

Hypotensive Agents

I. Physiology of Contraction

Smooth muscle contraction differs somewhat from skeletal muscle. Ca^{++} is involved in the initiation of contraction as it is in skeletal muscle. However, the myosin in smooth muscle must be phosphorylated for activation of the myosin ATPase. Phosphorylation and dephosphorylation of myosin also occurs in skeletal muscle, but phosphorylation is not necessary for activation of the ATPase. In smooth muscle, Ca^{++} binds to calmodulin, and the resulting complex activates myosin light chain kinase, the enzyme that catalyses the phosphorylation of myosin. Actin then slides on myosin, producing contraction. This is in contrast to skeletal and cardiac muscle, where contraction is triggered by the binding of Ca^{++} to troponin C.

Relaxation occurs via dephosphorylation of myosin (except where “latch bridges” occur).

Whilst contraction and relaxation all occur ultimately via the increase or decrease in $[\text{Ca}^{++}]$ intracellularly the manner by which this is achieved differs. Vascular smooth muscles behave differently whether the endothelium is intact or not. It is necessary to consider both of these when deciding the effects of a given drug or substance. Endothelium derived relaxing factor (EDRF) - which is now known to be Nitric Oxide (NO) - is released by the endothelium in response to a variety of factors and plays a major role in the tone of the underlying smooth muscle.

The recognition of the role of NO has allowed us to explain a number of otherwise confusing observations e.g. ACH is a vasoconstrictor in vitro but a vasodilator in vivo (ACH causes NO release).

II. Nitric Oxide

A. Pharmacology

1. Physical and Chemical Properties

Gaseous in solution, highly lipid soluble, highly diffusible.

2. Pharmacokinetics

Half life is very short (3-5 seconds in oxygenated, aqueous medium) i.e. very labile with rapid inactivation

In solution, rapidly oxidised to nitrite and nitrates.

In gas, oxidised to nitrogen dioxide and higher oxides of nitrogen

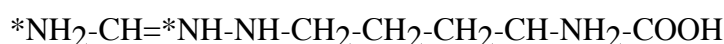
Inhibited by haemoglobin, myoglobin, methylene blue, and superoxide anion

Potentiated by superoxide dismutase, cytochrome C, and H^+

3. Biosynthesis

a) Pathway

Precursor: L-Arginine (main) with oxidation of terminal guanido-N* atoms of arginine facilitated by NO synthase (dioxygenase)



c) Nitric Oxide Synthase

Dioxygenase enzyme which converts L-Arginine to nitric oxide by incorporating molecular oxygen to terminal guanido N atom of arginine.

3 iso-enzymes:

(1) Constitutive

Endothelial (eNOS) present in normal endothelium and platelets
Neuronal (nNOS) present in the CNS

(2) Inducible (iNOS)

NO synthase induced in macrophages, neutrophils and Kupffer cells activated by interferon-1, tumour necrosis factor amongst others.
Production inhibited by glucocorticoids.

Similarities

Dioxygenase

Present in cytoplasm

NADPH dependent

inhibited by L-Arginine analogues e.g. L-NMMA (N^G-monomethyl arginine), L-NAME (N^G-nitro-L-arg-methyl ester), L-NA (N^G-nitro-L-arg), and L-NIO (N^G-iminoethyl-L-ornithine)

Differences

<u>Constitutive</u>	<u>Inducible</u>
Naturally present in soluble +? particulate form in cytoplasm	Only present in macrophages, neutrophils, and Kupffer cells activated by interferon-1, lipopolysaccharide, TNF
Ca ²⁺ /Calmodulin dependent	Ca ²⁺ /Calmodulin independent
Transient release (mins)	Sustained, long lasting release (10 hours)
Very small amounts (picomoles)	Larger amounts (nanomoles)
Not affected by glucocorticoids	Inhibited by glucocorticoids

Molecular Effects of Nitric Oxide

NO is either created outside the smooth muscle cell and diffuses in (e.g. when created in endothelial cells) or is produced inside the smooth muscle cell (e.g. as with SNP or TNG)

The NO then binds with the heme group on soluble guanylate cyclase to cause enzyme activation and the breakdown of MgGTP to form cyclic-GMP. Cyclic-GMP acts on the sarcoplasmic reticulum to increase uptake of Ca⁺⁺ producing muscle relaxation.

see attached diagram

4. Physiological roles

a) Endothelial cell-blood vessel interaction

(1) Basal Tone and Secretion

Vasodilator tone is highest in arterioles and lowest in veins. Induced vasodilation due to increased NO secretion is caused by increased flow and increased shear stress.

(2) Sensitivity

veins are more sensitive i.e. able to dilate to a greater capacity due to higher content of soluble guanylate cyclase.

(3) Autoregulation (local) due to flow and shear stress

(4) Pulmonary circulation

pulmonary hypoxic vasodilation due to decreased synthesis and release of NO due to hypoxia.

b) Platelet Interaction with Blood Vessel

(1) Generation of NO in platelet via L-arginine-NO pathway

(2) Basal release of NO by platelet and endothelium

Inhibits platelet adhesion to collagen and aggregation. Processes associated with increased cyclic GMP

see attached diagram

(3) NO-autocrine negative feedback mechanism to regulate platelet reactivity

regulates platelet reactivity

III. Drugs

A. Sodium Nitroprusside (SNP)

1. Vasodilator used for induced hypotension and control of blood pressure

2. History

First described in 1849. It was first used in animals in 1887 and in man in 1929. It was not until 1951-5 that it was used clinically by Page in a variety of hypertensive crises. By 1959 it was recognised as an effective treatment of malignant hypertensive. It was only in 1974 that an approved sterile form was available in the USA. Its potential toxicity was first recognised in 1886 when it was noticed by Hermann that the characteristic "bitter almond" odour of cyanide poisoning could be detected in the livers of animals after oral administration of nitroprusside.

3. Physical and Chemical Properties

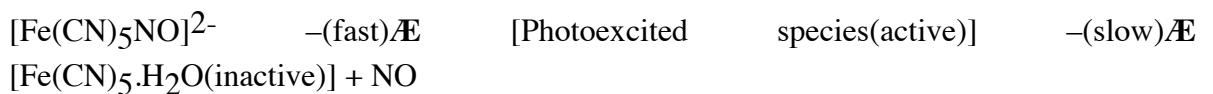
Sodium Nitroprusside has the molecular formula $\text{Na}_2\text{Fe}^{++}(\text{CN})_5\text{NO}\cdot 2\text{H}_2\text{O}$ and a MW of 297.9. It contains 44% cyanide by weight. The iron atom lies centrally, with one nitrosyl

and five cyanide groups disposed around it at the apices of an octahedron. Its red-brown crystals are formed by a lattice of these units, within which are trapped sodium atoms and water molecules. The crystals are soluble in water (40gms in 100ml in 16°C) the solution having a light pink-brown colour. It is available as 50mg of freeze-dried powder in an amber coloured, rubber -stoppered 5ml vial. It is unstable with exposure to light or alkaline solutions.

50mg is usually mixed in 500ml of either 0.9% NaCl or 5.0% Dextrose.

The stability to light depends on the strength of the light and to its colour. It is quite stable to red light, blue light produces maximal decay and white light inbetween. With white light at standard room strength ($20\mu\text{W}\cdot\text{cm}^{-2}$) $\approx 45\%$ has decayed by 6hrs but only 0.5% of the total CN^- is actually release during this same time.

Photodegradation



It is therefore usually recommended that once it is prepared that it be shielded from room light.

I think that this is still somewhat controversial because the degradation in-vitro (for short term infusions) does not release clinically important amounts of cyanide and the hypotensive effect of the solution is unaffected. The photodegradation presumably produces a compound that has an intact iron-nitrosyl complex and that this must be broken before cyanide is released. The breakdown of this intermediate compound by light is much slower. Under the same conditions only 0.5% of total cyanide is released by 6hrs. Despite this Arnold et al who performed these experiment adopted the conservative approach of recommending to still either cover the solution or use red coloured plastics. As an aside the red colour of blood prevents breakdown of nitroprusside so that if one takes blood for a cyanide assay it is not necessary to shield the sample. Apparently if marked degradation has occurred the solution changes to a blue colour due to the reduction of the iron atoms (from ferric to ferrous).

see attached diagrams

4. Pharmakokinetics

a) Administration/Disposition

It is a highly ionised substance and therefore has a volume of distribution that is approximately equal to the ECFV. Protein binding is not mentioned in any of the texts I looked at and I presume is limited. It is only given by intravenous solution due to it's extremely rapid metabolism and short half life (several minutes). It should only be given by a controlled infusion.

b) Metabolism

The metabolism of Nitroprusside is unclear. Most textbooks quote the diagram of Tinker and Michenfelder from 1976 (attached) in which it is purported that the initial breakdown is the non-enzymatic transfer of an electron from oxyhaemoglobin to

produce an unstable nitroprusside radical that rapidly breaks down to release the 5 CN⁻ ions. The methaemoglobin that was formed from the oxidation of oxyhaemoglobin combines with one of these to form cyanmethaemoglobin. The majority of what remains is rapidly metabolised by liver and kidney rhodanase to Thiocyanate. This reaction is dependent on the presence of sulphur donors (usually cysteine) and this is the rate limiting step in the metabolism of CN⁻. Any cyanide that is not rapidly converted to thiocyanate is available to bind with cytochrome oxidase leading to its inactivation, cessation of oxidative phosphorylation, and tissue (histotoxic) hypoxia.

Thiocyanate is cleared slowly by the kidney with an elimination half life of 4-7 days. Thiocyanate is itself toxic but much less so than cyanide. It accumulates with chronic usage or in the presence of renal failure. If the plasma concentration exceeds 10mg/dl then there may be skeletal weakness, nausea, and mental confusion. Prolonged elevations may lead to hypothyroidism as it interferes with iodine transport in the thyroid. Oxyhaemoglobin can slowly oxidise thiocyanate back to sulphate and cyanide but this is insufficient to cause cyanide toxicity.

The problem with this neat scheme is that it does not fit with many of the observations. The metabolism of nitroprusside is complete within minutes in haemoglobin solutions but has a half-time of 20 minutes with intact RBCs (and only with high [SNP] (Vesey et al 1976). Bisset et al (1981) demonstrated that if nitroprusside is incubated with blood in darkness for 90 minutes less than 0.5% is degraded and Arnold et al (1984) showed that Nitroprusside was stable in blood in or out of light for 4 hours. Regardless of the differences between these studies nitroprusside obviously degrades in vivo at a very much greater rate (half life in the order of several minutes) so that the initial site of metabolism is clearly not via haemoglobin.

Bates et al (1991) showed that nitroprusside needed the presence of tissue (rabbit aorta, subcellular fractions of aorta, and human plasma) to degrade and release nitric oxide. This occurs after nitroprusside has undergone reduction and lost CN⁻.

Rao et al (1991) demonstrated much greater reductive metabolism in rat hepatocytes than human erythrocytes. The metabolism was by a cytochrome P450 reductase and not by other cytochrome P450 enzymes.

Devlin et al (1990) showed more rapid metabolism of nitroprusside by isolated, perfused, bloodless liver and hindlimbs of the rat than incubations in blood. Metabolism was more rapid in the liver.

Shafer et al (1989) felt that the major metabolism occurred via an unknown reaction in various vascular beds.

Overall the reaction is probably the same but the trigger in vivo is not likely to be haemoglobin. Once the CN⁻ is released the metabolism is as described.

The release of CN⁻ is not affected by hypothermia but the metabolism of CN⁻ to SCN⁻ is delayed (Moore et al 1985).

c) Mechanism of Action

It is the release of nitric oxide which produces the vasodilation.

NO activates guanylate cyclase, increasing cAMP, and decreasing intracellular Ca⁺⁺ leading to smooth muscle relaxation.

Note that this mechanism differs somewhat to that of nitroglycerin (see later)

5. Systems Effects

a) CVS

Decreased SVR (primary site of action appears to be on the 4th order pre-capillary arterioles.

lesser effect on veins

Increased HR (reflexly) which may counteract the fall in BP due to the decreased SVR

Cardiac output either increases or stays the same in people with normal cardiac function. In people with LVF CO usually increases due to the reduction in afterload and decrease in ventricular size.

Myocardial perfusion may be worsened due to shunting (steal). SNP may increase infarct size (steal and increased HR).

No direct inotropic or chronotropic effects.

b) CNS

(1) ICP

Increased unless MAP is reduced by more than 30% (below normal pressure not reduced from a hypertensive baseline). Marked increases can occur if used to control hypertension.

Vasodilator action primarily act on capacitance vessels

The faster the fall in MAP the greater the initial increase in ICP.

(2) CBF

Effects on CBF are variable, depends on the effect on MAP

If MAP increases (i.e. being used to treat hypertension) marked increases may occur. If MAP remains the same some increase is likely.

If MAP fall then it also depends on the degree of hypotension. CBF is maintained best with SNP (better at marked hypotension <40mmHg, than Trimetaphan (TMP)). MAP <50mmHg are associated with falls in CBF (the exact effect depends on the patients autoregulatory responses). One can interpret the greater CBF with marked reductions in MAP than with TMP as indicating supraphysiological vasodilation (analogous to the effect of dipyridamole on the coronary circulation).

Interferes with autoregulation in a dose dependent fashion.

c) Respiratory

Interferes with hypoxic pulmonary vasoconstriction in a dose dependent manner. It is not uncommon to have to increase the inspired oxygen concentration when induced hypotension is used. This effect will be magnified if there is a greater degree of HPV present.

d) Endocrine system

(1) pituitary, adrenal cortex/medulla

(2) thyroid

(3) pancreas

(4) ADH/vasopressin

e) Blood

Potent inhibitor of platelet aggregation but no evidence of increased bleeding. Presumably it is reversible inhibition.

f) Placenta

Foetal toxicity has been described but only when toxic doses are used ($>10\mu\text{g}/\text{kg}/\text{min}$). Low doses are safe for the control of hypertension but because uterine blood flow is pressure dependent induced hypotension will cause foetal compromise and should not be used.

6. Clinical Uses

a) Doses

For normal people

Infusion rate $<8\mu\text{g}/\text{kg}/\text{min}$

Total dose 1.5mg/kg (short term), 0.5mg/kg/hr (chronic infusions)

These total dose recommendations are Michenfelders and some simple mathematics would seem to render them superfluous. The chronic infusion rate works out to be greater than the acute infusion rate ($8.33\mu\text{g}/\text{kg}/\text{min}$!). It would seem that the simple rule is avoid any infusion rate $>8\mu\text{g}/\text{kg}/\text{min}$ and monitor chronic infusions for signs of increased anaerobic metabolism.

Blood gases (?4hrly) and daily SCN levels are indicated for chronic infusions.

I wonder as an aside whether it is ever indicated to use a SNP infusion for more than 1-2 days, perhaps in this setting longer acting agents are indicated at least for baseline vasodilation.

Rebound is common after it's use. Relates to activation of the renin-angiotensin system. It can be moderated by β -blockers and angiotensin converting enzyme inhibitors. More marked with rapid discontinuation.

b) Cyanide Toxicity

$\approx 24\text{mg}$ of absorbed cyanide can be fatal (c.f. 22mg of available cyanide in 50mg of SNP!)

(1) Signs

Resistance of SNP is a common early sign. The exact mechanism is unclear.

Increased anaerobic metabolism lead to increased BE, and increased [lactate]

It is important to remember that [SCN] gives absolutely no indication of cyanide toxicity

(2) Increased sensitivity

B12 deficiency

Abnormalities of B12 metabolism eg Lebers Optic Atrophy, Tobacco Amblyopia

Impaired liver function

(3) Prophylaxis

hydroxycobalamine and Na Thiosulphate have both been used

(4) Treatment

Sodium Nitrite (to produce methaemoglobin) 10mls of a 3.0% solution

Sodium thiosulphate 150mg/kg

Hydroxycobalamine 1gm per 50mg of SNP (this is a very large amount and it is an expensive drug)

Cobalt Edetate 300mg increments

B. Nitroglycerine

1. Vasodilator

Used for induced hypotension and control of blood pressure, it is also used in the treatment of myocardial ischaemia

2. History

1846 first synthesised by Sobrero. He also described its cerebral vasodilator effects (unwittingly) by noting that when he put it on his tongue it caused headaches.

1847 it was used sublingually for the treatment of a number of diseases.

1857 Amyl Nitrate used for the treatment of angina

1879 Sublingual nitroglycerine used for angina

1975 IV TNG first used

1980s Commercial form of IV TNG became available "Tridil"

3. Physical and Chemical Properties

Glyceryl Trinitrate

CH₂- O-NO₂

CH- O-NO₂

CH₂- O-NO₂

Pale yellow oil MW 227.09

Specific Gravity 1.6

Melting Point 13.2°C

When absorbed in diatomaceous earth it is known as dynamite!

Tridil is 50mg/5ml (0.5%) in H₂O with 30% v/v ethanol and 30% v/v propylene glycol as stabilisers.

It is a clear, practically colourless liquid soluble in water only in weak solutions and is non-explosive at those concentrations.

It is light stable.

4. Pharmakokinetics

Vd ≈ 200l

t_{1/2} 1-4 minutes

Plasma protein binding (50-500ng/ml) ≈ 60%

a) Metabolism

Hepatic degradation

Denitration by glutathione organic nitrate reductase

TNG → glyceryl dinitrate
glyceryl mononitrate
inorganic nitrite

All these are water soluble and weak vasodilators.

They are all renally excreted

Nitrite Æ methaemoglobin (slight with TNG)

TNG and it's metabolites essentially non-toxic

b) Administration

Absorbed: transcutaneously, sublingually, intravenously, and intramuscularly

First pass metabolism is nearly 100% and it is therefore not active orally

Dilute in 0.9% NaCl or 5% Dextrose.

Binds to PVC plastics so it is necessary to use glass bottles or polyethylene burettes for dilution and polyethylene plastics for the infusion sets.

c) Mechanism of Action

Acts via NO

Slightly different pathway to SNP. This explains some of the differences between the two as well as the occurrence of tolerance to nitrates.

Nitrates need to be converted to inorganic nitrite.

R-SH (reduced) -----> R'-SS-R' (oxidised)

RONO₂ -----|-----> NO₂⁻ -----> NO

Depletion of reduced sulphydryl groups R-SH leads to tolerance

see attached diagram

5. Systems Effects

a) CVS

Vasodilator, venous > arterial

marked reduction in preload, lesser reduction in afterload

cardiac output is little changed (unless ischaemic dysfunction is corrected in which case it may increase)

Improves the supply/demand ratio for the heart (reduction in preload/afterload)

Heart rate increases but less than with SNP

Myocardial perfusion improved by increased endocardial perfusion. Acts to dilate large coronary conductance vessels thereby improving collateral flow and redistributing flow subendocardially (the subendocardium is the region of the heart most at risk for ischaemia). This contrasts with SNP which may be associated with steal.

Overall coronary flow may not increase.

May reverse coronary spasm.

Has no other direct cardiac actions.

b) CNS

Cerebral vasodilator ?venous > arterial

ICP increases consistently more than SNP

As with SNP the extent of the rise depends on the effects on MAP. Marked falls in MAP may be associated with no increase in ICP or a fall.

c) Respiratory

Abolishes HPV.

May have a more deleterious effect than SNP

Relaxes bronchial smooth muscle

d) GIT

Relaxes GIT smooth muscle

Relaxes sphincter of Odi

e) Haematological

Platelet function unchanged

6. Clinical Uses

Less satisfactory hypotensive agent than SNP as many patients resistant to its actions. Has a slower onset and offset than SNP. It causes much less rebound than SNP.

Mainly used for moderating blood pressure rises in patients with cardiac disease or those with myocardial ischaemia.

Doses are often quoted in $\mu\text{g}/\text{kg}/\text{min}$ but for induced hypotension one starts with 10mls/hr (50mg/500ml) and increase after observing the effects.

C. Trimetaphan

1. Ganglion blocker

Hypotensive and acute antihypertensive

2. History

1949 Randall et al first described

1953 First used in clinical practice as an induced hypotensive agent in the UK

3. Physical and Chemical Properties

Trimetaphan Camphorsulphonate

Thiophanium derivative

250mg of powder in a 5ml rubber stoppered vial

Stable for 24hrs once prepared

Incompatible with thiopentone, gallamine, strongly alkaline solutions, iodides, and bromides.

4. Pharmakokinetics

very short half life, in the order of minutes (slightly longer than SNP)

duration of action 5-10 minutes

Metabolised primarily by enzymatic hydrolysis, some is excreted unchanged in the urine.

Ganglion blocker primarily but also has some α -blocking properties and direct vasodilating effects. If given as a bolus will also cause some histamine release.

Inhibits plasma cholinesterase and may increase the duration of suxamethonium by 100%.

5. Systems Effects

Primarily due to ganglion blocking effects, so that the systemic effects depends on the dominant arm of the autonomic system.

a) CVS

Decreases MAP by arterial and venous dilation

Decreases SVR and Cardiac Output

Catecholamine and renin rises are much less than with SNP due to blockade of renal sympathetics therefore there is much less rebound.

HR increases due to loss of parasympathetic activity

Reductions in MAP may be associated with reduced coronary blood flow

b) CNS

No direct effects

Sudden decreases in MAP are associated with increased ICP. The exact mechanism is unclear ?histamine release, ?autoregulatory phenomenon

Slower falls in MAP are not associated with either increased cerebral blood flow or increased ICP.

When TMP is used to treat hypertension (i.e. to normalise the blood pressure) the ICP does not increase.

Cerebral Perfusion is well maintained (in the normal patient) down to a MAP of 50mmHg. It is maintained less well at pressures below this (cf. SNP).

The patients also develop cycloplegia which persists for 10-15 minutes after the cessation of TMPs use.

c) GIT

GIT Ileus has been reported but it is rare.

Hepatic blood flow is well maintained

d) GUT

Renal blood flow well maintained with reduced MAP.

6. Clinical Uses

Dilute in 125mls of 0.9% NaCl or 5% Dextrose

At this concentration use as for SNP/TNG i.e. start at 10mls/hr and increase as necessary. It has a slightly slower onset and offset than SNP and has limited rebound.

Not a good hypotensive agent as frequently it is ineffective at producing marked hypotension.

It is an ideal agent to use in neurosurgery to moderate the increases in blood pressure associated with surgical stimulation when it is preferred not to use “anaesthetic’ agents e.g. narcotics or inhalational agents as it has negligible effects on CBF and cerebral blood volume. If used for neurosurgery it is important to warn the recovery staff because the fixed and dilated pupils worry them a great deal even if the patient is talking to them!

It is very useful as an adjuvant to patients who are requiring large doses of SNP. It dramatically reduces the dose of SNP needed. A mixture of the two (TMP:SNP 10:1) has been studied and found to both minimise the dose of SNP and to reduce the rebound phenomenon.

D. Adenosine

1. Introduction

The adenine compounds are integral to the metabolism of all cells.

2. History

The vasodilator properties of the adenine compounds, adenosine and adenosine triphosphate were first described in 1929. They were first used for induced hypotension in 1959 in Japan by Hatano et al. In the 70’s further reports also originated from Japan.

Adenosine compounds appear to play a physiological role in autoregulation in some organs (e.g. brain and heart) Olsen et al 1982.

3. Physical and Chemical Properties

Adenosine and ATP belong to the class of compounds called purines.

Exact mechanism of action is unclear. They may produce preganglionic sympathetic blockade and they may have direct vasodilating properties on resistance vessels.

They are water soluble.

4. Pharmacokinetics

ATP is administered in a 10% solution at a rate of 0.2-0.6mg/kg/min.

It is converted so rapidly to adenosine that the major vasodilating effects are due to adenosine.

Adenosine has been used for neurosurgery at a dose range of 80-500 μ g/kg/min starting at 40 μ g/kg/min.

Half life is in the order of 10-30 seconds as blood pressure returns to normal within 1 minute after cessation of the infusion.

They have rapid metabolism and it is suggested that the site of metabolism is the endothelium. ATP is rapidly broken down to adenosine and phosphate ions by 5'-nucleotidase. Adenosine is metabolised to uric acid.

The doses needed can be reduced by giving a drug that blocks the uptake of adenosine e.g. dipyridamole.

The elevated phosphate and subsequent reduced calcium (and ?magnesium) may explain the high incidence of arrhythmias seen in ATP treated rats (n.b. these are not reported in humans).

5. Systems Effects

a) CVS

Reduces MAP by reducing SVR.

Cardiac output unchanged or increased

Heart rate is unchanged or slightly reduced

Little tachyphylaxis or rebound phenomenon

Renin and Catecholamine levels do not increase

Adenosine slows the heart rate by blocking A-V node conduction. This has been used to treat SVTs and may produce heart blocks during induced hypotension.

Coronary blood flow increases but left ventricular work in fact decreases slightly.

No reports of coronary ischaemia so presumably this does not produce a steal effect.

Filling pressures do not decrease much suggesting a limited effect on capacitance vessels.

b) CNS

In dog experiments it increases the ICP in dogs with both normal and elevated ICPs. It therefore should be treated the same as SNP/TNG in patients in which such elevations would be deleterious.

It has been used successfully for cerebral aneurysm surgery in which blood pressure control was reportedly good.

c) Respiratory

No specific reports

d) GIT

GFR is reduced and this potential for renal impairment will would be a factor against using it for induced hypotension.

6. Clinical Uses

It is reported to be a very controllable hypotensive agent with stable dose requirements for periods up to 120 mins. It has a slightly quicker onset and offset than SNP and has no rebound (presumably due to the lack of increased catecholamines and renin).

It is 1/40th the potency of SNP

It is available in Australia for the control of SVTs but I am unaware of anyone using it for induced hypotension.

Dose for SVT is by bolus 3mg and then 6mg two minutes later if the first dose is ineffective. It is also sometimes used to when a transient decrease in BP is needed to place endovascular stents. In this case 6-12mg boluses are used. This will decrease the BP by about 50% and lasts for 45-60 seconds.