%; 95% CI 15-42%).
High frequency oscillatory ventilation with a volume recruitment strategy and inhaled nitric oxide appeared promising,
but have not yet reduced mortality. Prenatal corticosteroids (absolute reduction in mortality 4%; 95% CI 2-6%) and
amnioinfusion (effect on mortality not yet possible to estimate) prevented respiratory failure, but routine endotracheal
intubation and suctioning of the airways at birth in vigorous meconium-stained term babies did not prove effective.
CONCLUSIONS: Assisted ventilation, surfactant therapy, and extra-corporeal membrane oxygenation are effective,
but it is uncertain how each should be applied in an individual infant. More research is needed to evaluate
combinations of effective interventions, and effectiveness of high frequency oscillation and inhaled nitric oxide. Routine
intubation and suctioning of the airways at birth in meconium-stained vigorous neonates is not

recommended. Publication Types: Review

Arch Pediatr 1997 Oct;4(10):988-1003

[Inhaled nitric oxide: a physiologic treatment of persistent pulmonary arterial hypertension in the newborn].

[Article in French]

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Fetal pulmonary circulation is characterized by high resistance and low pulmonary blood flow. Right-to-left shunting through the foramen ovale and/or patent ductus arteriosus is necessary to perfuse the placenta and insure fetal life. At birth, pulmonary arterial blood flow increases immediately by 8- to 10-fold, and allows pulmonary gas exchange and postnatal life. In some circumstances, this adaptation to extra-uterine life is inadequate, because of persistent high pulmonary resistance (PPHN). Due to the lack of a selective pulmonary vasodilator, the treatment of this syndrome remained purely symptomatic using high oxygen levels and barotraumatic mechanical hyperventilation. When this medical treatment failed, the only alternative was extracorporeal membrane oxygenation (ECMO). The discovery of the major role of various endothelium-derived factors including nitric oxide (NO) in the control of vascular reactivity led to dramatic switches in the concepts of severe neonatal respiratory failure and the therapeutic approach of PPHN.
It was shown, first in experimental animals then in a few infants with hypoxemic respiratory failure, that NO inhalation selectively vasodilated the vasoconstricted pulmonary vessels, and reversed right-to-left shunting and refractory hypoxemia. Whether inhaled NO also reduces mortality and/or morbidity in hypoxic infants remains to be proven by appropriate randomized clinical trials. However, not only PPHN is associated with pulmonary diseases of various etiologies and underlying pathophysiologic mechanisms, but also inhaled NO is used in conjunction with other validated therapeutic strategies including ante- or postnatal steroids, exogenous surfactants, and high-frequency oscillatory ventilation. Thus, the relevant primary endpoint might be not only crude survival but the most physiological and economical way of obtaining it.

Publication Types: Clinical trial

Drugs 1997;54 Suppl 5:1-11

Cardioprotective mechanisms of ACE inhibition. The angiotensin II-nitric oxide balance.

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Massachusetts, USA.

The current challenge facing clinicians is to develop pharmacotherapies that move beyond the treatment of symptoms
towards a new agenda in cardiovascular therapeutics that includes interventions to actually prevent the development of
end-stage coronary heart disease. The development of new strategies to alter the natural history of cardiovascular
disease will be fostered by gaining insights into the fundamental pathobiological mechanisms that promote the
morbidity and mortality associated with these disorders. An emerging body of evidence indicates that locally generated
vasoactive substances such as angiotensin II and nitric oxide are important determinants of the natural history of
vascular disease. It is anticipated that ongoing clinical trials will extend the concept that modulating the activity of
vasoactive substances generated by the endothelium has important implications for altering the course of coronary
heart disease.

Publication Types: Review

Respir Care Clin N Am 1997 Sep;3(3):371-410

Delivery systems for inhaled nitric oxide.

Hess D, Ritz R, Branson RD

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From a practical standpoint, technical issues related to NO delivery are as important as therapeutic issues. The
benefits can be appreciated only if a reliable delivery system is used. Further, hazards and toxicity may be more
problematic with an unreliable delivery system. It is incumbent on clinicians using inhaled NO to ensure that the
delivery system is safe and reliable.

Publication Types: Review

Heart Lung 1997 Sep-Oct;26(5):358-62

Inhaled nitric oxide for severe acute respiratory distress syndrome: a blessing or a curse?

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The effects of inhaled nitric oxide (NO) in two young adults who developed severe acute respiratory distress
syndrome are presented. Modest improvements in gas exchange and reductions in pulmonary artery pressures
occurred after the initiation of treatment with inhaled NO. However, both patients became "dependent" on the inhaled
NO for stabilization of their cardiopulmonary function. Repeated attempts to discontinue the inhaled NO resulted in
life-threatening deterioration in gas exchange and hemodynamic instability. Prolonged family discussions were held
regarding the withdrawal of inhaled NO and other life-sustaining therapies, when the irreversible nature of the patients'
lung disease became apparent. However, both families were strong in their desire to continue all therapies--due in
large part to the single organ nature of the disease process. Both patients died while receiving inhaled NO and
escalating doses of sedative and analgesics. Based on this experience, it is recommended that clearly defined goals or
endpoints for the discontinuation of inhaled NO should be established before its initial administration. If these goals are
not achieved, then the therapy should be considered a failure and withdrawn. A similar strategy should be applied to
all life-sustaining therapies in the intensive care unit setting (e.g., mechanical ventilation, vasopressors, dialysis). This
requires that critical care clinicians effectively communicate the difference between aggressive supportive care and
definitive treatment of the underlying disease process to patients or their families, or both. Furthermore, until the results
of ongoing clinical trials of inhaled NO become available, it is recommended that its administration be restricted to
medical centers examining its use in clinical trials.

Arch Pediatr 1998 Oct;5(10):1107-21

[Recent developments in the treatment of pediatric acute respiratory
distress syndrome].

[Article in French]

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Acute respiratory distress syndrome (ARDS) is a severe condition with a high mortality rate, despite conventional
treatment using mechanical ventilation. Better understanding of the pathophysiology and awareness of important
iatrogenic lung injury secondary to mechanical ventilation has led to new therapeutic principles. Mechanical ventilation
strategy during ARDS is characterized by positive end-expiratory pressure, increase in the inspiratory time, high

inspiratory oxygen concentration and, more recently, use of permissive hypercapnia. High frequency ventilation allows
optimal lung recruitment under small tidal volume. The effectiveness of extracorporeal oxygenation techniques is
demonstrated, but because of their cost and morbidity these therapies are rational only in patients who seem likely to
die. Partial liquid ventilation and inhaled nitric oxide have great potential but require further studies. Intratracheal
exogenous surfactant might be beneficial but controlled trials are needed to confirm the usefulness of this expensive
therapy. Finally, a number of adjuncts to mechanical ventilation are currently available to minimize iatrogenic lung injury
and improve the outcome. The role of these new treatments must be defined with randomized and controlled clinical
trials using homogenous inclusion criteria.

Pediatr Clin North Am 1998 Jun;45(3):475-509

New ways to ventilate newborns in acute respiratory failure.

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Out treatment options for acute neonatal failure have expanded greatly in the last 20 to 30 years. This article reviews
patient-triggered ventilation, high frequency ventilation, negative extrathoracic pressure ventilation, nitric oxide therapy,
liquid ventilation, extracorporeal membrane oxygenation, and advances in pulmonary function monitoring. The authors
present background theories, describe equipment, review clinical strategies, and the results of recent trials.

Pediatrics 1999 Mar;103(3):610-8

Changes in oxygenation with inhaled nitric oxide in severe bronchopulmonary dysplasia.

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Philadelphia, USA.

BACKGROUND: Severe bronchopulmonary dysplasia (BPD), which is associated with high mortality and morbidity,
is thought to be the result of mechanical, inflammatory, and oxidant injury to the immature lung, and includes the
development of pulmonary hypertension with vascular remodeling. METHODS: A phase II pilot study was conducted
to determine the effect of inhaled nitric oxide (iNO) on oxygenation in severe BPD. This was an open-labeled,
noncontrolled trial to evaluate safety and determine appropriate dosing for a future randomized

controlled trial. Infants
were eligible for enrollment if they were >/=4 weeks of age and ventilator dependent with a mean airway pressure of
>/=10 cm H2O and an FIO2 of >/=0.45. Study infants received iNO (20 ppm) for 72 hours, and FIO2 was adjusted
to maintain oxygen saturations of >92%. Infants who had a >/=15% reduction in FIO2 after 72 hours received
prolonged treatment with low-dose iNO, weaning by 20% every 3 days as tolerated. FINDINGS: Sixteen preterm
infants (23-29 weeks of gestation), age 1 to 7 months, were enrolled. Eleven of 16 infants had a significant increase in
PaO2 after 1 hour of iNO (median change, 24 mm Hg; range, -15 to 59 mm Hg; P <.01), but there was no significant
change in PaCO2. After 72 hours of iNO, 11 infants had >/=15% reduction in FIO2, and 7 of the 11 had >/=35%
reduction (P <. 01). Among the 11 infants who responded to iNO after 72 hours, 10 had a sustained improvement in
oxygenation throughout their course of treatment (duration, 8-90 days), and ventilator support could also be
decreased. No adverse effects from iNO (increased methemoglobin, bleeding, or increased plasma 3-nitrotyrosine)
were observed. Four of the 11 infants (36%) who responded to iNO ultimately weaned off mechanical ventilation and
4 died, whereas all the infants who failed to respond to iNO either died or continue to require mechanical ventilation.
INTERPRETATION: We conclude that the use of low-dose iNO may improve oxygenation in some infants with
severe BPD, allowing decreased FIO2 and ventilator support without evidence of adverse effects. Randomized
clinical trials of low-dose iNO for BPD are warranted.
Publication Types: Clinical trial

Crit Care Nurse 1998 Dec;18(6):21-7

Inhaled nitric oxide therapy for adult respiratory distress syndrome.

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The selective pulmonary vasodilatory effects of inhaled nitric oxide decrease pulmonary artery hypertension and
improve arterial oxygenation in patients with ARDS without causing concomitant systemic vasodilation. Inhaled nitrix
oxide therapy may decrease the prevalence of pulmonary edema, pulmonary barotrauma, and oxygen toxicity that
occur with current ARDS treatment. The effect of nitric oxide on oxygenation and pulmonary artery pressure may
allow more time for the lungs to recover. Initial results of clinical trials are encouraging; however, the impact of inhaled
nitric oxide therapy on patients with ARDS remains unclear. Further research is needed to develop safe delivery
systems and monitoring techniques for routine clinical use, to determine potential adverse and toxic

effects of nitric
oxide therapy on patients, and to determine the effects of long-term exposure to nitric oxide among healthcare
workers. Concomitant administration of other medications with inhaled nitric oxide should also be investigated.
Publication Types: Review

Eur J Pharmacol 1998 Feb 19;343(2-3):217-23

Correction of neurovascular deficits in diabetic rats by
beta2-adrenoceptor agonist and alpha1-adrenoceptor antagonist
treatment: interactions with the nitric oxide system.

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The aims were to test whether 2 weeks treatment with the beta2-adrenoceptor agonist, salbutamol, or the
alpha1-adrenoceptor antagonist, doxazosin, could correct nerve blood flow and conduction velocity deficits in 8 week
streptozotocin-diabetic rats and to examine neurovascular mechanisms using co-treatment with the nitric oxide
synthase inhibitor, NG-nitro-L-arginine. Sciatic motor conduction velocity, 20.3% reduced by diabetes, was
corrected by 88.2 and 88.5% for salbutamol and doxazosin, respectively. A 47.6% diabetic deficit in sciatic nutritive
endoneurial blood, was substantially reversed by salbutamol (117.0%) and doxazosin (61.0%) treatment. The effects
of alpha1-adrenoceptor blockade and beta2-adrenoceptor stimulation on nerve blood flow and conduction velocity
were almost completely (76.7-91.7%) attenuated by NG-nitro-L-arginine co-treatment. Thus, the data stress the
importance of vasa nervorum alpha1 and beta2 adrenoceptors and the permissive role of nitric oxide in nerve blood
flow control mechanisms. They also indicate that beta2-adrenoceptor agonists may be suitable for clinical trials of diabetic neuropathy.

Clin Neurosci 1998;5(1):28-33

Nitric oxide theory of migraine.

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The molecular mechanisms of migraine pain have not yet been clarified. Neurogenic inflammation and a subsequent
plasma extravasation in the dura mater have been suggested. However, monoamine and peptide neurotransmitters
involved in neurogenic inflammation do not cause significant head pain. Based on our previous studies of headache
induced by i.v.infusions of glyceryl trinitrate (exogenous nitric oxide donor) and histamine (which

liberates nitric oxide
from vascular endothelium), we suggest that nitric oxide (NO) is a more likely candidate molecule. The present review
deals with the biology of this small messenger molecule and the scientific evidence suggesting a key role for this
molecule in migraine headache. We hypothesise that the release of NO from either blood vessels, perivascular nerve
endings, or brain tissue is a molecule trigger mechanism of spontaneous migraine pain. These novel observations
dictate new approaches to the pharmacological treatment of migraine.
Publication Types: Review

Rev Reprod 1996 Jan;1(1):61-8

Nitric oxide in the human uterus.

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UK.

Nitric oxide (NO) plays a crucial role in many biological systems. Recent evidence indicates that NO is found in the
human uterus. During pregnancy, it is produced in the placenta, the decidua and the myometrium. In the nonpregnant
state, nitric oxide synthase, the enzyme that catalyses the production of NO, has been identified in both the
myometrium and the endometrium. Potential roles for NO in the human uterus are speculative, but include
vasodilatation (both before implantation, and in the uteroplacental and systemic circulation during pregnancy),
inhibition of platelet activation during menstruation, and suppression of myometrial contractility during pregnancy.
Nitric oxide may also be involved in uterine pathology. Excessive NO production by the uterus during menstruation
could lead to menorrhagia. During pregnancy, a change in NO production may be implicated in pre-eclampsia, and
animal studies have shown that inhibition of NO production leads to intrauterine growth retardation. If a role for NO is
confirmed in these various uterine conditions, pharmacological modification of NO activity may lead to novel
therapeutic applications. However, these notions are still conjectural, and extensive work is required before such
treatments can be introduced into clinical practice.

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[Septic shock and nitric oxide].

[Article in Spanish]

Lorente JA, Delgado MA, Landin L

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Refractory hypotension is the main cause of death of patients with septic shock. It has been shown that an excessive release of NO is responsible for the sepsis-induced hypotension and vascular hyporeactivity. Nitric oxide is produced under normal conditions by a constitutive enzyme present, among other cell types, in the endothelial cell, and is necessary for maintenance of normal organ perfusion. Under inflammatory or septic conditions, a new enzyme is expressed in phagocytic cells and vascular smooth muscle cells, giving rise to an uncontrolled NO production that is associated with cytotoxic effects and vasodilatation. Randomized clinical trials have shown that the administration of inhibitors of NO synthesis to patients with septic shock is associated with a greater incidence of shock resolution, without significant adverse effects. The recent discovery of the different biological functions of NO, both under normal and inflammatory conditions, has allowed the development of new concepts about the pathophysiology of septic shock, and has provided the bases to design novel therapeutic strategies for the treatment of septic shock, based on the inhibition of NO synthesis.
Publication Types: Review

124:280283

Pharmacology of cotransmission in the autonomic nervous system: Integrative aspects on amines, neuropeptides, adenosine triphosphate, amino acids and nitric oxide.

Lundberg, Jan M. (Department Physiology and Pharmacology, Karolinska Institute, Stockholm, Swed.). Pharmacol. Rev., 48(1), 113-78 (English) 1996. CODEN: PAREAQ. ISSN: 0031-6997. DOCUMENT TYPE: Journal; General Review CA Section: 3 (Biochemical Genetics) Section cross-reference(s): 13

Keywords

review autonomic nervous system neurotransmission ATP
pharmacol neurotransmission neuropeptide amino acid review

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Neurotransmission
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56-65-5, biological studies
10102-43-9, biological studies
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Keywords

nitric oxide liberating drug anticoagulant

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120:28053
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Wennmalm, Aake; Benthin, Guenther; Edlund, Anders; Jungersten, Lennart; Kieler-Jensen, Niels; Lundin, Stefan; Westfelt, Ulla Nathorst; Petersson, Ann Sofi; Waagstein, Finn (Div. Clin. Physiol., Sahlgrenska Hosp., Goeteborg S-413 45, Swed.). Circ. Res., 73(6), 1121-7 (English) 1993. CODEN: CIRUAL. ISSN: 0009-7330. DOCUMENT TYPE: Journal CA Section: 13 (Mammalian Biochemistry) Section cross-reference(s): 14

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nitric oxide metab excretion

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10102-43-9, biological studies
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Clinical applications of inhaled nitric oxide in children with pulmonary hypertension.

Wessel, David L.; Adatia, Ian (Cardiac Intensive Care Unit, Children's Hospital, Boston, MA 02115, USA). Adv. Pharmacol. (San Diego), 34(Nitric Oxide), 475-504 (English) 1995. CODEN: ADPHEL. ISSN: 1054-3589. DOCUMENT TYPE: Journal; General Review CA Section: 1 (Pharmacology)

Keywords

review nitric oxide pulmonary hypertension child

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child, clin. applications of inhaled nitric oxide in children with pulmonary hypertension in relation to congenital heart disease
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Bauer, John Anthony; Booth, Brian P.; Fung, Ho-Leung (School Pharmacy, State University New York, Buffalo, NY 14260, USA). Adv. Pharmacol. (San Diego), 34(Nitric Oxide), 361-81 (English) 1995. CODEN: ADPHEL. ISSN: 1054-3589. DOCUMENT TYPE: Journal; General Review CA Section: 1 (Pharmacology)

Keywords

review nitric oxide donor cardiovascular drug

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nitric oxide donors: biochem. pharmacol. and therapeutics
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124:82755
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Keywords

review brain nitric oxide synthase

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Keywords

review nitric oxide metallonitrosyls pharmacol

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