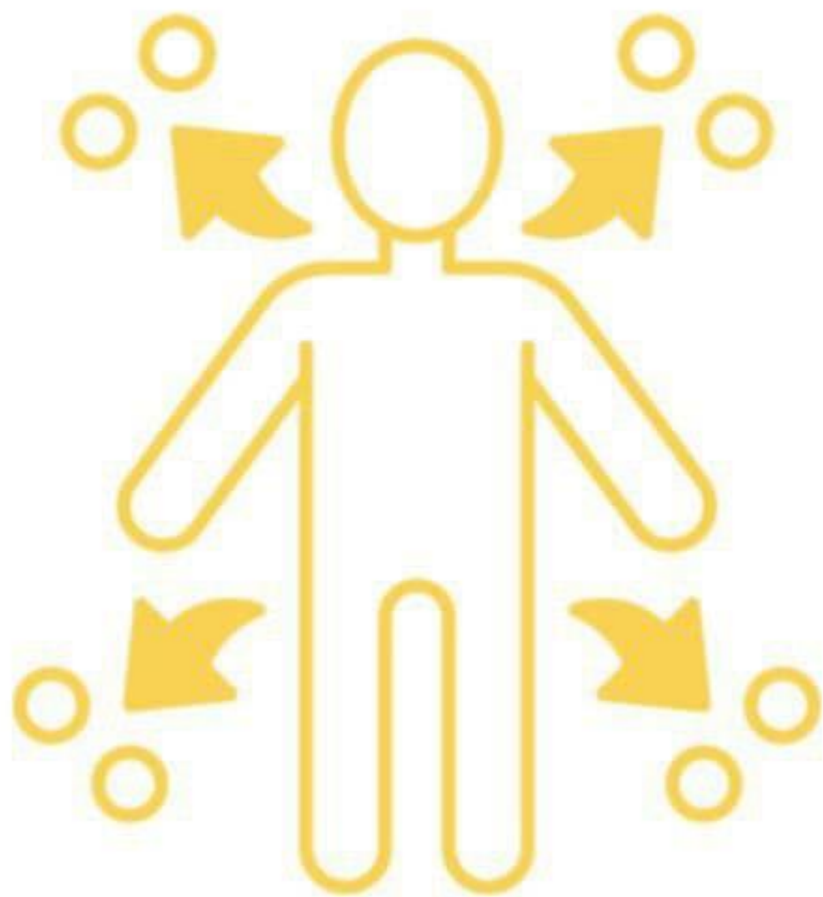


Industrial and household toxicology

Nitrates and nitrites



MIRACLE Academy

سموم
زميلتكم نهى حسن



لجان الرفعات

قال تعالى (يَرْفَعُ اللَّهُ الَّذِينَ آمَنُوا مِنْكُمْ وَالَّذِينَ أُوتُوا الْعِلْمَ دَرَجَاتٍ)

- Sources
- Mechanism of toxicity
- Mechanism of toxicity
- Clinical presentation
- Diagnosis
- Treatment

Sources

معلوماته سهله حتى الي رح اكتبه رح يكون قليل لانه
الدكتور ه كانت تحكي نفس الي بالسلايد بالضبط

A. Nitrates (organic): widely used as **vasodilators** for the treatment of **ischemic heart disease** and heart failure

✓ **glyceryl trinitrate, Isosorbide dinitrate, Isosorbide mononitrate**

- ❖ Rapidly absorbed from the GIT and skin
- ❖ Undergo 1st pass effect which markedly reduces their activity
- ❖ Orally at high conc.
- ❖ Sublingual route of administration
- ❖ Trans dermal patches

بقدر بعطيه orally ولكن رح يصير الـ first pass
لهيك لما واحد تصيبه جلطه لاسمح الله
بعطيه حبه تحت اللسان حتى ما يقل مفعولها
ويكون مفعولها طبعاً اسرع

Sources

ننتبه انو هون يعتبر nitroglycerinorganic
صح نستخدمه للعلاج وكمان بستخدمه بالمتفجرات لانه
بسرعه ينفجر
هسا الي يصير انو بسرعه يتأكسد ولما يتأكسد يطلع غازات
كثير سامه

A. Nitrates (organic):

- Organic nitrates such as nitroglycerin also are used in explosives....
-where the rapid oxidation of carbon compounds liberates large volumes of gases

Sources

A. Nitrates (inorganic):

✓ **Potassium nitrate, sodium nitrate:** (white crystalline salt, water soluble)

- Food additive to preserve color
- Fertilizers
- Explosives
- Occur naturally in root vegetables spinach, carrots, cabbage and in some well water

هدول بالاكل موجودين
وبالاسمده والمتفجرات وموجود بالجزر(الأطفال
عرضه لتسمم ب النايتريت لانه هاد الجزر نهرسه
للأطفال بكميات محترمه)ر والسبانخ
ومياه البير

❖ Gunpowder: mixture of sulfur, charcoal, and potassium nitrate

وهلول يدخلو بتركيب ابارود كمان

❖ Rapidly absorbed through gastric mucosa and excreted unchanged in urine

بسرعه يتم امتصاصهم ويتم
افرازهم زي ما هم عن طريق
urine

Sources

A. Nitrates (inorganic):

- ✓ **Bismuth sub-nitrate:** white powder insoluble in water
 - Antidiarrheal, antacid
- ✓ **Silver nitrate:** white powder with metallic taste
 - Used for its astringent and disinfectant properties
 - Paste form used to treat burns
- ❖ Both absorbed through the skin and the GIT
- ❖ Nitrate is converted to nitrite by intestinal bact....denitrification

بنستخدمه على الحروق ولما تكون
مساحه الحرق كبيره رح يزييد
امتصاصه وازيد السميّه وكمان اذا
اخذّه عن طريق ثمه انو orally

Sources

هو غاز وسميته من
خلال الاشتتاشاق

B. Nitrites (organic):

✓ **Amyl nitrite:** yellow volatile flammable liquid

- Used as antianginal
- Used to treat cyanide poisoning
- Used as drug of abuse (“poppers” induces a brief euphoric state)

معناها الناس الي يضلوا
يزيدو الدوز ونخاف منهم
لانو يعمل تسمم بكل
واضح

❖ Absorbed most rapidly by the lungs

❖ Inactive when taken by mouth....rapidly hydrolyzed

Sources

B. Nitrites (organic or inorganic):

✓ Isobutyl nitrite:

- Rapidly absorbed into circulation through mucous membrane and rapidly hydrolyzed

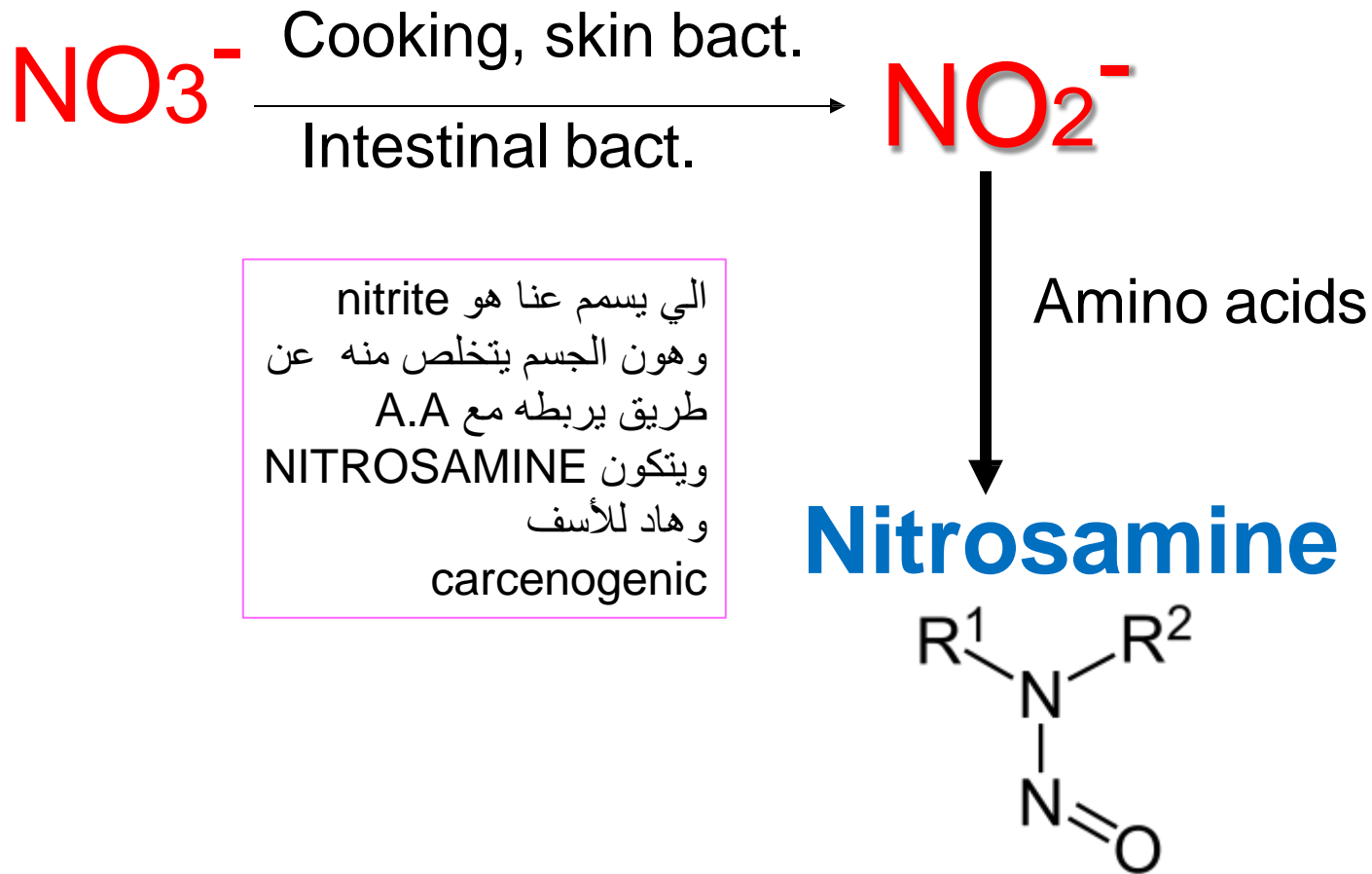
معطرات
الجو

- Room deodorizer
- Inhaled for abuse purposes

✓ Sodium nitrite:

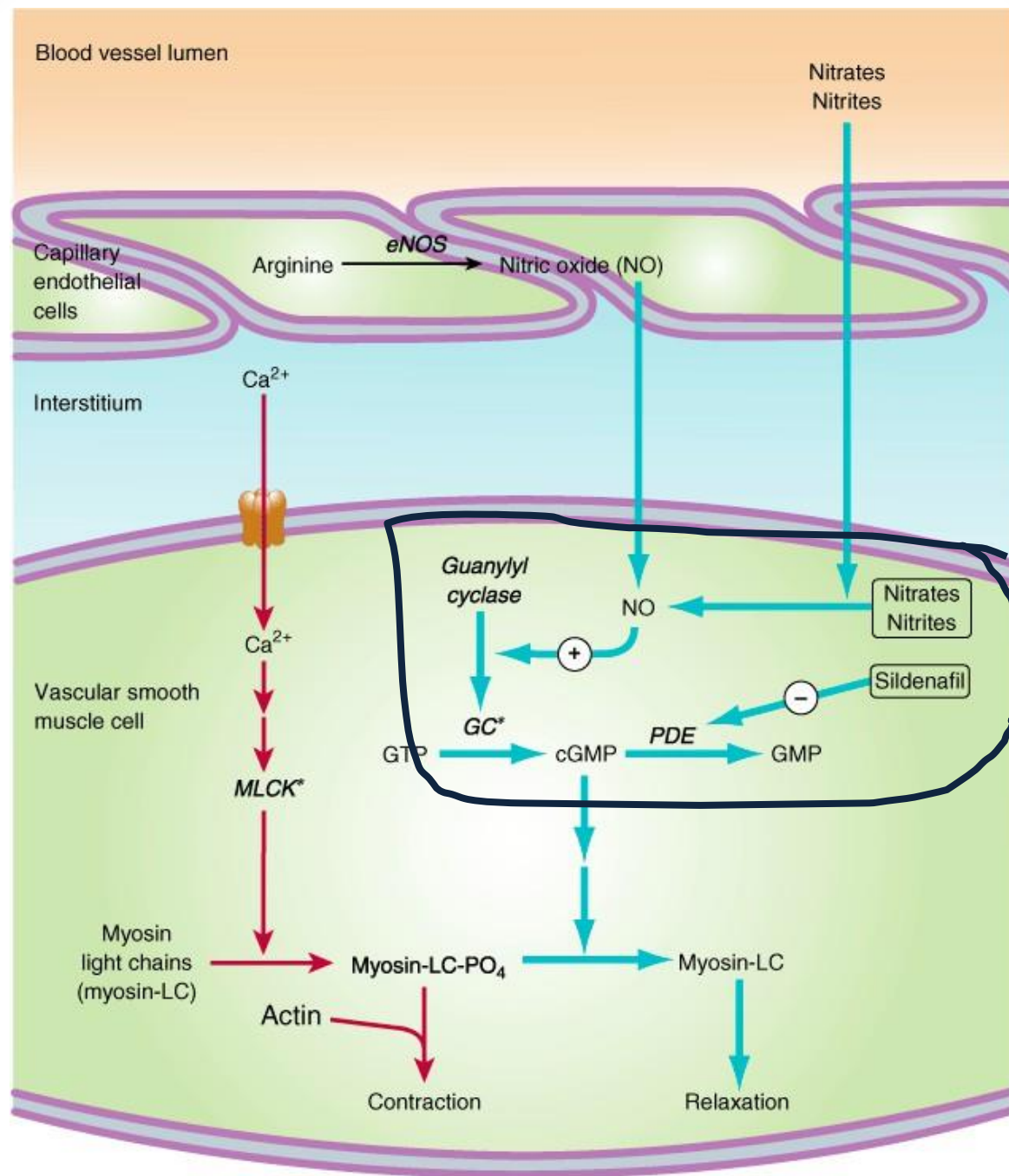
- Used to treat cyanide poisoning
- Reduce burn infection

❖ Nitrate is converted to nitrite by intestinal bact....denitrification



Mechanism of toxicity

- The major acute toxicities are extensions of therapeutic vasodilation
- Nitrates and nitrites **activate guanylate cyclase** and **increase the synthesis of cGMP**
- cGMP dephosphorylate the myosin light chain causing **smooth muscle relaxation**...all smooth muscle
- **Relax veins at lower doses and arteries at higher doses**



Mechanism of toxicity

- Toxic dose produce intense vasodilatation and precipitate:
 - Orthostatic hypotension
 - Reflex tachycardia
 - Cardiogenic shock
 - Throbbing headache

لما يصير الهبوط بالضغط احسن اشي الواحد
يعمله يتمدد ويرفع اجريه وبتتقع يصير كمان
زياده بدقات القلب ولما يقل الاكسجين عن
القلب رح يصير carcinogenic shock
ويقل الاكسجين على الدماغ ويصير راسه
يوجعه

Mechanism of toxicity

نحكي عن الناس الي بالمصانع ف ممكن يتعرضو لسيانيد فتره طويله عن طريق inhalation وهيك يصير معهم vasodilation

فهدول الناس خلال أسابيع يصير معهم tolerance كل يوم هاد المريض لازم يكون عنده اقل شي 12 ساعه ما يوخذهم مثلا اخذهم 12 الظهر تكون المره الثانيه على 6 المسا وهيك نعمل هيك حتى يروح tolerance

- Workers or patients regularly exposed to nitrates may develop tolerance:

- “Monday disease”**.....can occur in chemical industry, the workers suffer for **headache, dizziness** that disappear the next day coz of tolerance

- May suffer **angina** or **myocardial infarction** owing to **rebound coronary vasoconstriction** upon sudden withdrawal of the drug

معرضين
لهي
المشاكل

هسا هذول العاملين لما صار معهم tolerance لما روجو على البيت راح ال tolerance لانه صار معهم walwithdra tolerance ولما يرجع المصنع رح يرجع يستنشقههم ويصير معه tolerance وهبوط بالضغط

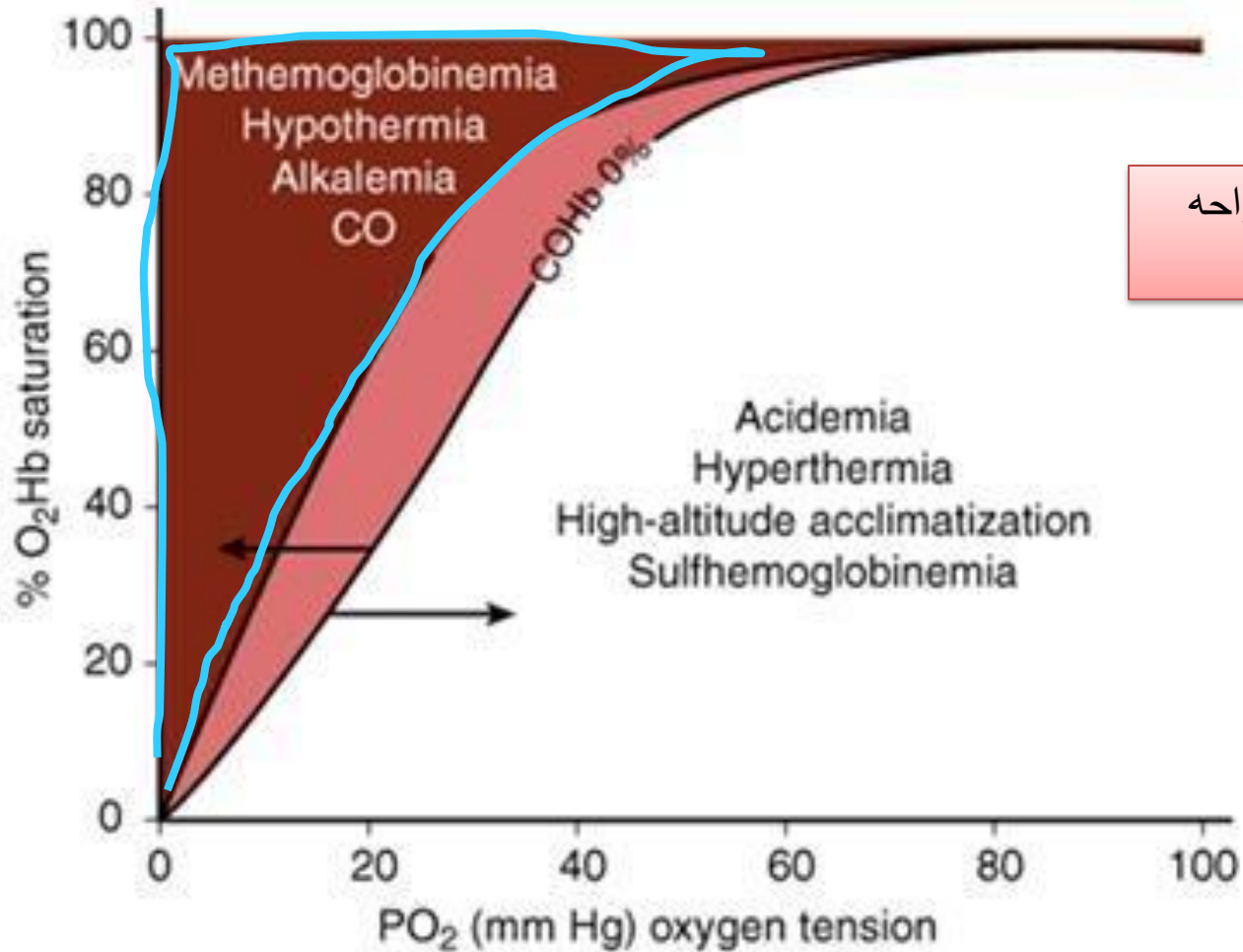
Mechanism of toxicity

- 1- vasodilator
- 2- methemoglobin

هون انا عندي جزء من
ferrous ferric يتحول الى وها
ما يربط مع الهيموغلوبين اذا ما
يرتبط يعني فش اكسجين يربط

- **Methemoglobinemia:**
- **Nitrites** are potent oxidizing agents
- Oxidation of the ferrous iron (Fe^{2+}) into ferric (Fe^{3+}) producing **methemoglobin**
- Iron in the ferric state is **incapable of binding oxygen**
- The conformity of methemoglobin causes the affinity of the remaining hemes to be increased....cause a **shift to the left of the oxyhemoglobin curve** (such CO) and consequently **impairs unloading of oxygen to tissue**

مش
مطلوب
حكت ما
تجيب
هيك



هون صار ازاحه
لليسا

Source: Nelson LS, Lewin NA, Howland MA, Hoffman RS, Goldfrank LR, Flomenbaum NE: *Goldfrank's Toxicologic Emergencies*, 9th Edition: <http://www.accessemergencymedicine.com>

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Mechanism of toxicity

- **Methemoglobinemia:**
- The skin is **cyanotic** even at levels low enough for the individual to be otherwise asymptomatic (eg, 15%)
- Use of **selective phosphodiesterase inhibitors** can prolong and intensify the vasodilating effects of nitrates, causing severe **hypotension**

صار معه هبوط بالضغط طيب
ممکن یزید وضعه سوء هاد
وهاد یعمل vasodilation ویزید
اکثر من هبوط الضغط

ممکن ما یبین الاعراض ولكن على
15% یبلش لون الجلد یصیر ازرق
وعلى 70 خلص ودع

Methemoglobinemia

- Methemoglobinemia does not cause hemolysis directly
- However, **hemolysis** may occur in particular patients with low tolerance for oxidative stress
- **Infants, pregnant women** and persons with **congenital NADH-methemoglobin reductase deficiency** or **G6PD deficiency** have an impaired ability to regenerate normal hemoglobin and are therefore more likely to accumulate methemoglobin after oxidant exposure
- **Infants in particular:**
 1. **Hb fetal is more oxidizable**
 2. **Hepatic microsomal enz incompletely developed (diaphorase I is less active)**

هنا هاد الميث يكون
عالي عند الناس الي
عندها oxidation
سهلو
وممكن يعمل
hemolysis وبالا
صل ما لازم يعمل
هاي تصير عند
enfant
ولان الانزيم تبعت
liver امش مكتمله
وكمان الناس الي
عندها تقول عرضه
للاصابة
وكمان NADH

Clinical Presentation

1. History:

A. Oral ingestion:

- Unintentional vs Intentional

- **Babies given concentrated vegetable juice** (spinach, carrots).....convert nitrate to nitrite, metHb and their hemoglobin is more susceptible to oxidation than is that of adults

- **Contaminated water** (limit of nitrate ion is 45mg/L in drinking water)

- The estimated adult lethal oral dose of nitroglycerin is **200–1200 mg**.....hypotension occurs at low doses, but massive doses are required to produce methemoglobinemia

في عنا ناس تبلع النايتريت
وهولنوعين الي يكونو قاصدين وفي
الي مش قاصدين
الي مش قاصدين بالغالب هم الأطفال
لانو حكيئا يكون بالسبانخ بالجزر
وهيك يصير معهم ميثيموغوبين

على الجرعه القليله يعمل هبوط بالضغط
على العاليه يعمل ميثيموغلوبين

Clinical Presentation

1. History:

A. Oral ingestion:

- **Unintentional vs Intentional**
- **Suicide attempts** with oral antianginal drugs or ingestion of **butyl nitrite**...lethargic disoriented, comatose and cyanosis
- Ingestion of as little as 15 mL of butyl nitrite produced 40% methemoglobinemia in an adult
- The estimated adult lethal oral dose **of Na nitrite** is 1g
- Ingestion of 2 to 10 mg of **silver nitrate** may be fatal....associated with black vomitus

Clinical Presentation

1. History:

A. Inhalation:

- Unintentional vs Intentional
- Workers bottling isobutyl nitrite
- Amyl nitrite and isobutyl nitrite **abused** for recreational purposes
- Symptoms: dizziness, lightheadedness, heart pounding, feeling warm, blurred vision

DIAGNOSIS

- Hypotension with reflex tachycardia
- Depending on % of total metHb, the clinical picture is that of oxygen deprivation
- Dizziness, and nausea,
- Cellular hypoxia including headache
- Progressing to dyspnea,
- May be agitated...confusion, seizures, and coma
- Even at low levels, skin discoloration ("blue/chocolate cyanosis"), especially of the nails, lips, and ears, and warm skin



Table 2. Signs and Symptoms of Methemoglobinemia

Methemoglobin Concentration (%)	Clinical Findings
10–20	Central cyanosis of limbs/trunk; usually asymptomatic
20–45	Central nervous system depression (headache, dizziness, fatigue, lethargy, syncope), dyspnea
45–55	Coma, arrhythmias, shock, convulsions
>70	High risk for mortality

From Dabney et al. (1990).

- Normally meth Hb is about 1-2%
- Immediate treatment to relief symptoms; if untreated cardiopulmonary arrest due to asphyxiation

Laboratory analysis:

يصير TACY وبعدين Brady
السبب لانه تكيا بدها طاقه وانا حتى اقلل
من الاجهاد والحاجه لطاقه بيصير بردي

- Arterial blood gases show an **acidotic pH**
- ECG reflects degree of hypoxemia, beginning with **tachycardia**, and advancing to **bradycardia**, and ultimately **asystole**
- Toxicology screen frequently show presence of **cocaine, ethanol, marijuana.....abuse substances**
- Serum metHb levels must be determined...need time
- Good, rapid & rough test...drop of blood on filter paper if remained **brown....metHb of > 15%**
- **Comatose patients usually metHb > 30%**

اهم شي بشوف الميثيموغلوبين
كيف بجيب فلتر بيبير وبخط عليه نقطه دم اذا تحول لونها
ل بني بيكون اكثر من 15 بالميه

TREATMENT....ABC

1. Maintain an open airway and assist ventilation if necessary. Administer **supplemental oxygen**
2. **Cardiovascular support:**
 - A. Keep warm
 - B. Treat **hypotension** with supine positioning (lying down)
 - C. **i.v. saline** to support B.P
 - D. **low-dose pressors if needed (dopamine)**
 - E. **Atropine for bradycardia**
 - F. Monitor vital **signs and ECG for 4–6 hours**
3. **Seizures: diazepam, phenytoin**
4. **Hyperbaric Oxygen.** supply sufficient O₂ independent of hemoglobin

DECONTAMINATION

4. **Inhalation.**
5. **Skin.**
6. **Eyes.**
7. **Ingestion.** Administer **activated charcoal** orally if conditions are appropriate
8. **Gastric lavage is not necessary** after small to moderate ingestions
9. **Enhanced elimination.** Hemodialysis and hemoperfusion are not effective

TREATMENT.....Antidote

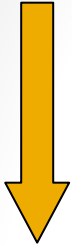
حتى اتخلص من الميثيموغلوبين
بعطيه ميثيلين بلو بس هاد ما
بزيط لناس الي معهم تفول

- **Methylene blue** is a thiazine dye that increases the conversion of methemoglobin to hemoglobin
- a. Methylene blue is reduced via methemoglobin reductase and nicotinamide adenosine dinucleotide phosphate (NADPH) to *leukomethylene blue*,
- b. which in turn reduces methemoglobin
- c. **Glucose-6-phosphate dehydrogenase** is essential for generation of NADPH and is thus essential for the function of methylene blue as an antidote

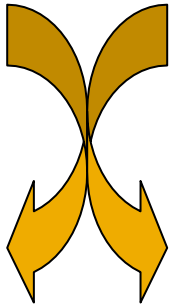
هاد الميثيلين بلو بدو NADH ليتحول
وهاي NADH لحتى يصير لها
reduction بدھا G6P

الميكانيزيم مش
مطلوب يكفي
نعرف الي كتبتهم
انا بالمختصر

G6PD



NADPH



NADP⁺

Methemoglobin
reductase II
(ox.)

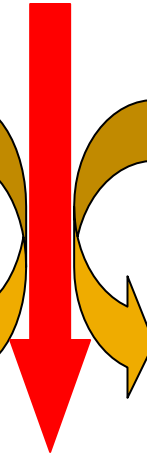
Methemoglobin
reductase II
(red.)



Methylene
blue (red.)

Methylene
blue (ox.)

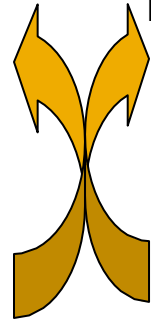
Meth Hb



Hb

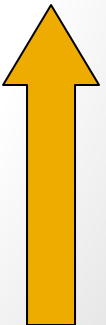
Methemoglobin
reductase I
(red.)

Methemoglobin
reductase I (ox.)

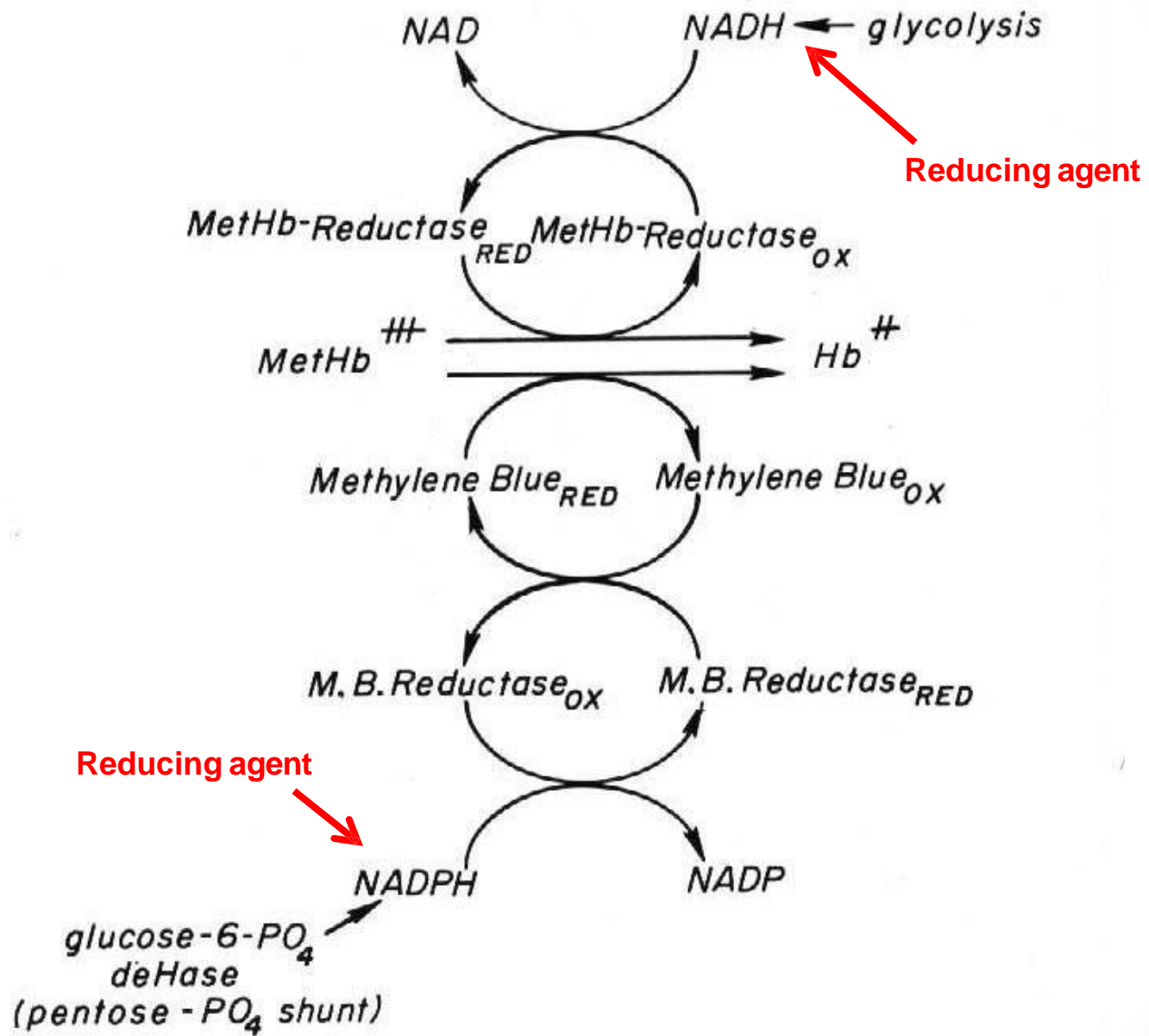


NAD⁺

NADH



Glycolysis



TREATMENT.....Antidote

بعطي هاد البلو لناس
الي وصلت نسبه الميث
بدهم اكثر من 20 بالميه

- a. If methemoglobin >20%.....inject **methylene blue** (1 to 2 mg/kg i.v infusion over 5min)...repeat once
- Generally **well tolerated**
 - Patient needs to **have normal G6PD**
 - **Excreted in bile and urine...feces and urine discoloration**
 - **Anemia**
 - **HTN**
 - Therapeutic **effect is seen within 30 minutes**

TREATMENT

- Severe **methemoglobinemia in infants** not responsive to methylene blue therapy may require **exchange transfusion**

عند الأطفال صعب اعطي ميثيلين
بلو لذلك الحل الاحسن ببذل دمهم
وبعمها لناس الي ما استجابو للبلو
هاد خلال ساعه

- ✓ Also in patients....
 - Not responding to methylene blue within 30-60min
 - G6PD deficient patients
....contraindicated, may cause hemolysis
 - Severe renal failure
 - If metHb higher than 70%



اڤلن بعد المذاكره الي بنذاكرها دي
الي هيقتولي اعاليجه ببلاش يخلي باله من نفسه