EFFECT OF CALCIUM CHANNEL BLOCKERS ON RADIOCONTRAST NEPHROPATHY

THESIS

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Master Degree of Internal Medicine

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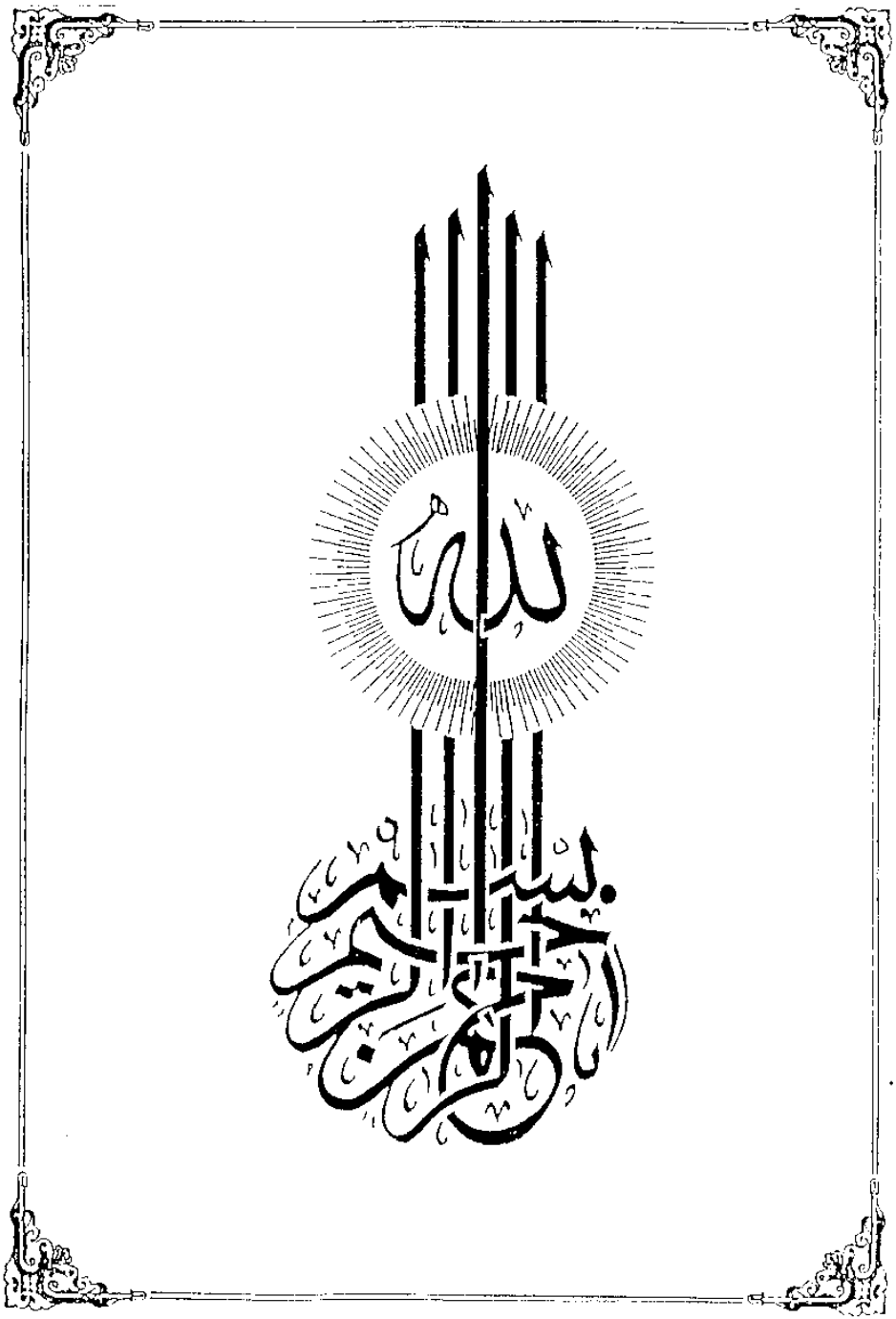

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INTRODUCTION

INTRODUCTION AND AIM OF THE WORK

Contrast nephropathy can be defined as an acute impairment of renal function that follows exposure to radiocontrast media and for which alternative etiologies for renal impairment have been excluded *(Harkonen and Kjellstrand, 1981)*.

Exposure to contrast media is the most common cause of hospital acquired renal insufficiency and exceeds amino-glycosides as a cause of renal failure *(Hou et al, 1983)*.

The risk factors for radiocontrast nephropathy are controversial *(Fischer, 1980)* although pre-existing renal insufficiency and diabetes mellitus (D.M.) are the most universally accepted risk factors *(Hou et al, 1983; Schwab, 1986 and Evans et al, 1987)*.

It is likely that there is no single pathogenic mechanism for radiocontrast nephropathy, however, renal ischemia is the most favourable mechanism *(Eisenberg et al, 1980)*.

Calcium channel blockers have been found to protect from the consequences of ischemia in a variety of experimental models & organ systems *(Cacoub et al, 1987)*.

So, the aim of this study is to evaluate the effect of ***verapamil***, a calcium channel blocker, infusion in preventing renal ischemia precipitated by radiocontrast materials.

REVIEW OF LITERATURE

CONTRAST MEDIA

HISTORICAL DEVELOPMENT OF CONTRAST MEDIA AND THEIR PHARMACOLOGY.

Sodium iodide was first suggested as a contrast medium in 1918 and was administered intravenously for studying the urinary tract by *Osborne et al. (1923).*

In 1950, the modern water soluble contrast media were introduced into clinical radiology. They were all derivatives of tri-iodobenzoic acid. In 1955 a much safer derivative called *diatrizoate* was introduced. Isomerization of diatrizoate and substitution at position 5 of N-methyl carbamyl produced the *iothalamate* in 1962 *(Chapmann, 1986).*

The majority of the modern conventional water soluble contrast media are distinguished by differences at position 5 of the anion and by the cation sodium and meglumine.

Further development in 1972 was the production of *iocarmate* by joining two iothalamate molecules *(Chapmann, 1986).* Because of low *PK* of carboxyl group, these weak organic acids exist biologically as anions and are distributed only to the extracellular space *(Mudge, 1980).*

All conventional ionic water soluble contrast media "CM" are hypertonic with osmolality range of *"1200-2000 mosm/kg water" and designated as high osmolality media "HOM" (Chapmann, 1986).*

The *hyperosmolality* is responsible for many of the contrast media side effects such as nephrotoxicity, venous thrombosis, cardiovascular and CNS side effects. Thus, in order to reduce these side effects, the *lower osmolality contrast media "LOM"* were introduced, with osmolality range of *470-800 mosm/kg water*. These compounds do not ionize in solution, and do not provide radiologically useless cations. Contrast media of this type include: *Metrizamide, Iohexole, Ioxaglate and Iopamidol (Chapmann, 1986).*

Plasma protein binding is insignificant *(Schirantarelli et al., 1973)*. Thus, these compounds are entirely excreted by the kidneys. The half life being 30-60 minutes in patients with normal renal function.

Secondary routes of excretion in renal failure include, "bile", small intestine mucosa, tears and saliva *(Talner, 1972)*.

Additional pharmacological effects include enhancement of uric acid and oxalate secretion and stimulation of ADH release *(Gelman et al., 1979)*. They have a maximum effect within 7 hours and duration of 24 hours and can double the urinary excretion of uric acid *(Mudge, 1971)*.

Uricosuria is due to enhancement of tubular secretion of uric acid because this effect can be blocked by pyrazinamide *(Steele, 1973)*.

Diatrizoate has been shown to cause 96% increase in the 24 hour excretion of oxalate, the exact mechanism is unknown *(Gelman et al., 1979)*.

Fig. 1

LD_{50}	2?	1.5	15.7	22
	A	B	Sodium acetrizoate (Urokon ; Diaginol)	Sodium diatrizoate (Urografin ; Hypaque)

(after Hoppe et al 1952)

Addition of amine group ($-NH_2$) to sodium benzoate (A) permits tri-iodination at C_3, C_5 and C_6 (B), but LD_{50} is reduced from 20 to 1.5. This product is far too toxic. Acetylation of amine group (sodium acetrizoate (Diaginol)) increases LD_{50} to 15.7. Addition of a second amino-acetyl group at C_5 (sodium diatrizoate (Hypaque, Urografin)) further increases LD_{50} to 22.

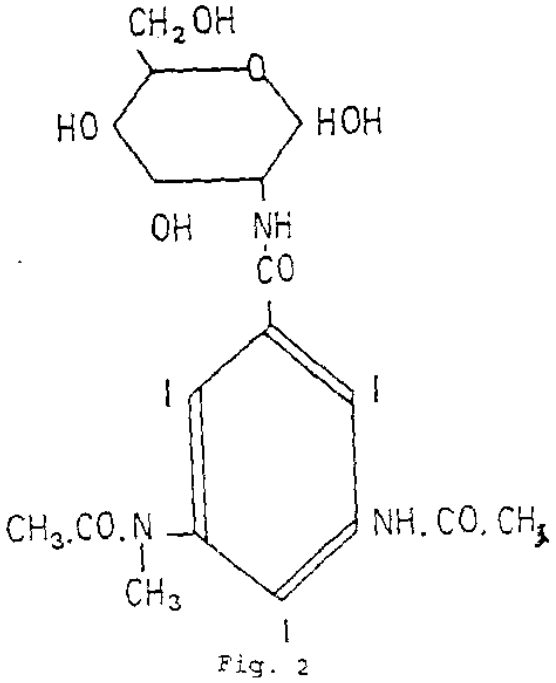

Fig. 2

Metrizamide (Amipaque). Note substituted amide ($CONH_2$ group at C_1 instead of $COONa$ in sodium diatrizoate (Fig. 1)) No ionization—therefore low osmolality

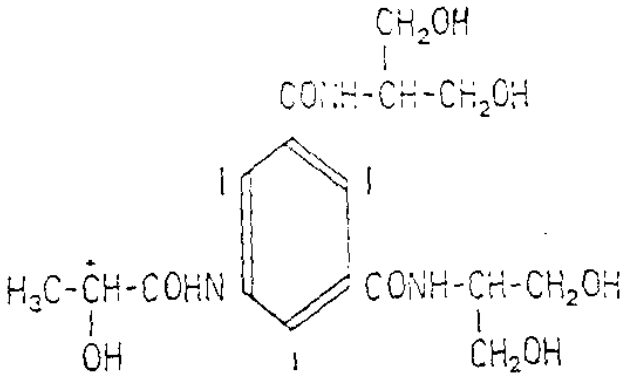

Fig. 3

IOPAMIDOL (B.15000)

B.15000 (Iopamidol). A substituted amide of another substituted tri-iodinated benzoic acid.

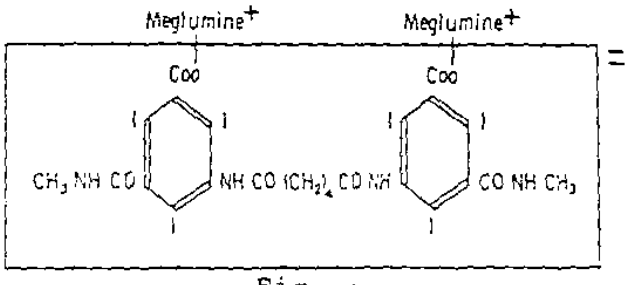

Fig. 4

Meglumine iocarmate (Dimer X). Meglumine salt of a dicarboxylic dimeric acid.

IOXAGLIC ACID

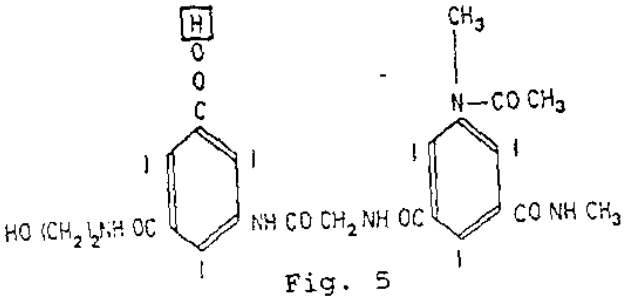

Fig. 5

Ioxaglic acid (Hexabrix is a mixture of sodium and meglumine ioxaglate). A mono-acid dimer. The hydrogen ion indicated is replaced by a sodium or meglumine ion to form a salt.