USE OF S.N.P.AS A HYPOTENSIVE AGENT IN SEVERE HYPERTENSION ASSOCIATING P.I.H.

THESIS SUBMITTED FOR PARTIAL FULFILMENT OF M.SC.DEGREE (OBSTETRICS & GYNECOLOGY)

BY

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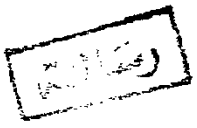

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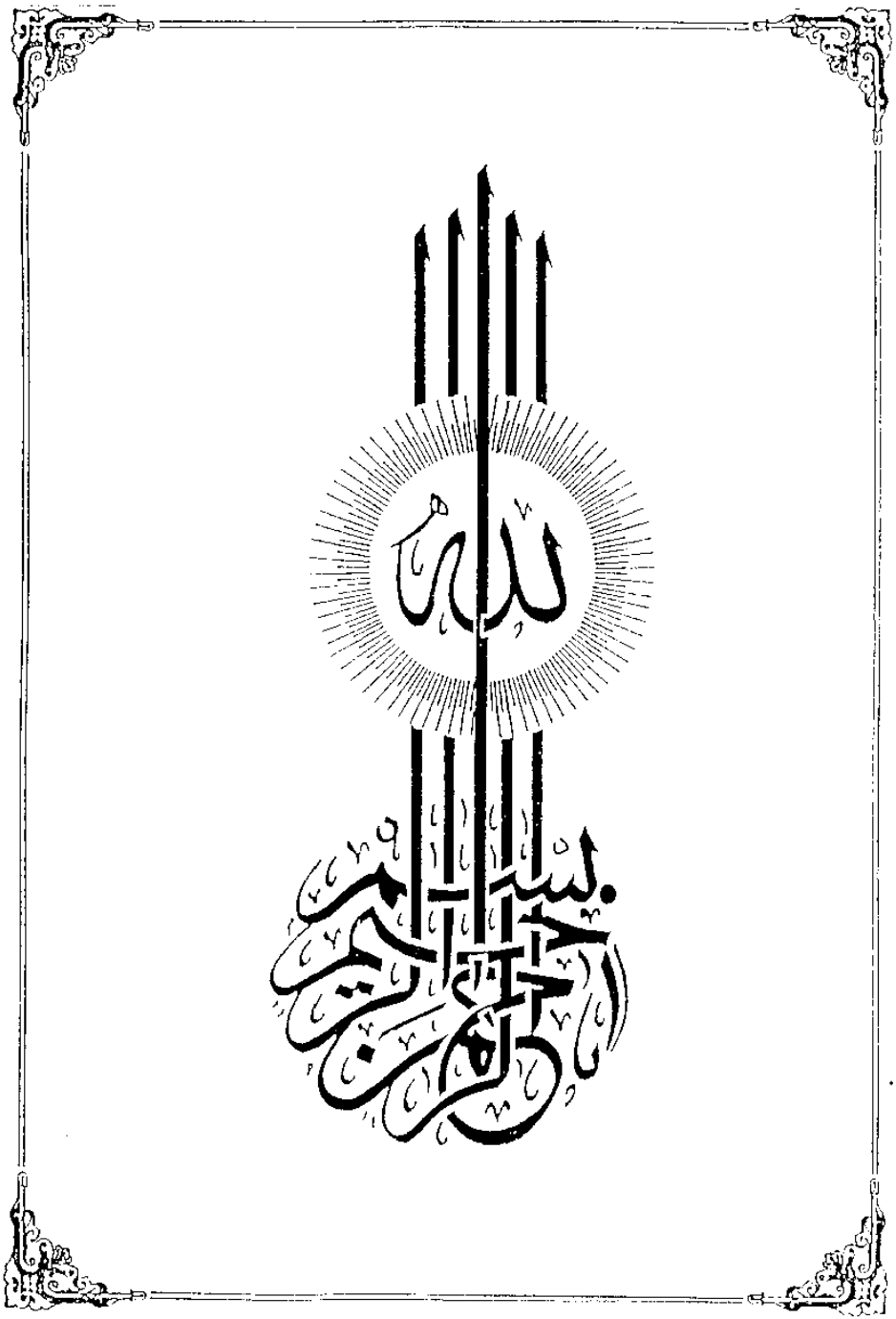

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The candidate..

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Review of the literature

SODIUM NITROPRUSSIDE (SNP)

HISTORICAL REVIEW

Nitroprusside has been known since 1850. It was used as colour indicator for acetone,adelhydes,alkali sulfides & sulfur dioxide.

The action of SNP was first described in 1886 by Hermann who attributed the toxic effects of the compound to the liberation of cyanogen in the organism .Hermann's student ,Davidson;(1887) as well as subsequent investigators also associated acute Nitroprusside poisoning with the liberated cyanide.

Hermann's erroneous concept remained unchanged untill Johnson (1928) in a preliminary report on the action & toxicity of SNP indicated that the toxicity of the compound was not due to the liberation of cyanogen.He believed that the earlier investigators,used large fatal doses,& postulated that the actions of smaller doses might be different or masked by the effects of the larger doses.Then in a series of further experiments Johnson demonstrated that the systemic action of SNP was due to the Nitroso group which is similar to,but 50-1000 times more potent than,the closely related nitrite group.He concluded that the hypotensive effects of SNP were due to peripheral vascular relaxation independent of the innervation & described the hypotensive effects of the drug in 3 subjects.

Johnson's suggestions for the therapeutic usefulness of SNP were largely ignored until the early 1950's when Page et al reported on the cardiovascular & therapeutic actions of SNP.

Page & his co-workers (1955) confirmed Johnson's earlier findings of the drug's therapeutic usefulness & described the beneficial clinical effects of constant intravenous infusions during period of hypertensive crisis.They further demonstrated that SNP is decomposed through the interaction of its iron atom with sulhydryl groups in the blood or tissue,and concluded that decomposition of the compound was not essantial for its depressor activity since this reaction is completed only after a delay,while the depressor effect of SNP is rapid in onset & of short duration.

In 1959,the first of several reports by Gifford on the therapeutic value of SNP during hypertensive emergencies was published.Gifford (1961,1962) considered SNP the most potent & consistently effective drug for parentral use during hypertensive emergencies & found it effective when other hypotensive drugs had failed to produce a satisfactory response. In the years following these initial clinical reports,there was a gradually increasing interest in the Pharmacologic and clinical effects of SNP.Subsequent clinical trial has confirmed the earlier reports on the drug's safety & effectiveness as a hypotensive agent.

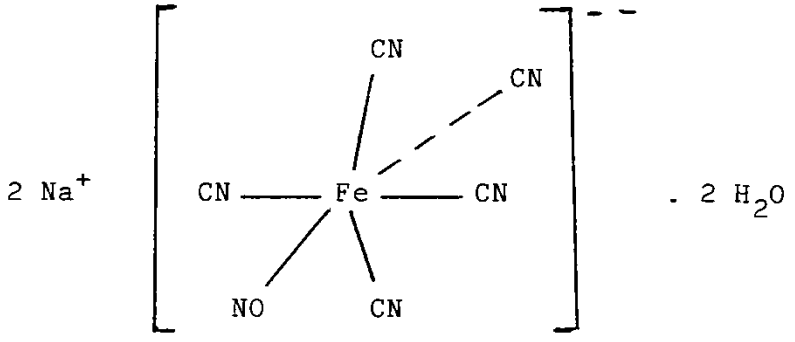
PHARMACOLOGICAL PROPERTIES OF SNP

SOURCE:

SNP is a ferrous,hydrated,penta-cyanocompound,first described in 1849 by Playfair.It is produced by action of 30% nitric acid on ferro or ferricyanide.It occurs in the form of rhomboid red crystals.

PHYSICAL & CHEMICAL PROPERTIES:

SNP or sodium nitrosylpentacyanoferrate dihydrate,has the chemical formula: Na_2 Fe $(CN)_5$ NO . $2H_2O$
Molecular weight is 298 (297.97) and the following structural formula:



It is a reddish brown odourless crystals or powder. It dissolves readily in water to form a brownish solution.It is slightly soluble in alcohol & very slightly soluble in cloroform.The specific gravity is 1.72.

Aqueous solutions of SNP are unstable upon standing.Upon exposure to light the colour of the solution changes from brown to blue,a result of the transition from the ferric ion to the ferrous ion.Dilute solutions exposed to bright day light undergo 10% decrease in potency after 3 hours & up to 50% after 48 hours.(Fig.1) If the container is protected from the light,the loss become negligible.A useful warning sign of undue breakdown of the drug is the appearance of a blue colour (Prussian Blue).

Such solutions should immediately be rejected. Solutions may be sterilized by filtration.

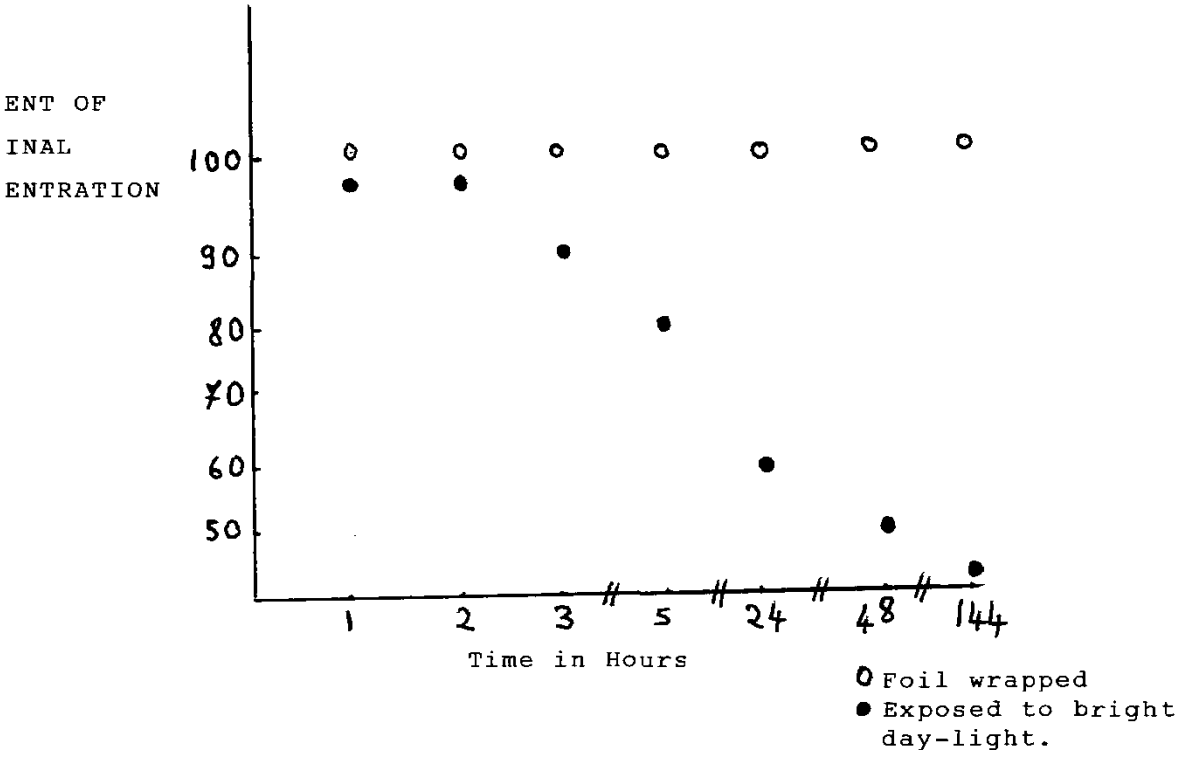


Fig I: Breakdown of infusion solution of SNP when exposed to or protected from bright day light.

Covering with tin-foil or a black valvet bag is a convenient method & should be used if the infusion is expected to exceed 3 hours.(After Peter Cole,1979) "Sodium nitroprusside in anaesthesia & analgesia (No.13) Edited by Langton C. and Atkinson R.S.(P 139-150).

PHARMACODYNAMIC ACTION OF SNP:

* THE SITE OF ACTION :

SNP is a powerful direct smooth muscle relaxant.Its action is specific to vascular smooth muscle.The nitroso group is a relaxant acting directly & specifically on arterial & venous smooth muscles.

Johnson (1929) reported,relaxation of uterine smooth muscle at concentration about 100 times those required to relax vascular smooth muscle.There is no effect on isolated cardiac muscle at concentrations 100 times those required to relax rabbit aorta.Page et al (1955) on other hand found no effect on uterine or duodenal smooth muscle at markedly hypotensive doses.Unpublished observation of Van Breeman,Gerber,& Palmer showed that the drug relaxed both potassium chloride & norepinephrine induced contracture of rabbit aortic strips (Palmer & Lasseter 1975).It is clear from whole animal studies that the major site of action is vascular smooth muscle.

Administered as i.v.infusion,SNP is a highly potent vasodilator.Its effect on the blood vessels begins immediately after the start of the infusion (average 2 minutes),is easy to control & ceases shortly after the infusion has been ended (5 minutes).The drug exerts its effect at first on

spasm-constricted blood vessels,whereas general dilatation of the peripheral vessels occurs with higher dosages.

These vessels include both the arterioles & to lesser extent the post capillary (venous) capacitance bed.The action of SNP is directed exclusively at the vascular musculature & is achieved independently of the autonomic nervous system.

A Microvascular Site Of Action of SNP :

Since SNP is believed to lower arterial blood pressure by direct action of vascular smooth muscle.There must be additional factors that increase the responsiveness of the small arterioles to the drug.This property is however,not unique to SNP.In fact Duling & Berne (1968) reported that maximum, responses to both acetylcholine & norepinephrine occured in the precapillary arterioles of the hamster cheek pouch,with decreasing effect in progressively larger arterioles.Furness & Marshall (1972) reported a similar distribution of constrictor responses to catecholamines in the rats mesenteric microvasculature.Eriksson & Lisander (1972) found a similar distribution of drug effectiveness in the cat terruissimus muscle arterioles following the intra-arterial administration of either acetylcholine or papaverine.Several factors could account for the increased activity of small arterioles to SNP. These would include the relative amounts of vascular smooth muscle in the vessel wall,neural or humoral influences

on vascular tone,and the initial wall tension.The relationship between wall tension & vessel radius is an important determinant of vascular reactivity.Core (1974) observed that vascular reactivity was most pronounced in vessels with a calculated wall stress of 1-1.5 X 10^5 dynes/Cm^2, a value that is found only in the terminal arterioles (approximately 12-25 µm in diameter) of mammalian microvasculature under resting conditions.

The microvasculatur effects of SNP were studied by Longnecker et al,(1975) to determine the peripheral vascular site of action of the drug,using the striated cremaster from 11 male rats anaesthetized with pentobarbital.The internal diameter of 3 arterioles & 2 venules were measured in each preparation before,during & after SNP infusion,& they observed that :-

a)Firt-order arterioles(with internal diameter 133 +/- 7 um) showed no significant reponse to SNP & their internal diameter correlated poorly with decrease in mean arterial pressure.

b)Third-order arterioles (with internal diameter42 +/- 2 um) correlated well with mean arterial pressure,but did not significantly dilate during drug infusion.