Sodium Nitrite for Out-of-Hospital Cardiac Arrest

MICHAEL SAYRE, MD
MEDICAL DIRECTOR, SEATTLE FIRE DEPARTMENT
Disclosures

EMS Medicine Fellowship Director, University of Washington

Physio-Control provides a significant grant to partially fund the fellow’s salary and benefits.

◦ I receive travel reimbursement from the fund.

We will discuss a potential indication, not approved by FDA, for an approved drug.
Half of OHCA patients admitted to hospital following restoration of pulses die of brain injury.

The Hot Dog Study
Electrical Defibrillation
Hemodynamic

Time

CPR + ? Epinephrine
It’s all about the mitochondria.
Known protective effects of nitric oxide

- Vascular smooth muscle relaxation and vasodilation
- Suppression of smooth muscle proliferation
- Inhibits leukocyte adhesion
- Inhibits platelet aggregation
Question

Will increasing nitric oxide (NO) levels in brain tissue improve neurologic outcome following resuscitation from cardiac arrest?
Possible approaches

Inhaled nitric oxide gas

Drugs that directly increase nitric oxide
  ◦ Nitroglycerin, Sodium nitroprusside

Drugs that indirectly increase nitric oxide’s effect
  ◦ Sildenafil
Experimental paper

Sodium nitroprusside enhanced cardiopulmonary resuscitation improves short term survival in a porcine model of ischemic refractory ventricular fibrillation

Demetris Yannopoulos a, *, Jason A. Bartos a, Stephen A. George a, George Sideris b, Sebastian Voicu b, Brett Oestreich a, Timothy Matsuura c, Kadambari Shekar c, Jennifer Rees a, Tom P. Aufrèrehe d

a Division of Cardiology, Department of Medicine, University of Minnesota, Minneapolis, MN, United States
b Department of Cardiology, Inserm U942, Lariboisière Hospital, AP-HP, Paris Diderot University, Paris, France
c Department of Integrated Biology & Physiology, University of Minnesota, Minneapolis, MN, United States
d Department of Emergency Medicine, Medical College of Wisconsin, Milwaukee, WI, United States
Sodium nitroprusside is not affordable.

Outrage over the cost of the two drugs began in February of last year, when Valeant bought Nitropress and Isuprel and immediately raised their prices. In 2015, the price of Nitropress, an emergency blood-pressure drug, went from $215 a vial to $881, an increase of more than 300 percent, according to the Cleveland Clinic. Isuprel, which treats abnormal heart rhythms, went from $180 to $1,472 a vial, a 718 percent increase.
Can a different FDA approved drug serve as a source for nitric oxide?
NO $\rightarrow$ NO$_2^-$ $\rightarrow$ NO$_3^-$
\[
\text{NO} \xrightarrow{\text{Oxy-Hb}} \text{NO}_2^- \xrightarrow{\text{De-Oxy-Hb}} \text{NO}_3^- \xrightarrow{} \text{NO}
\]
a Healthy tissue

Blood vessel

b Ischaemic tissue

Occlusion

Healthy tissue

NO$_2^-$

NO$_3^-$

No side effects

Revascularized tissue

NO

Revascularization, vasodilation and ischaemic tolerance
The bad
Nitrite functions as a food preservative.
FDA regulates it.
- Nitrosamines produced during acidic/high heat
Beet Juice: 22-50 mg nitrite

A Single Dose of Beetroot Juice Enhances Cycling Performance in Simulated Altitude

DAVID J. MUGGERIDGE\textsuperscript{1,2}, CHRISTOPHER C. F. HOWE\textsuperscript{2}, OWEN SPENDIFF\textsuperscript{2}, CHARLES PEDLAR\textsuperscript{3}, PHILIP E. JAMES\textsuperscript{4}, and CHRIS EASTON\textsuperscript{1,2}

\textsuperscript{1}Institute for Clinical Exercise and Health Science, University of the West of Scotland, Hamilton, Scotland, UNITED KINGDOM; \textsuperscript{2}School of Life Sciences, Kingston University, Kingston upon Thames, England, UNITED KINGDOM; \textsuperscript{3}School of Sport, Health and Applied Science, St Mary’s University College, Twickenham, England, UNITED KINGDOM; and \textsuperscript{4}Wales Heart Research Institute, Cardiff University School of Medicine, Cardiff, Wales, UNITED KINGDOM
What happens to nitrite levels during cardiac arrest?
Add nitrite to restore Blood levels

Nitrite Levels

Time

Arrest  ROSC
Figure 6. Nitrite therapy improves survival after cardiac arrest

After successful resuscitation, animals died between 1 and 6 hours after CPR. Nitrite therapy resulted in improved survival to 22 hours post-CPR compared to placebo (* p=0.033; n=28/27 for placebo/nitrite groups).
SNOCAT Study Hypothesis

Infusion of sodium nitrite during resuscitation (before ROSC) will improve neurologic outcome and survival after cardiac arrest.
SNOCAT: Sodium nitrite out of hospital cardiac arrest trial

Phase 1 (dose finding and safety trial)
- n=100, expect 40 to survive to ED admission
- Open label, start dose of 25 mg.
- Achieve plasma level of 10 uM?
Eligibility

Out-of-hospital cardiac arrest (VF, non-VF)
Unconscious/not following commands
IV access/IO

Not in the three P’s: Pregnant, Pediatric, Prisoners
Safety Data Being Collected

Re-arrest

Use of vasopressors: norepinephrine or epinephrine infusions

Blood Draws for NO₂ levels at ED or in field
  - For Harborview Medical Center only additional draws at 20, 40, 60, 80, 100, 120 minute time points
Endpoints
Plasma level of nitrite at hospital, ED arrival
Safety: re-arrest, use of pressors
N=100 (expect 40 to be admitted to ED)
SNOCAT: Sodium nitrite out of hospital cardiac arrest trial

Phase 2 (safety and efficacy)
- n=1000, expect 400 to survive to ED
- Randomized/blinded
- Primary endpoint: Survival to ED (safety endpoint)
- Secondary endpoint: Survival to discharge
SNOCAT Investigators

Francis Kim
Peter Kudenchuk
Graham Nichol
Michele Olsufka
Michael Sayre
Sue Scruggs

Chuck Maynard
Susanne May
Safety

Low risk for hypotension
No risk for methemoglobin
“Restores nitrite level to baseline”
Given post-arrest at doses up to 9 mg, no significant effects
Effect during resuscitation unknown?
The good

Increases NO levels in blood (blood pressure lowering effects)

May protect blood vessels

Found in supplements (increase endurance)
Ischemia/reperfusion

Superoxide

Nitric oxide
Hydrogen sulfide
Carbon monoxide
<table>
<thead>
<tr>
<th></th>
<th>NO</th>
<th>CO</th>
<th>H₂S</th>
</tr>
</thead>
<tbody>
<tr>
<td>Toxic Gas?</td>
<td>Exhaust, air pollution</td>
<td>Air pollution</td>
<td>Sewers, swamps</td>
</tr>
<tr>
<td>Produced by cells</td>
<td>Nitric oxide synthase (NOS) nitrite</td>
<td>Made from hemoglobin</td>
<td>Synthesized from L-cysteine</td>
</tr>
<tr>
<td>Vascular effects</td>
<td>Vasodilates</td>
<td>Vasodilates</td>
<td>Vasodilates</td>
</tr>
<tr>
<td>Anti-inflammatory effects</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Mitochondrial</td>
<td>Decrease</td>
<td>Decrease</td>
<td>Decrease</td>
</tr>
</tbody>
</table>
Ischemia
Reperfusion Injury

Brain cell injury/death

Coagulation activation

Membrane permeability

Inflammatory Response

Ca$^{2+}$, glutamate

NO
NO-ischemia

Protective role of nitric oxide in ischemia reperfusion (liver, heart, brain)

- Genetic overexpression studies
- Drug (NO-donor) (different structures)
NO production is reduced during ischemia

Nitric oxide production by NOS requires oxygen (not suitable for ischemia)

Nitric oxide production requires cofactors (limited during ischemia)
The NO-nitrite-nitrate pool

1. NO is constitutively synthesized by eNOS and a portion is converted by plasma Cp to \( \text{NO}_2^- \). \( \text{NO}_2^- \) is a stable chemical reservoir for this NO, capable of later reacting with oxy-Hb and deoxy-Hb to make \( \text{NO}_3^- \) and NO.

2. Dietary \( \text{NO}_2^- \) and \( \text{NO}_3^- \) are ingested along with \( \text{NO}_2^- \) secreted by the salivary glands into the mouth. Denitrifying bacteria convert \( \text{NO}_2^- \) to \( \text{NO}_3^- \) and this mixture is swallowed.

3. \( \text{NO}_2^- \) may be reduced to NO in the stomach by acidic disproportionation. The remaining \( \text{NO}_2^- \) and \( \text{NO}_3^- \) can be absorbed into the bloodstream by the gut.
### Figure 3. Nitrite Therapy after Cardiac Arrest: Dose Titration with Brain Histology and Blood Nitrite Levels

Results of three separate studies examining different doses of nitrite given at the initiation of CPR (mice) or 5 minutes after the start of CPR as a 20 minute infusion (rats). In the mouse studies, * indicates that only a single blood draw was performed; pre-arrest levels are derived from a single sham group that did not receive cardiac arrest and there is no post-arrest pre-drug level since the drug was given at the initiation of CPR. In the hematoxylin and eosin stained brain slices, the bar indicates 40 micrometer distance. † indicates p<0.05 and ‡ indicates p<0.01. Note that nitrite depletion was seen in the mouse but not rat models. Consistent with other animals studies, the low and moderate doses of nitrite which produced blood levels of 1 and 25.8 μM appear to be neuroprotective but not the highest dose which appeared to cause harm.
IV nitrite in acute ST elevation MI

229 pts randomized (70 uM, 5 mg over 5 minutes) or placebo before coronary intervention

Mean nitrite level at randomization (.70 uM)

Nitrite (1.42 uM) vs. placebo (.18 uM) 5 min after completion of infusion

Siddiqui N, European Heart Journal 2014
Clinical-nitrites

Peripheral arterial disease (oral doses 40-80 mg)-2014
CHF (17.5 mg)-2015
Organ preservation for transplant
Cardiac arrest (post) (1-14 mg)
A

B

C

D

Mean Arterial Pressure (mm Hg)

Heart Rate (bpm)

Methemoglobin (%)

Nitrite Level (μM)

Time after Infusion Start (min)

Time after Infusion Start (min)

Time after Infusion Start (min)

Time after Infusion Start (min)

A (1mg)

B (5.6 mg)

C (14.5 mg)

Nitrite Infusion
Ischemia
Reperfusion Injury

Membrane permeability

Inflammatory Response

Coagulation activation

Ca\(^{2+}\) glutamate

Brain cell injury/death
The diagram illustrates the electron transport chain in mitochondrial respiration. The chain begins with the oxidation of NADH and FADH₂, which are generated during the citric acid cycle. These electron carriers transfer electrons through a series of complexes (I, II, III, and IV), each of which is embedded in the mitochondrial inner membrane.

- **Complex I (NADH dehydrogenase)**: Accepts electrons from NADH and transfers them to ubiquinone (Q).
- **Complex II (Succinate dehydrogenase)**: Accepts electrons from succinate and transfers them to ubiquinone (Q).
- **Complex III (Cytochrome b-c₁ complex)**: Accepts electrons from ubiquinone (Q) and transfers them to oxygen.
- **Complex IV (Cytochrome c oxidase)**: Accepts electrons from cytochrome c and transfers them to oxygen, ultimately reducing oxygen to water.

Throughout the process, protons (H⁺) are pumped from the matrix into the intermembrane space, creating a proton gradient (ΔΨ) that drives ATP synthesis through ATP synthase. Inhibitors such as rotenone, malonate, antimycin, cyanide, and oligomycin can block different steps in the chain, highlighting the importance of each complex in the overall process of ATP production.
Ischemia/reperfusion

Superoxide