Nonsteroidal Anti-Inflammatory Drugs and Prostaglandin Synthesis Inhibitors in the Treatment of Urinary Diseases and Their Effects on Renal Functions: Clinical Studies

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A thesis submitted in partial fulfillment of the requirements of the University of Abertay Dundee for the degree of Doctor of Philosophy

June 2001

I certify that this thesis is a true and accurate version of the thesis approved by the examiners.

Signed [redacted] Date 30/08/02

(Director of Studies)

In the name of Allah, the Beneficent, the Merciful

1. ACKNOWLEDGEMENTS

Praise be to Almighty Allah who gave me the ability and strength to undertake scientific research and afforded me the opportunity to commit to writing and publish that research works and to submission them to the award of PhD degree in my field of investigation. The task would surely not have been accomplished without Almighty Allah's boundless bounty and grace for which I thank Him from the core of my heart.

I also offer my deep sense of gratitude to my supervisors, Dr. P.J. Collier and Dr. T.E.J. Buultjens, University of Abertay Dundee, for their valuable guidance that enabled me to complete my thesis on urogenital diseases for presentation to the Abertay Dundee University. I particularly express my appreciation and gratitude to Dr Collier who took personal interest in the day-to-day progress of my work of writing the thesis and presenting it in the proper scientific and academic form.

I also place on record my great affection and appreciation for all those patients of mine who not only volunteered to participate and cooperate with me in this scientific research but also showed their keenness in receiving the treatment and getting to know the results of these researches. But for their spirit of understanding and support, this type of scientific enterprise would not have been made possible. I also owe sincere gratitude to my co-authors for their consistent cooperation and keenness to see the project through in a standard scientific format.

Sincere thanks are also due to my teachers Prof. Hani Al-Azzawi, Prof. Abdul Jaleel Thewani and Prof. Miqdad Abdul Jabbar (Urologist) for their encouragement to me to engage in the work of scientific research during my stay as at the Medical College of Baghdad University, as a student.

Loving thanks are also due to my wife Dr. Kholood Y. Saloom and to my sons Dhia, Ali, Hamza and Wail for their unflinching support and encouragement in

my endeavour and their gesture of condoning long hours of my absence from home on account of my research and treatment of the patients.

No words with me will be truly sufficient to express the indebtedness and gratitude I owe to my dad who extended all possible moral and financial support to me in the building up of my career until this day.

I am very grateful to Prof. J. Williams, Institute of Nephrology, University of Wales College of Medicine (my examiner), and Prof. P. Lobo, Division of Nephrology, Internal Medicine, University of Virginia, USA, for their kindness to read my works and for their opinion that my works are interesting.

Last but not least, I feel it my bounden duty to acknowledge my indebtedness and gratitude to Saeed Bin Ahmed Āl Lootah, Chairman Advisory Committee of the Dubai Medical College for Girls for his fatherly affection and support.

2. DEDICATION

It gives me a sense of immense pleasure and comfort to dedicate this humble work of mine to:

the memory of my mother (M.H Al-Waili) who breathed her last on the dialysis machine following a prolonged and agonizing bout of illness as a result of renal failure,

all my patients, brothers and sisters, suffering from various ailments and physical debilities whom I always keep close to my heart

and all those patients who spend sleepless nights fighting their illnesses and bear their pain and suffering with courage and fortitude.

3-Abstract

Prostaglandins increase urine production, electrolytes excretion, detrusor contraction, micturition pressure, lower urethral pressure and inhibit antidiuretic hormone. We hypothesized that high production of prostaglandins or their dominant action on the urinary system may play a role in the pathogenesis of primary enuresis and nocturnal frequency of micturition. To test this, inhibition of prostaglandin synthesis by nonsteroidal anti-inflammatory drugs (NSAIDs), indomethacin suppositories or diclofenac sodium, or by carbamazepine, were used in their management. Measurement of urine volume and urinary and serum electrolytes and osmolality were performed before and after treatment with indomethacin. Similar to prostaglandins, nitric oxide (NO) causes natriuresis and diuresis, decreases antidiuretic hormone and relaxes trigone and urethra. We hypothesized that NO may play a role in the primary enuresis. Urinary nitrite, the end product of NO, was measured in enuretics before and after treatment with indomethacin and compared with normal control.

Prostaglandins are increased in urinary obstruction and implicated in the urinary calculus formation. The other aspect of the thesis is to determine whether inhibition of prostaglandin synthesis by short acting NSAID (eg: indomethacin suppository), long acting NSAIDs (eg: tenoxicam i.m or i.v, or piroxicam i.m), selective cyclooxygenase inhibitor (eg: sublingual meloxicam), and by calcium antagonist (eg: sublingual nifedipine), could relieve acute or resistant renal colic and facilitate urinary calculus expulsion. The other aims of the thesis are to demonstrate the efficacy and safety of different methods of drug delivery as i.v, i.m, sublingual, oral or rectal routs and their effects on renal function tests and their importance in emergency situations.

Results showed that indomethacin, diclofenac sodium or carbamazepine significantly reduced frequency of bedwetting in most of the patients with enuresis. Urinary nitrite excretion is elevated in enuretics and was decreased significantly when bedwetting episodes decreased by indomethacin. Indomethacin suppository decreased urine volume, urine electrolytes, clearance of free water, filtered sodium, fractional sodium excretion and reduced significantly bedwetting in patients with small as well as normal functioning bladder capacity. Regarding renal colic, indomethacin, tenoxicam, piroxicam, nifedipine and meloxicam alleviated pain of acute renal colic. Long acting NSAIDs had lower incidence of pain relapse and fewer drug administrations when compared to short acting NSAIDs and spasmolytic/analgesic. Indomethacin or nifedipine facilitated passage of urinary calculus and prevented or reduced pain recurrence.

It could be concluded for the first time that prostaglandin and NO might play a role in the pathogenesis of primary enuresis and frequency of micturition, and inhibition of their production might represent a new line for the management. The mechanism of action of indomethacin might be attributed to the significant reduction of urine volume and sodium excretion in addition to its possible effects on bladder and urethral contraction through inhibition of prostaglandin and NO. Short and long acting NSAIDs, COX-2 inhibitor and calcium antagonist, are safe and effective to alleviate pain of acute renal colic and could facilitate passage of urinary calculus. The different methods of drug administration, including rectal or sublingual which could be self-administered, are effective and safe in the treatment of the diseases. No significant deterioration in renal functions was encountered after treatment with the drugs. The mode of actions of the drugs in respect to prostaglandin inhibition, NO and calcium influx are discussed.

6- Contents

5. List of Abbreviation

Nonsteroidal anti-inflammatory drugs	NSAIDs
Central nervous system	CNS
Cyclooxygenase	COX
Intramuscular	i.m.
Intravenous	i.v.
Loop of Henle	LOH
Nitric oxide	NO
Thromboxan A2	TXA2
Thromboxan B2	TXB2

6. INTRODUCTION

6.1. Morphogenesis of the urinary system

The primary excretory duct begins to develop in 23 to 24 days (Figure 1). Three different systems are formed: the pronephrons, the mesonephrons and the metanephrons. The first system disappears at the end of the 4th week. By the end of second month the majority of the mesonephrons have disappeared (Williams & Warwick 1985d). The metanephrons appears in the 5th week to form permanent kidney. The ureteric bud, an outgrowth of the mesonephric duct, gives rise to the ureter, the renal pelvis, the major and minor calyces and collecting tubule. The distal end of the collecting tubule is covered by a metanephric tissue cap, forming the renal vesicle, which gives rise to small tubules. These tubules together with tufts of capillaries known as glomeruli. The proximal end of the nephron forms the Bowman's capsule.

The urorectal septum divides the cloaca into the anorectal canal and primitive urogenital sinus. The latter give rise to: (1) the urinary bladder, from the upper part, (2) the prostatic and membranous parts of the urethra from the pelvic part of the urogenital sinus and (3) the phallic part of the urogenital sinus.

The genital system consists: (1) the primitive sex glands (eg: testes and ovaries), (2) the genital duct, and (3) the external genitalia. The prostate arises from the proximal part of the urethra. In female, the urethra is derived from vesico-urethral portion of the cloaca. In the male, the prostatic urethra is derived from vesico-urethral part of the cloaca. The remainder part of the urethra is derived from the urogenital sinus.

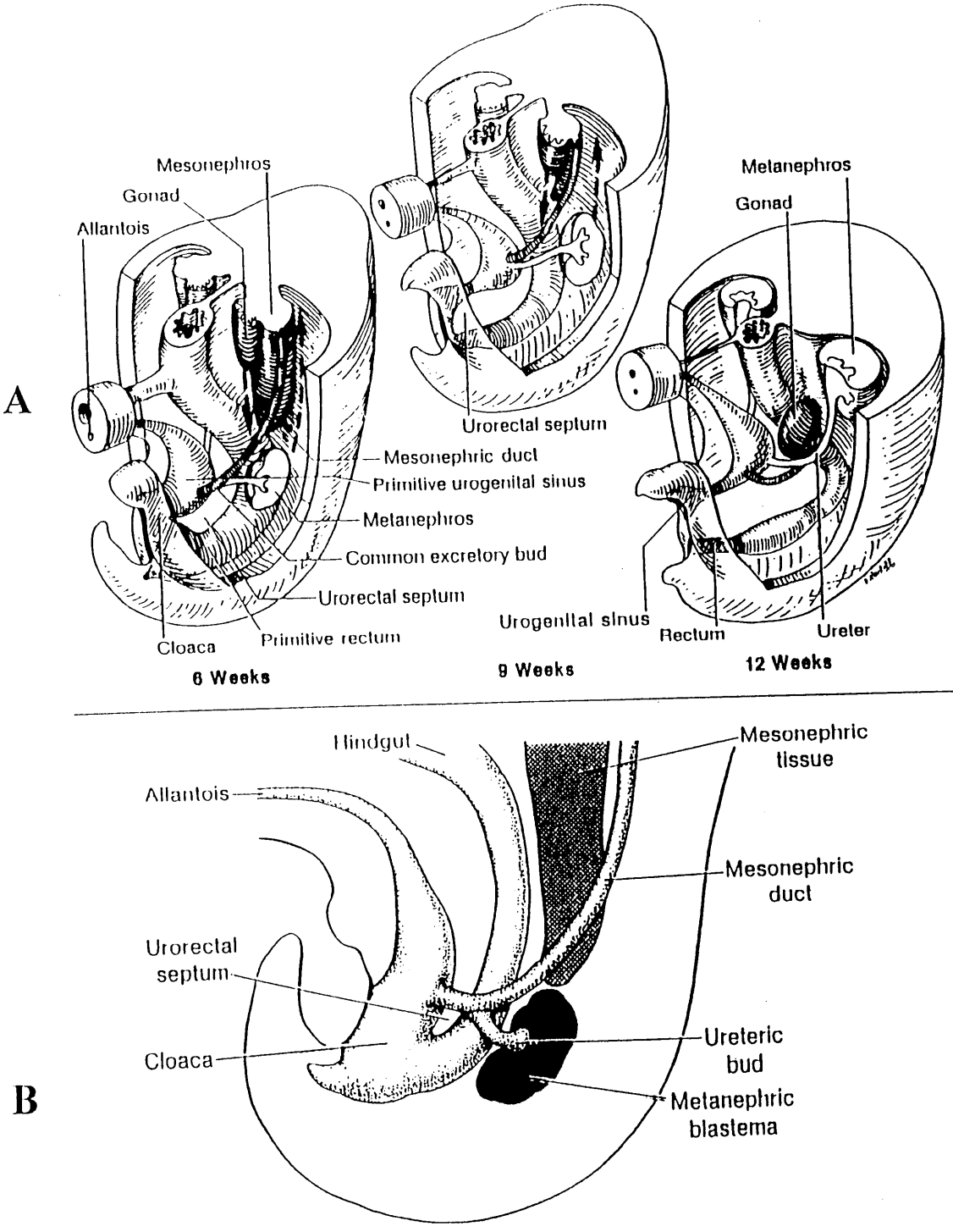


Figure 1 : Schematic drawing to show urogenital organs developments ***(A; From Johson,K. (1988) Human Developmental Anatomy. Jhon Wiley & Sons,Inc., USA, pp.269, B; From; Sadler, T.(1993) Langman Medical Embryology, 6th edition, Williams & Wilkins, pp. 263).***

6.2. Anatomy of the Urinary System

The urinary system comprises; (1) the paired kidneys, (2) the paired ureters, (3) the urinary bladder, and (4) the urethra (Figure 2). The female urethra is a purely urinary duct while the male urethra serves two functions, urinary and reproductive (William & Warwick, 1985a).

6.2.1. The Kidneys

The kidneys are two reddish-brown organs and approximately 10 cm long, 5 cm wide and 2.5 cm thick. In adult male the weight of the kidney averages about 150g, in adult female 135g.

Each kidney has a concave medial border. The hilum, where blood and lymph vessels enter and exit, nerves enter and the ureter exits. The lateral border is convex. The renal pelvis, the upper part of the ureter, is divided into 2 or 3 major calyces. Several small, minor calyces arise from each major calyx. The kidney has an internal medulla and an external cortex. The renal medulla consists of 10 to 18 pale conical or pyramidal masses termed the renal pyramids.

The kidney is composed of very large number of tortuous uniferous tubules; each consists of two parts (1) nephron and (2) collecting tubules. Each kidney contains 1 to 4 million nephrons (Romanes 1985a).

The nephron comprises a dilated portion, the renal corpuscle, the proximal convoluted tubule; the thin and thick limbs of loop of Henle (LOH); and the distal convoluted tubule. The collecting tubule carries the fluid from a number of renal tubules to a terminal papillary duct, which opens into a minor calyx (Figure 3).

Renal corpuscle consists of a tuft of capillaries, the glomerulus, surrounded by a double-walled epithelial capsule, called Bowman's capsule.

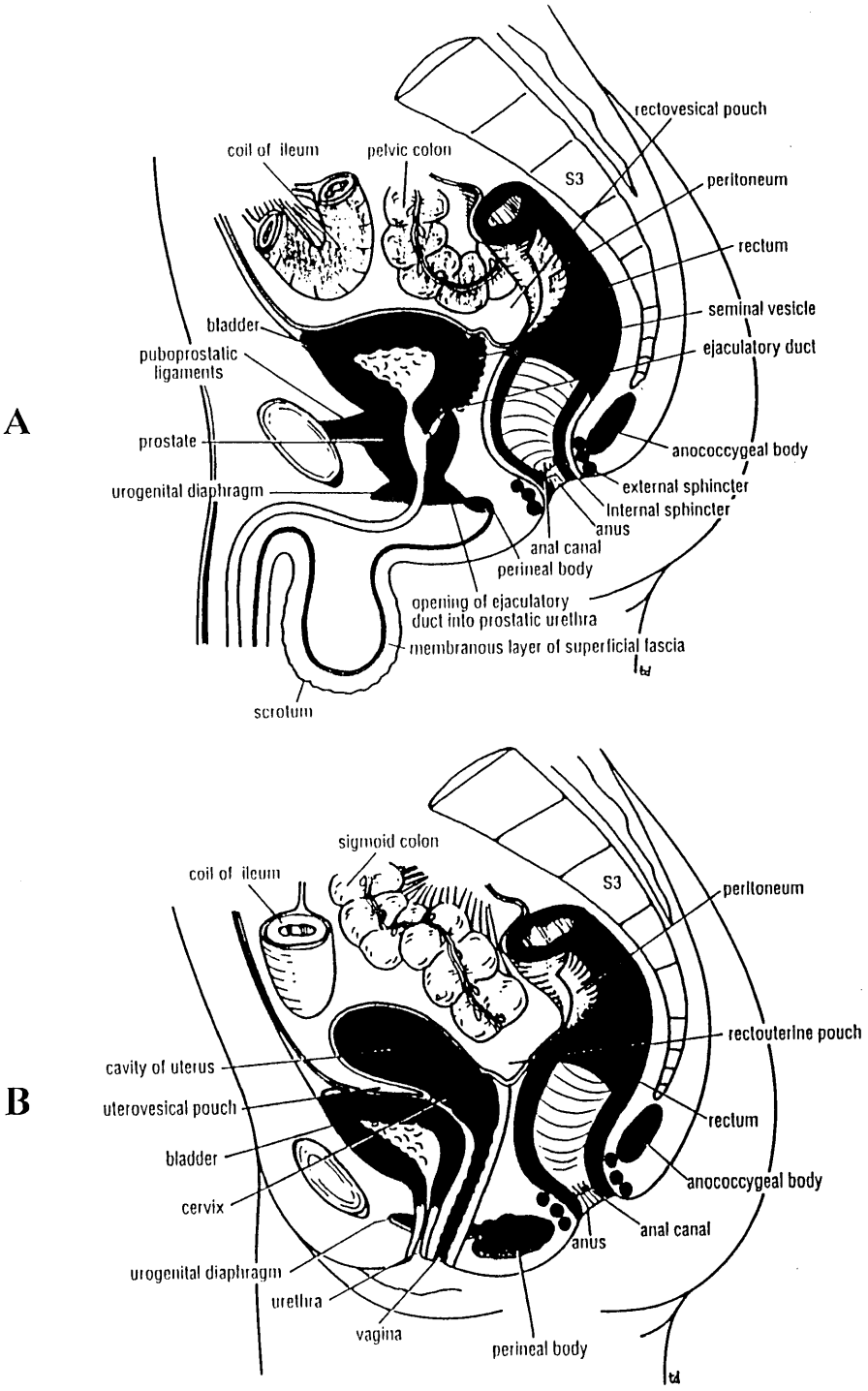


Figure 2: **(A) Sagittal section of male pelvis and (B) female pelvis showing genitourinary organs (** *From: Snell, R.(1995) Clinical Anatomy for Medical Students, 5th edition, Lippincoot Williams and Wilkins, Phildelphia, pp: 311 (A), pp: 320 (B).)*

The internal visceral layer envelops the capillaries of the glomerulus. The external parietal layer forms the outer limits of the corpuscle. Urinary space presents between the two layers of Bowman's capsule which receive the fluid filtered through the capillary wall and the visceral layer. The afferent arteriole enters and the efferent arteriole leaves the renal corpuscle through a vascular pole. Proximal convoluted tubule begins at another pole, a urinary pole (Williams & Warwick 1985b).

A thick basement membrane presents between the fenestrated endothelial cells of the glomerular capillaries and the podocytes. The glomerular basement membrane acts as a selective filter, allowing the passage from blood of water and small molecule. The proximal convoluted tubule is second part of the renal tubule, just after glomerular capsule. It runs toward medulla to become the descending of LOH. The later is a U-shaped structure consisting of a thick descending limb, becoming a thin descending limb; which in turn becomes the thin ascending limb and the thick ascending limb (Junqueir *et al.* 1998a).

Distal convoluted tubule is the last segment of the nephron, which is lined with simple cuboidal epithelium. It establishes contact with afferent arteriole at which the distal tubule is modified, as is the afferent arteriole. The modified segment of the wall of distal tubule is called the macula densa. Adjacent to the renal corpuscle the tunica media of the afferent arteriole has modified smooth muscle cells called juxtaglomerular cells. This portion of arteriole and the macula densa form the juxtaglomerular apparatus. Macula densa produces signals that promote constriction of the afferent arteriole. Juxtaglomerular cells play a role in the regulation of blood pressure.

6.2.2.The Ureters

The ureters are the two muscular tubes, each measures from 25 to 30 cm in length and 3 to 5 mm in width (Williams & Warwick 1985b). The abdominal part of ureter descends almost vertically along the line of the tips of the lumbar transverse processes and it enters the pelvis. The pelvic part of ureter is the same length as the abdominal part. In the pelvis, opposite the

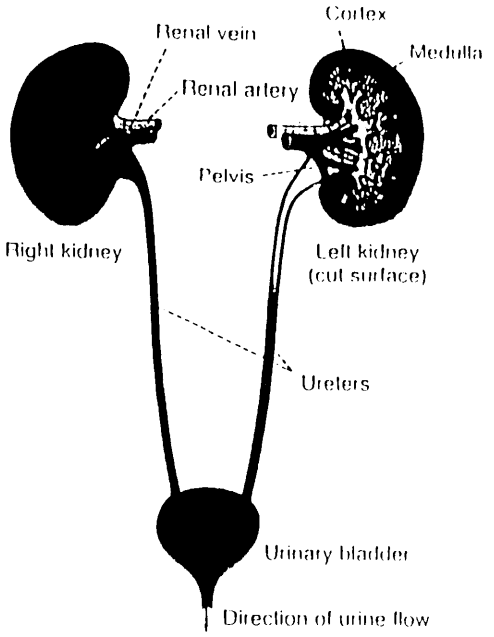
ischial spine, it turns anteromedially to reach the base of the bladder. The ureter has fibrous, muscular and mucous coats. The muscular coats in the pelvis, calyces, and upper two-thirds of the ureter consist of inner longitudinal and outer circular layers of non-striated myocytes. In the lower third of the ureter a longitudinal muscular layer is added. The ureter is lined by the transitional epithelium. Blood supply of the ureter consists of small branches passing to the ureter from the renal, testicular or ovarian aorta, common and internal iliac, and vesical or uterine arteries. The nerves are derived from the renal, aortic, and superior and interior hypo-gastric plexuses. The ureteric plexuses contain sympathetic and parasympathetic fibres, which are sensory in nature (Snell 1992).

The pain is referred to cutaneous areas innervated from the same segments of the spinal cord as supply the ureter, mainly L_1 to L_2, the front of the thigh through genitofemoral nerve (L1, 2), and cremaster may under go reflex contraction and retract the testis.

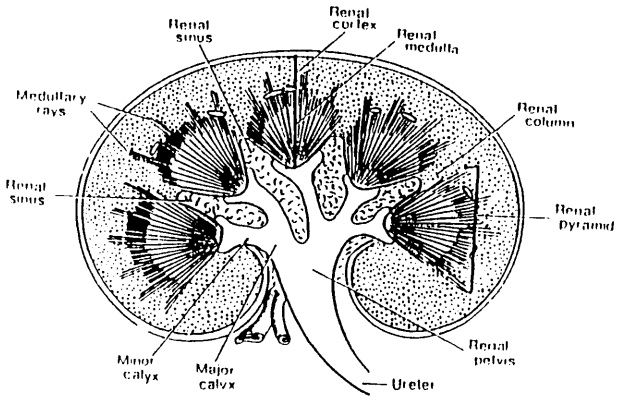
6.2.3.The Urinary Bladder and Urethra

The bladder has the shape of a three-sided pyramid that has a base, neck, apex, superior surface and two interio-lateral surfaces (Romanes 1985b).

The bladder and the urinary passages are covered externally by an adventitial membrane except for the upper part of the bladder, which is covered by peritoneum. The bladder wall has three layers: adventitia, muscular and mucous. The muscular layer constitutes the detrusor muscles that consist of three layers of nonstriated myocytes: an external and internal longitudinal layers and a middle layer of circular fibers. There is no muscularis mucosa in the urinary bladder wall. The internal sphincter composed of nonstriated muscle and the external sphincter composed of *striated muscle (*Fawcett & Jendh 1997a*).*



Urinary system



Cross section of kidney

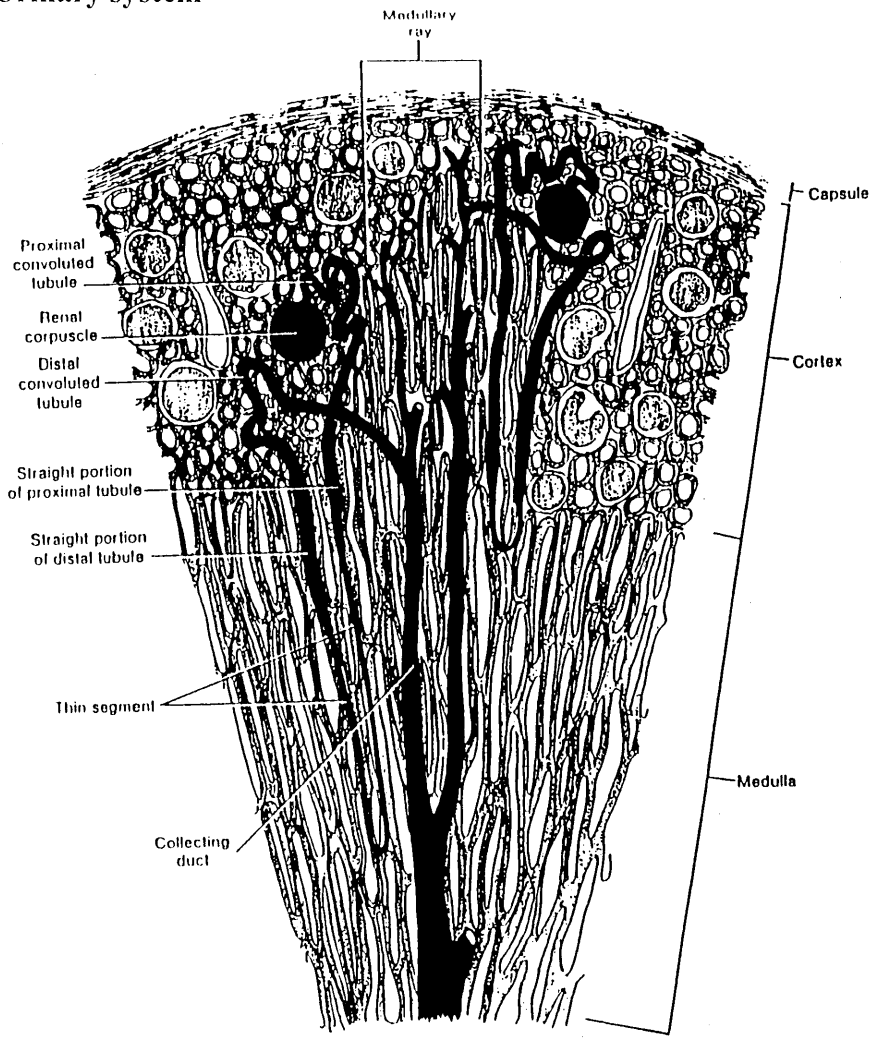


Figure 3. **Diagram of the uniferous** (*From: Krause, J., Cutts, H. (1986) Concise text of Histology, 2 th edition, Baltimore, Williams and Wilkins)*

The ureters pass through the wall of the bladder obliquely, forming a valve that prevents the backflow of the urine to the ureter.

The mucosa of the urinary bladder and other urinary passages consist of transitional epithelium. The mucous membrane is urine-proof and stretchable. The blood supply of the urinary bladder comes from three branches of each internal iliac artery. Veins drain to the internal iliac vein and external iliac. The lymph vessels drain to the external and internal iliac nodes. The nerves supplying the bladder consist of both sympathetic and parasympathetic components; each contains motor and sensory fibers. The motor parasympathetic fibers arise from the second to the fourth sacral segments of spinal nerves, supplying the detrusor muscle. They are inhibitory fibres to the internal sphincter. The efferent sympathetic fibers arise from the lower two thoracic and upper two lumber segments of the spinal cord to supply inhibitory fibers to the detrusor muscle and motor fibers to the internal sphincter. The pudendal nerve supplies the external sphincter. The sensory nerves supplying the bladder are: (1) pain fibres run in sympathetic and parasympathetic nerves and (2) fibres concerned with conscious awareness of bladder distension run in the posterior columns of the spinal cord (fasciculus gracilis).

The male urethra extends from an internal orifice in the urinary bladder to an external opening at the end of the penis (Figure 2). The male urethra consists of prostatic, membranous, bulbous and pendulous parts. The urethra is composed of a mucous membrane, submucous tissues, and muscle. The female urethra is about 4 cm long and 6 mm in diameter, the female urethra begins at the internal urethral orifice of the bladder and is embedded in the anterior wall of the vagina. The external urethral orifice is situated anterior to the opening of the vagina and about 2 to 5 cm behind the clitoris (Junqueira *et al.* 1998b).

The muscular layer consists of internal longitudinal and external circular fibers. The circular fibres of the bladder form the internal sphincter at the vesical end of the urethra. The urethra is also surrounded by external sphincter just above the perineal membrane. The mucous membrane near the

bladder consists of transitional epithelium, which becomes non-keratating stratified squamous epithelium distally (Fawcett & Jesh 1997a).

6.2.4. Innervations of the Kidney, Lower Urinary Tract and Micturition

The sympathetic preganglionic innervation comes primarily from the lower thoracic and upper lumber segments of the spinal cord. They supply afferent and efferent arterioles, the proximal and distal tubules, and the juxtraglomerular cells.

Pain in the kidney is mediated by nociceptive afferent that enter the spinal cord in the thoracic and upper lumber dorsal roots. The storage and periodic release of urine are controlled by the activity of the bladder (reservoir) and an outlet (bladder neck, urethra, and striated muscles of the pelvic floor). Their functions are regulated by neural circuitry in the brain and spinal cord (de Groat 1993; Lincoln & Burstock 1993). The innervations of the lower urinary tract are derived from sacral parasympathetic, thoracolumbar sympathetic and sacral somatic (de Groat 1992 & 1993). The sacral parasympathetic nerves, originated from the S2 to S4 segments of the spinal cord, provide the excitatory input to the bladder. Transmission in bladder ganglia is mediated by a nicotinic cholinergic mechanism. The ganglionic cells excite the bladder smooth muscle. The thoracolumbar sympathetic includes preganglionic pathways that arise from the T11 to L2 spinal cord segments. These pathways pass to the sympathetic chain ganglia and then to prevertebral ganglia in the superior hypogastric and pelvic plexuses and also to short adrenergic neurones in the bladder and urethra (de Groat & Booth 1993).

Sympathetic postganglionic nerves (releasing norepinephrine) provide an excitatory input to smooth muscle of the bladder base and the urethra, an inhibitory input to smooth muscle in the body of the bladder, and inhibitory and facilitory input to vesical parasympathetic ganglia (de Groat & Theobald 1976; de Groat 1987). The sacral somatic efferent pathways to the external urethral sphincter are carried in the pudendal nerve from anterior horn cells in

the 3rd and 4th sacral segment. Autonomic nerves transmit afferent activity arising in the bladder to the central nervous system (CNS) (de Groat 1986). The sympathetic nerve afferents carry nociceptive information from the lower urinary tract. Pudendal nerve carries afferents pathways from urethra, which induce the sensation of temperature, passage of urine and pain to the lumbosacral spinal segment. CNS controls the peripheral and autonomic nervous systems innervating the lower urinary tract (Figure 4). The control occurs at the sacral reflex micturition centre, the pontine micturition centre, the corpus collosum and the supramedial portion of the frontal lobe (Mallory *et al.* 1991). The afferent and efferent pathways and nervous system controlling bladder function and micturition are (Chai & Steers 1996):

1-The Afferent Pathways

(1) Parasympathetic afferent pathways are conveyed from the bladder to the CNS by the pelvic nerve and the dorsal root ganglia.

(2) Somatic afferent signals are conveyed from the urethral sphincter, by the pudendal nerve and overlap with the parasympathetic pathway.

2- The Efferent Pathways

(1) The parasympathetic efferent nerves convey efferent signals by cholinergic preganglionic neurones from 2, 3 and 4th ventral nerve roots.

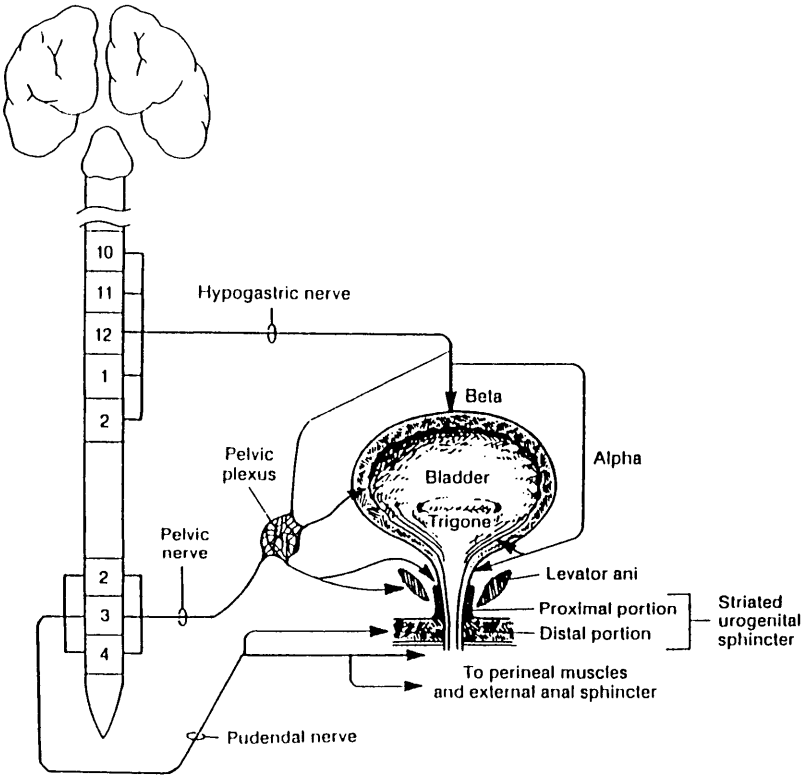
(2) The sympathetic efferent conveys signals from T_{11} to L_2 spinal nerve root.

(3) Somatic motor neurones originate at the 2nd, 3rd and 4th sacral segments, in Onuf's nucleus, and travel by pudendal nerve to the striated urogenital sphincter muscle and pelvic floor.

3- CNS and reflexes

Included storage reflexes, voiding reflexes, primary micturition centre, frontal cortex, hypothalamus and brain stem.

A



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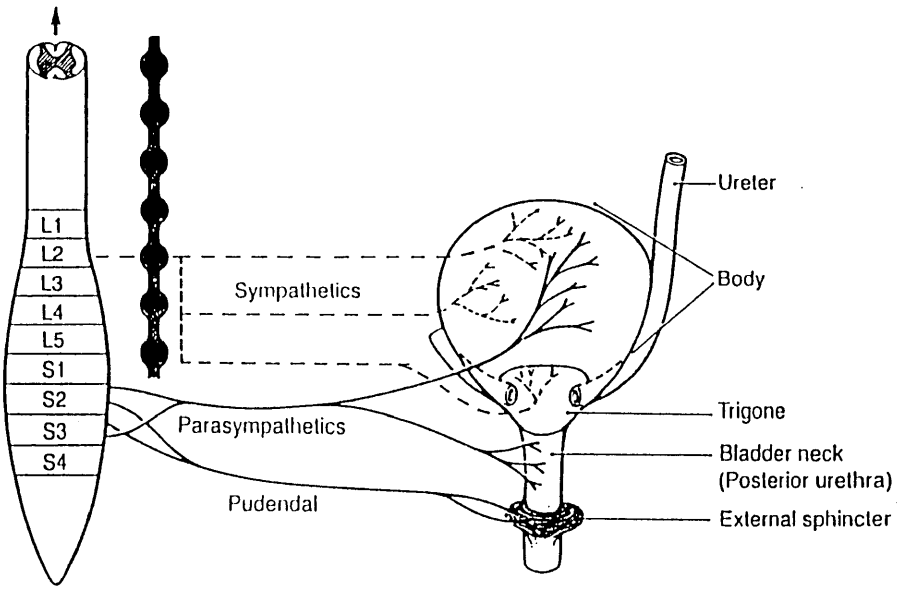

Figure 4 : A; Peripheral innervations of the lower urinary tract (*From Benson, T., Walkers, D.(1993) Neurophysiology of lower urinary tract, In; Walkers, D., Karram, M.(eds), Clinical Urogynecology, St. Louis: Mosby- Yearbook,Inc. pp.19*). B; Urinary bladder innervations (*From Guyton, A.,(1991) renal diseases, diuresis and micturition, In: Textbook of Medical Physiology, 8th edition, W. B. Saunders, p. 352.*

6.3. Physiology of the Urinary System

6.3.1.The Kidney

The main functions of kidney are;

(1) Excretion of metabolic waste products and foreign chemicals. Waste products include urea, uric acid, creatinine, and products of haemoglobin breakdown, metabolites of hormones.

(2) Regulation of blood pressur.

(3) Regulation of acid-base balances.

(4) Regulation of vitamin D3 and erythrocyte production. The kidneys secrete erthropoietin which stimulates the production of red blood cells from bone marrow. Hydroxylation of vitamin D to active form occurs in the kidneys.

(5) Glucose synthesis during prolong fasting, the kidneys synthesise glucose from amino acid.

Three processes occur in the functional unit of the kidney, the nephron, which determine the rates at which different substance are excreted in the urine. These processes are;

(1) Glomerular filtration.

(2) Reabsorption from the renal tubules.

(3) Secretion of substances from the blood into the renal tubules.

Renal Blood Flow

The kidneys receive 1.2 to 1.3 litres of blood per minute (25% of the cardiac output) (Figure 5). Prostaglandins increase blood flow in the renal cortex and decrease renal blood flow in renal medulla.

Glomerular Filtration Rate

The glomerular filtration rate is approximated 125 ml min^{-1}. This is about 180 l d^{-1}. 99% of the filtrate is normally reabsorbed. The factor governing filtration across the glomerular capillaries the size of the capillary bed, the hydrostatic and osmotic pressure gradient and the permeability of the capillaries. Natural substances with

molecular diameter of less than 4 nm are freely filtered. 20 percent of the plasma flowing through the kidneys filtered by the glomerular capillaries. The filtered fluid is essentially protein free and devoid of cells. Water, Na^+ ions and glucose are freely filtered. Positively charged molecules are filtered much more easily than negatively charged molecules. Negative charges of the basement membrane cause restricting charged molecules. A greater rate of blood flow into the glomerulus tends to increase glomerular filtration rate and a lower rate tends to decrease glomerular filtration rate.

Increase in glomerular hydrostatic pressure raise glomerular filtration rate, and decrease in glomerular hydrostatic pressure reduces glomerular filtration rate. Dilatation of the afferent arterioles increase both the glomerular hydrostatic pressure and glomerular filtration rate (Ganong & Hall 1997a).

Tubular Functions

Some peptide hormones and small protein are reabsorbed in the proximal convoluted tubule by endocytosis. Other substances are secreted or reabsorbed by passive diffusion and facilitated diffusion down chemical or electrical gradient or active transport against such gradient.

Sodium moves by co-transport or exchange from tubular lumen into the tubular epithelial cells down its concentration and electrical gradient (Figure 6).
It is actively pumped from epithelial cells into interstitial space by Na^+/K^+ ATPase. Sodium actively transported out of all parts of the renal tubule except the thin portion of the LOH. Negative ions such as Cl^- ions are transported along with the Na^+ because of electrical potentials.

Glucose, bicarbonate and amino acids are reabsorbed along with sodium in the early portion of the proximal convoluted tubule. All the glucose is absorbed by secondary active transport. Glucose and sodium bind to the common carrier. Amino acids leave epithelial cells by passive or facilitated diffusion to the interstitial fluid.
Some chloride is reabsorbed with Na^+ and K^+ in the thick ascending limb of the LOH. About 25% of Na^+, CL^- and K^+ are reabsorbed in the LOH.

In the proximal convoluted tubule, water moves passively through the tubule along the osmotic gradients set up by active transport of solutes. The movement is

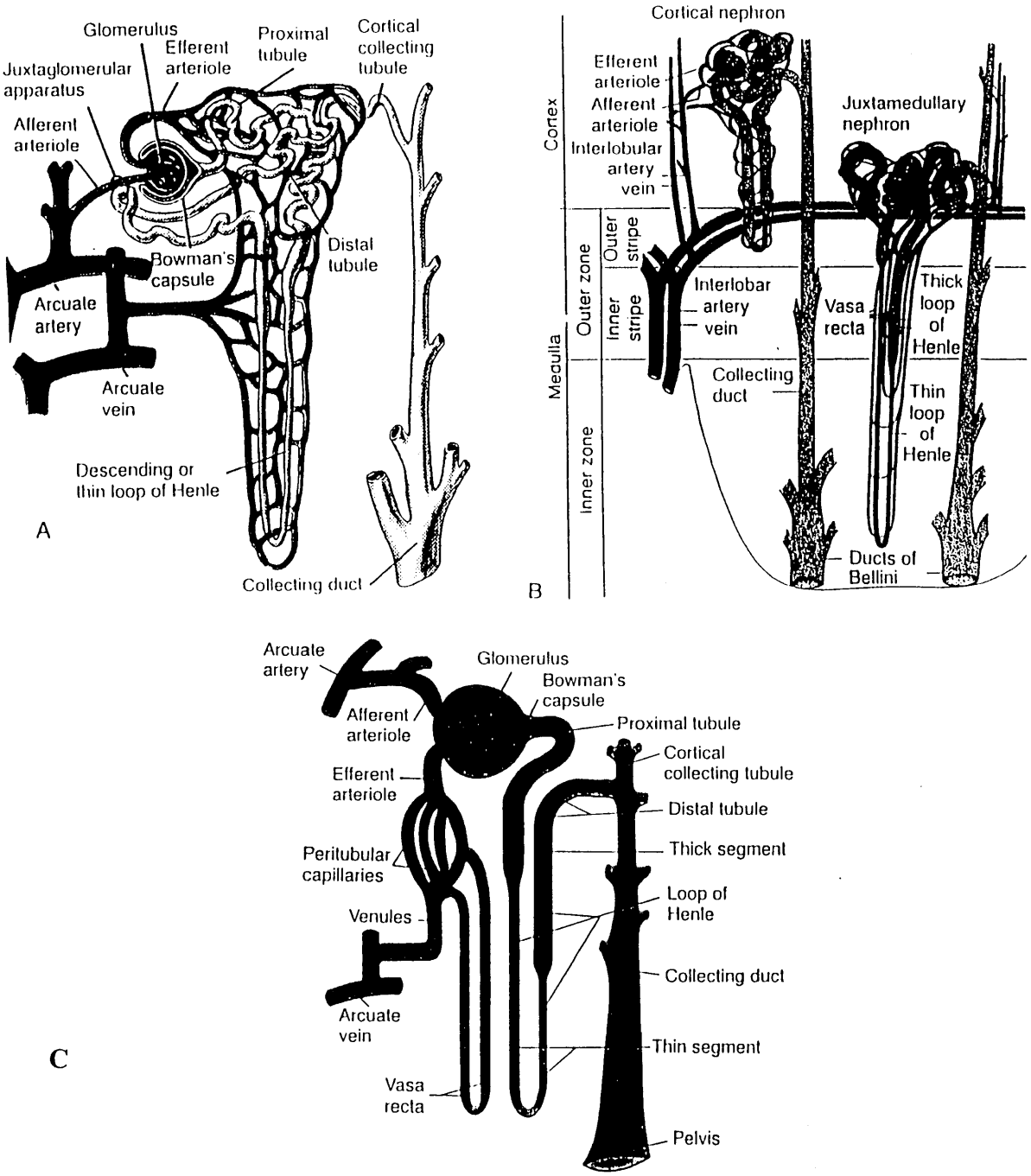

Figure 5 : A; The nephron (*From Smith (1951) The kidney: Structure & Functions in Health and Diseases. New York, Oxford University Press*). B; Differences between a cortical and juxtramedullary nephron (*From Pitts (1974): Physiology of kidney and Body Fluids, Chicago, Year Book Medical Publishers*), C; The functional nephron (*From Guyton, A.(1991) Formation of urine by kidney: 1. Renal blood flow, glomerular filtration and their control, In; Textbook of Medical Physiology, 8th edition, W.B. Saunders, pp. 288).*

facilitated by water channels, which facilitate the movement by the action of a protein called aquaporien-1. The descending limb of the LOH is permeable to water, but the ascending limb is impermeable. Approximately 20% of the filtered water enters the distal tubules. Na^+, K^+ and CL^- ions are co-transported out of the thick segment of the ascending limb. 5% of the filtered water is removed in the distal convoluted tubule. Collecting tubule has a cortical and a medullary portion (Figure 5). In presence of vasopressin, water moves out of cortical collecting duct into the interstium of the cortex. 10% of the filtered water is removed and 4.7% or more of the filtrate is reabsorbed into interstitium of the medulla (Guyton 1996a).

The first part of distal tubule forms part of the juxtaglomerular complex that control glomerular filtration rate and renal blood flow. The convoluted part of distal tubule reabsorbs most of Na^+, K^+ and Cl^- ions, but is impermeable to water. The second half of the distal tubule and cortical collecting tubule has similar action. They are composed of principal cells (reabsorb Na^+ and water from lumen and secrete K^+) and intercalated cells (reabsorb K^+ and secrete H^+) (Figure 6). The rate of reabsorption of Na^+ is controlled by aldosterone and the permeability to water is controlled by vasopressin. The medullar collecting tubule reabsorbs less than 10% of water and Na^+. When vasopressin is absent the collecting duct is relatively impermeable to water and 13% of the filtered water may be excreted.

Urea moves passively out of the proximal convoluted tubule. The rest of the tubular epithelium is impermeable to urea except the inner portion of the collecting tubule. About one and half of the filtered urea is passively reabsorbed and the remainder pass into urine. Creatinine is impermeable to the tubular membrane. Almost none of the creatinine is reabsorbed. Hydrogen ion is secreted by proximal and distal tubules. In the proximal tubule the reaction that is responsible for proton secretion is Na^+/H^+ exchange. For each H^+ ion secreted one Na^+ and one bicarbonate ion enter the interstitial fluid. When the plasma bicarbonate concentration is low all the filleted bicarbonate is reabsorbed.

Regulation of Tubule Functions: -

(1) Arterial blood pressure: Small increase in blood pressure causes a large increase in Na^+ and water excretion

(2) Hormones: Aldosterone is secreted by the zona glomerulosa cells of the adrenal gland. The primary site of action is the principle cell of the cortical collecting tubule. Aldosterone stimulates the Na^+/K^+ ATPase pump. Angiotensin 11 stimulates aldosterone secretion and increases Na^+ reabsorption. Angiotenisn 11 constricts the efferent arterioles which cause increases of Na^+ and water reabsorption in the proximal convoluted tubule. Antidiuretic hormone increases water permeability of the distal tubule, collecting tubule and collecting duct. Aterial natriuretic peptide is secreted from cardiac atria and inhibits the reabsorption of Na+ and water by collecting tubule.

(3) Sympathetic nervous system: Activation of sympathetic nerves increases Na^+ reabsorption in the proximal convoluted tubule and the thick ascending limb of LOH. Na^+ excretion can be decreased by constricting both the afferent and the efferent arterioles. In addition, sympathetic activation increases renin release and angiotensin 11 formation.

Regulation of Na^+ ion and Chloride Excretion

Factors affecting Na^+ and Cl^- reabsorption and excretion are factors affecting glomerular filtration rate, oncotic pressure in the peritubular capillaries, aldosterone, arterial natriuretic peptide, angiotensine and PGE2. Aldosterone increases Na^+ reabsorption and increases K^+ and H^+ secretion. PGE2 inhibit Na^+/K^+ ATPase and increase intracellular calcium. Endothelin and interleukin-1 (IL-1) cause natriuresis by increasing PGE2.

Antidiuretic hormone is synthesised in supraoptic and paraventricular nuclei of the hypothalamus and it is released from the posterior pituitary gland. Increased osmolarity decreases arterial blood pressure and decreased blood volume increase antidiuretic hormone secretion. The osmoreceptor-antiduretic hormone and thirst regulate extracellular fluid osmolarity and sodium concentration. Aldosterone causes Na^+ and water retention.

K^+ secretion is stimulated by increased aldosterone, increased tubular flow rate, and increased extracellular fluid K^+ concentration. Acute acidosis decreases K^+ secretion. Kidney filters and reabsorbs calcium. 50% of calcium is filtered at the

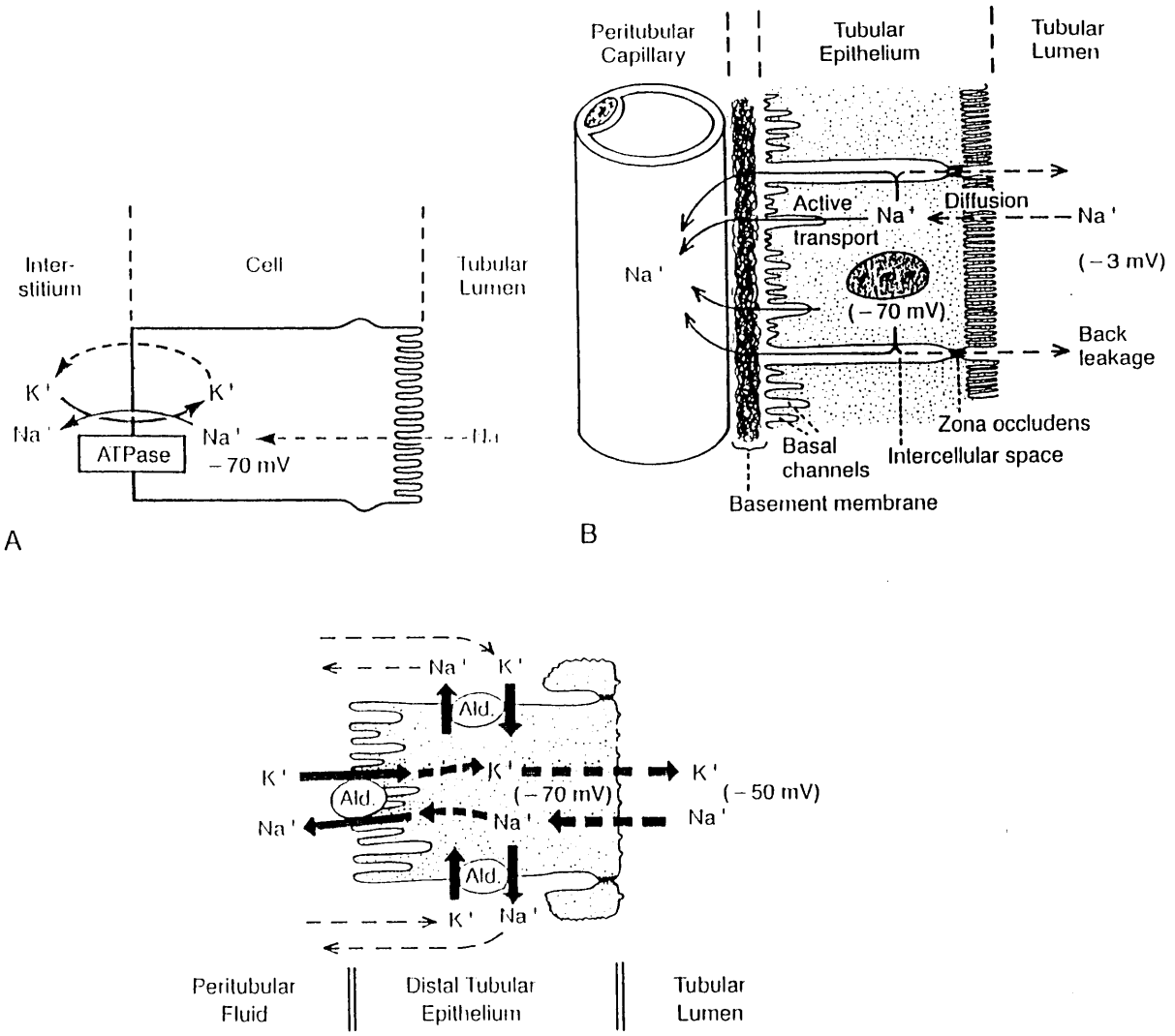

Figure 6: A, Active transport of sodium through tubular epithelial cell. B, Mechanism for active transport of sodium from tubular lumen all the way into the peritubular capillary. C, Mechanism of sodium and potassium transport through the distal tubular epithelium. (*From Guyton, A.(1991) Formation of urine by the kidney 11. Processing of the filtrate in the tubules. In; Textbook of Medical Physiology, 8th edition, W.B. Saunders)*

glomerulus and 99% of the filtered calcium is reabsorbed by the renal tubules. Increased Mg^{2+} excretion is caused by increased extra-cellular calcium.

6.3.2. Renal Pelvis and Ureter

The main function of the pyeloureteral complex is unidirectional transport of urine from the kidney to the urinary bladder. This is achieved with ureteral peristalsis, which is myogenic, and initiated by spontaneously active pacemaker cells in the renal pelvis. Urine flowing from the collecting tubule into the renal calices stretches these calyces and triggers pacemaker activity in renal pelvis. This, in turn, initiates peristaltic contractions that spread to the renal pelvis and ureter. Peristaltic contractions in ureter are evoked by parasympathetic stimulation and inhibited by sympathetic stimulation.

Removal of extracellular calcium totally eliminates the action potential (Brading *et al.* 1983). Prostaglandins regulate the pacemaker potentials of the renal pelvis and ureter (Thulesius et al. 1986). Substance P and Neurokin A are stimulants of pyeloureteral motility (Maggi *et al.* 1993).

Distension of the kidney, pelvis, or ureter and electrical stimulation of renal pelvis or ureter causes severe pain (Cervero 1994).

6.3.3. The Urinary bladder and Micturition

Control of bladder storage and micturition is mediated by co-ordination of the peripheral somatic, autonomic and CNS (Guyton & Hall 1996b). Detrusor muscle can increase the pressure in the bladder to 40 to 60 mmHg. Action potential can spread throughout the detrusor muscle, from one muscle cell to the next to cause contraction to entire urinary bladder. When there is no urine in the urinary bladder, the intravesicular pressure is about zero, but by 30 to 50 ml of urine, the pressure rise to 5 to 10 cm of water. 200 to 300 ml of urine can be accumulated in the urinary bladder without large rise in the pressure. However, beyond 300 to 400ml, the pressure rises markedly. Accommodation of the bladder to increased volumes of urine is primarily a passive phenomenon that depends on internist properties of detrusor and quiescence of the parasympathetic (Chai *et al.* 1996). The storage phase

of urinary bladder can be switched to the voids phase either involuntarily or voluntarily.

Micturition is under voluntary control and depends on learned behaviour that develops during maturation of nervous system. Micturition is the process by which the urinary bladder empties when it becomes filled by urine. Micturition is a spinal reflex, which is facilitated and inhibited by higher neuronal centres and by voluntary control. Contracted smooth muscle of urinary bladder can increase the pressure in the bladder to 40 to 60 mmHg. The first desire to void is initiated at a bladder volume of about 150 ml and a marked sense of fullness at about 400 ml.

6.3.4. The Storage Reflexes

During bladder filling, activation of the storage reflexes causes low detrusor pressure, absence of involuntary contraction and maximal urethral pressure. The inhibition of micturition and bladder activity to allow the bladder to accommodate large volume of urine are due to:

(1) Viscoelastic properties of the bladder wall and electromechanical properties of smooth muscle.

(2) Inhibition of parasympathetic effects and activation of the sympathetic efferent and activation of the sympathetic and somatic effects (Chai & Steers 1996).

(3) Supraspinal centre in the dorsolateral pons (Griffiths *et al.* 1990). Stimulation in the lateral pontine reticular formation causes an increase in sphincter tone and inhibition of bladder activities. Stimulation of primary micturition centre excites the bladder and inhibits sphincter tone.

(4) Visceral-visceral reflex. Activation of afferent nerves from the vagina and cervix inhibit the sacral pre-ganglionics to the bladder and increase uretheral resistance (Fall *et al.* 1978).

(5) Somato-visceral reflex is evoked by cutaneous stimulation which inhibits micturition (Vodusek *et al.* 1986).

(6) Somatic efferent pathway to urethral sphincter. During bladder filling, pudendal motor neurones are activated by vesical afferent input whereas during micturiton, the motorneurones are suppressed.

6.3.5.The Voiding Reflexes

Activation of the sacral parasympathetic efferent pathway to the bladder and inhibition of the somatic pathway to the uretheral sphincter mediate Micturition. As the bladder fills with urine, bladder afferent activity (through the mechanoceptive neurones) triggers a micturition reflex. The afferents synapse on the neurones in the sacral spinal cord. Second-order neurones project to the pons, which elicits a bladder contraction and inhibition of the external uretheral sphincter (Griffiths *et al.* 1990; Kruse *et al.* 1991). Parasympathetic pathways in the pelvic nerve are involved in relaxation of the bladder outlet and a fall in ureteral pressure occurs seconds before the increases in intravesical pressure (Van Waalwisk *et al.* 1991). Release of NO from uretheral nerves may cause relaxation of the urethra (Bennet *et al.* 1993).

6.4.Prostaglandins and Natural Effectors of the Urinary System

6.4.1. Prostaglandins

Prostaglandins comprise a diverse family of lipid autocoids derived from cycloxygenase (COX)-mediated metabolism of arachidonic acid , generating five primary bioactive prostanoids: PGE2, PGF2 alpha, PGD2, PG12 and TXA2 (Smith 1992). The families of prostaglandins, Leukotriens and related compounds are called eicosanoids because they are derived from 20-carbon essential fatty acid that contains 3, 4 or 5 double bonds. Arachidonic acid is either derived from dietary linoleic acid or is ingested as a dietary constituent. Arachidonate is then esterified to the phospholipids of cell membrane. Phospholipase A2 liberates arachidonic acid from phospholipid in cell membranes under noxious stimuli. Arachidonic acid may be metabolised through three pathways (Willoughby *et al.* 2000) (Figures 7&8). Pathway 1 involves COX or PGH synthase (Regier *et al.* 1993). This enzyme has two distinct activities, an endoperoxide synthase activity that converts arachidonic acid into PGG: and a peroxidase activity which converts PGG into PGH COX has two isoforms, COX-1 and COX-2. COX-1 is a constitutively expressed form and its

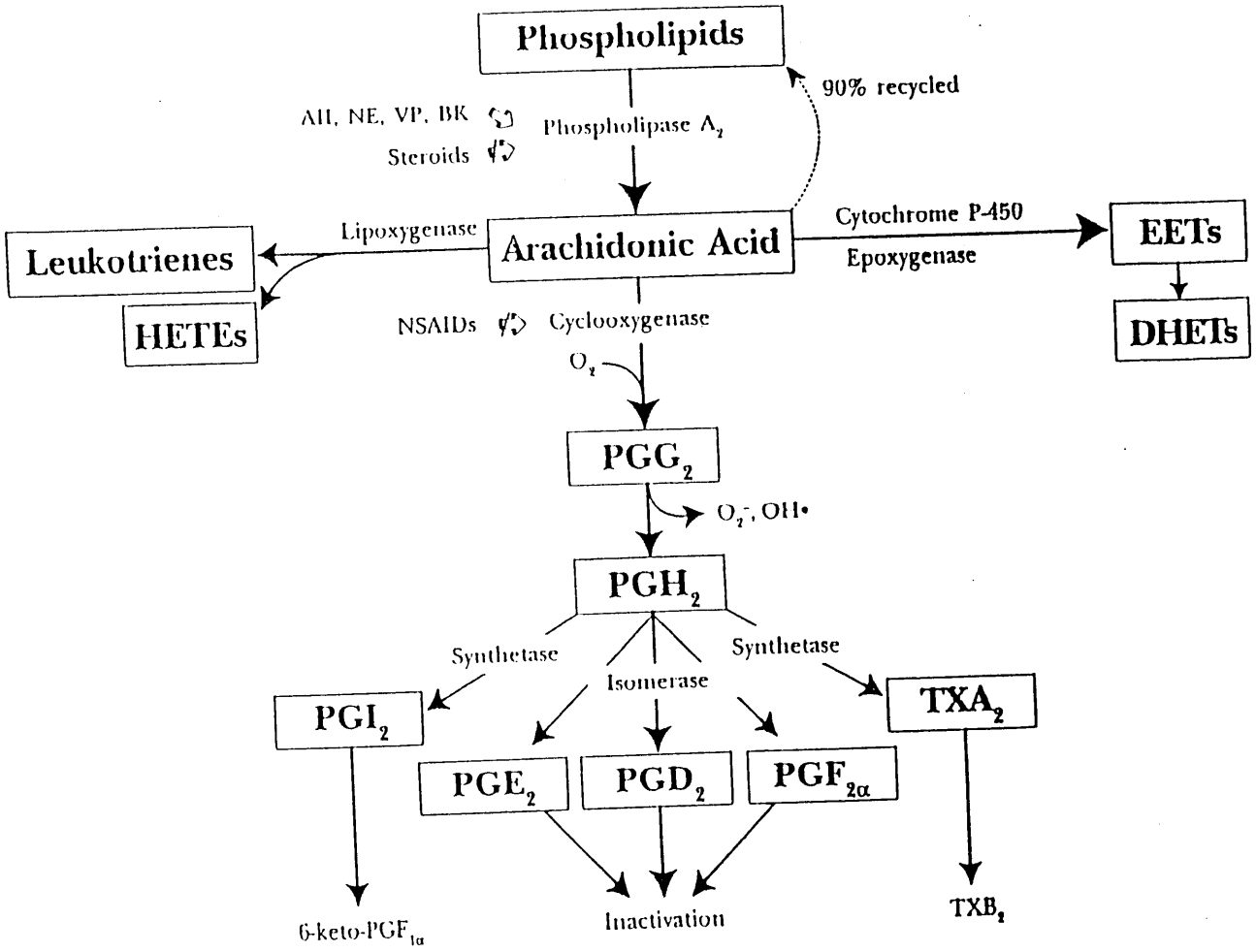

Figure 7 : Arachidonic acid metabolism. Open arrow indicates stimulation and slashed open arrow indicates inhibition of the enzyme. PG: prostaglandin, TX: thromboxane, All: angiotensin 11, NE: norepinephrine, VP: vasopressin, BK: Bradykinin, HETE: hydroxyeicosatetraenoic acid, EET: epoxyeicosatrienoic acid, DHET: dihydroxyeicosatrienoic acid (*From Wen, S.(1997), J Formos Med Assoc, 96, p.158)*

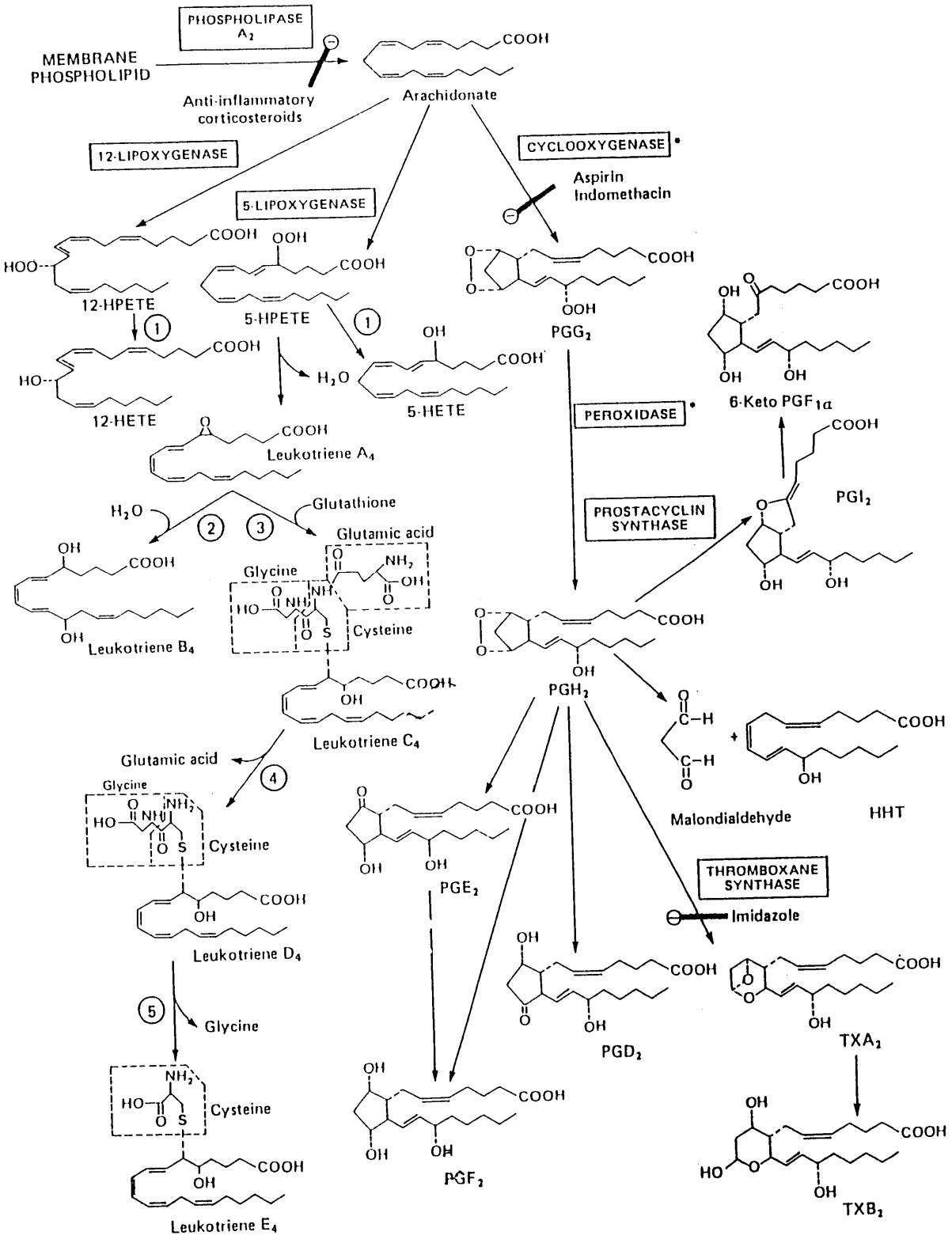

Figure 8: Conversion of arachidonic acid to prostaglandin and thromboxane of series 2 and Leukotrienes of series 4. * Both of these activities are attributed to one enzyme-prostaglandin endoperoxide synthase. 1- Peroxidase, 2- Leukotrien A4 epoxide hydrolase, 3- Glutathione S-transferase, 4- Y-glutamyltransferase, 5- Cysteinyl-glycine dipeptidase (From: Mayers, P.(1985) Metabolisms of lipids: 1-Fatty Acids, In; Harpers Review of Biochemistry, Martin, D. et al.(eds), 20th edition, Lange Medical Publications, California, p. 227.

concentration within a cell is constant once the cell is fully grown (Brannon *et al.* 1994), but may be increased by 2 to 4 fold following a physiological stimulus (Wu *et al.* 1991). COX-2 is an inducible enzyme which is very low or undetectable in normal body tissues (Feng *et al.* 1993; Kam & See 2000). COX1 is responsible for formation of eicosanioids for normal physiological function while COX2 for increased biosynthesis of eicosanoid following an inflammatory response, stimulated cell growth or cell activity (Kam & See 2000).

Pathway 2 involves a group of Lipooxygenase enzymes. The 5-lipoxygenase is the most important enzymes which leads to the synthesis of the leukotrienes (Samuelsson *et al.* 1987).

Pathway 3, where arachidonate is metabolised by enzymes that contain cytochrome P450 to a variety of metabolites including HETE (epoxycicosatrienoic acids) and 19- or 20- hydroxyarachidonate (Fitzpatrick & Murphy 1989).

To date 10 groups of prostaglandins have been discovered. All of these have five members ring. Depending upon the substitution on cyclopentane ring, prostaglandins have been given alphabetical names which ranged from A to J. With exception of PG1, each group of prostaglandins has at least three members. Most of prostaglandins are inactivated during passage through the pulmonary circulation.

6.4.1.1. Prostaglandins and the Kidney

Prostaglandins play a critical role in regulating Na^+ excretion, blood pressure and renal function (Table 1). In the cortex, major sites of prostaglandin synthesis include arteries and arterioles as well as the glomerulus to maintain blood flow and filtration (Bonvalet et al. 1987). Both the cortical and the medullary collecting tubules produce large amounts of prostaglandins (Schlondorff 1986). These prostaglandins act locally by specific heptahelical transmembrane G-Protein-coupled receptors, designated EP, FP, DP, IP and TP receptors (Narumiya *et al.* 1999). Thromboxan A2 (TXA2) is a labile arachidonic acid metabolite that is a potent vasoconstrictor and a stimulant of platelet aggregation (Furel & Fitzgerald 1991). Evidences are accumulated suggesting that all four EP prostanoid receptors subtypes (EP1, EP2, EP3, and EP4) may be expressed in the kidney.

The EP1 receptor was described as a smooth muscle constrictor. In the collecting tubule, activation of the EP2 receptor inhibits Na+ and water reabsorption suggesting that activation of the renal EP1 receptor might be responsible for the natriuretic and diuretic effects of PGE2. (Gugn *et al.*. 1998; Herbert *et al.* 1991). The EP3 receptor acts as a constrictor of smooth muscle and might contribute to fibril reaction (Coleman et al. 1994). PGF2 alpha regulates NaCl and Ca^{2+} absorption in the distal convoluted tubule, increases cell Ca^{2+} and inhibits water permeability in the cortical collecting tubules (Asboth et al. 1996, Fernande-Ligme *et al.*1999).

PGI2 has been demonstrated to play an important vasodilator role in the glomerular microvasculature as well as regulating renin release (Jackson 1989; Bugge *et al.* 1990;Jenson *et al.*1996).

Preglomerular function is under the control of PGI2, whereas postglomerular function is mediated by PGE2 (Frolich 1990). PGI2 induced a 15% elevation of urinary Na^{+} excretion by intrarenal infusion (Villa et al. 1997). PGE2 is the major prostanoid synthesised along the nephron (Bonvalet 1987) and regulates renal microcirculation and water and salt transport (Breyer & Badr 1996). It inhibits water and salt absorption in the thick ascending limb and collecting tubule directly (Herbert *et al.* 1991 & 1993).

PGE2 rapidly induced an increase in urine flow concomitantly with a decrease in urine osmolality and the water diuresis was mediated by an inhibition of vasopressin antiduretic effect (Herbert et al. 1991; Good & George 1996). PGE2 increase intracellular Ca^{2+} in cortical ducts, which might contribute to PGE2-mediated inhibition of Na^{+} absorption (Takaichi & Kurokawa 1988). Prostaglandins increase calcium and magnesium excretion through diminished reabsorption in the loop (Mandon *et al.* 1993).

PGI2 increases distal tubule carbonate ion secretion (Good & George 1996; Wesson 1996). Medullary prostaglandins antagonise effects of different vaso-constrictors such as angiotensin II, norepinephrine, and vasopressin (Mene & Dunn

1992). PGE2 antagonises the action of antidiuretic hormone on collecting tubule water permeability by activation of aquaprin-2 retrieval (Zelenina *et al.* 2000). Prostaglandins lower aldosterone secretion and the diuretic effect of prostaglandin demonstrated after surgery could be mediated by inhibition of the action of antidiuretic hormone (Enzan *et al.* 1994). Atrial natriuretic peptide increases the synthesis of prostaglandin, which might be responsible for diuretic effect of atrial natriuretic peptide (Benzoni *et al.* 1989; Salzar *et al.* 1988).

6.4.1.2. Prostaglandin and Renal Pelvis and Ureter

There was a significant quantitative predominance of the smooth muscle constrictor PGF2 alpha and TXA2 over the dilatory PGE2 in renal pelvis, ureter and bladder (Zwergel *et al.* 1991).

The majority of the afferent renal sensory nerves are located in the renal pelvic wall (Liu & Barajas 1993; Zheng & Lawson 1997). Activation of these nerves by increasing renal pelvic pressure results in an increase in afferent renal activity (Kopp *et al.* 1994). Prostaglandins are importantly involved in the activation of renal sensory nerves by increased renal pelvic pressure and bradykinin (Kopp *et al.* 1994 & 1996). Activation of renal sensory neurones by these stimuli increases the release of PGE2 into the renal pelvic efferent (Kopp *et al.* 1994 & 1996). Substance P is important mediator of the afferent renal nerve activity response to increased renal pelvic pressure and bradykinin (Kopp & Smith 1993).

PGE2 increases the release of substance P from renal pelvic sensory nerves by a calcium-dependent mechanism that requires influx of calcium via N-type calcium channels (Andersson 1993; Kopp & Cicha. 1999). Substance P is a known mediator of pain, which not only activates the inhibitory renorenal reflexes, but also increases pelvic and ureteral peristalsis. Acetylcholine stimulates the endothelial release of prostaglandins, which mediates Ach-induced increase in renal blood flow and urine volume (Kopp & Smith 1993).

Increases in ureteral pressure due to renal stone or clots, distend the renal pelvis and activate renal mechanoreceptors with a resultant increase in ipsilateral afferent renal nerve activity (Kopp *et al.* 1984 & 1995). Ureteral obstruction is associated with increased renal PGE2 synthesis (Kekomaki *et al.* 1989). Increased ureteral pressure results in a renal pelvic release of PGE, which facilitates the release of substance P and activation of renal pelvic mechano- receptor (Kopp *et al.* 1996). Both PGE2 and substance P have been shown to increase renal pelvic contraction. (Kopp *et al.* 1996).

Prostaglandins of the E and F series produce excitatory effects on the motility of the ureter or renal pelvis (Thulesius *et al.* 1986). The rhythmic contractile activity of the ureter is dependent on the local synthesis of prostaglandins (Angelo-Kattar *et al.* 1985; Angelo-Kattar *et al.* 1989).

6.4.1.3.Prostaglandins and the Urinary Bladder and Urethra

Prostaglandins are synthesised locally in both bladder muscle and mucus (Gotoh *et al.*1986; Pairet & Engelhard 1996). The synthesis initiated by nerve stimulation, ATP, bradykinin, stretching of the detrusor muscle, and injury to the vesicle mucosa (Maggi 1992). PGE1, PGE2, TXA2 and PGF2 alpha contract detrusor muscle, whereas PGE1 and PE2 relax the urethra (Palea *et al.* 1998). Prostaglandins may effect the excitation –contraction coupling in the bladder smooth muscle in two ways directly by effect on smooth muscle and / or indirectly via effects on neurotransmission (Andersson & Sjogren 1983; Maggi 1992). PGE2 and PGF2 alpha enhance Ca^{2+} induced detrusor contraction and spontaneous activity (Santicili & Maggi 1998). The human detrusor may contain prejunctional prostaglandin (FP and TXA2) receptor potentiating Ach release from cholinergic nerve terminals (Palea *et al.* 1998). Capsaicin-sensitive afferent in the bladder is chemosensitive and can be activated by prostaglandins to increase the afferent input produced by given degree of bladder filling (Meggi 1992). Distension of the bladder wall can increase the synthesis of prostaglandins (Meggi 1992). Neurones are capable of synthesising and releasing prostaglandins (Franco-cereceda 1989). Endogenous prostaglandins enhance voiding efficiency through an action, direct or indirect, on sensory nerves (Meggi 1992). Intravesical PGE2 increased micturition

and basal pressure and decreased bladder capacity and micturition volume (Pandita *et al.* 1997). Prostaglandins inhibit GABA, which has inhibitory effect on excitatory neurotransmission in human detrusor muscles (Chen *et al.*1994; Ibrahim *et al.*1999).

Prostaglandins can induce bladder overactivity due to release of tackykinins from nerves, a lowering of the threshold for afferent firing and a direct contract effect on the detrusor (Ishizuka *et al.* 1995). PGF2 alpha production increases in conditions associated with oxidative stress such as ageing. In the aged bladder, it was observed that there is super sensitive response to ATP and serotonin (Saito *et al.* 1990). The contractile response to norepinephrine, adenosine 5 triphosphate and serotonin increased with age (Saito *et al.* 1993).

Detrusor instability increases in men from 23.4% (40 to 60 years) to 46.7% (more than 80 years) (Madersbacher *et al.* 1998). PGE1 and PGE2 relaxed contracted urethra induced by noradrenaline and adrenaline (Andersson *et al.* 1988). PGE2 produced a reduction of intra-urethral pressure (Khalaf *et al.* 1981). PGE and PGE2 reduced urethral contraction in a dose dependent manner which is mediated by cAMP (Morita *et al.* 1994).

ATP, VIP, NO and PGE2 elicited concentration dependent relaxation on the proximal urethra (Pinna *et al.* 1996; Ho *et al.* 1998). Prostaglandins caused a strong sensation resulting in reduced bladder capacity and leading to bladder instability (Schussler 1990). The reduction of urethral resistance was most significant with PGE2. Micturition was most provoked by i.v. administration of PGE1 (Kondo *et al.* 1983). Summary of actions of prostaglandins on the urinary system is shown in the table 1.

Action	References	
Inhibit Na+ reabsorption	Gugn *et al.*	1998
Inhibit Na+ reabsorption	Herbert *et al.*	1991
Natriuresis & diuresis	Herbert *et al.*	1998
Inhibit antiduretic hormone.	Good & George	1996
Glomerular vasodilatation.	Bugge *et al.*	1990
Decrease aldosterone secretion.	Enzan *et al.*	1994
Increase HCO3 secretion.	Wesson	1996
Increase calcium & magnesium secretion.	Mandon *et al.*	1993
Increase renin secretion.	Jemsen *et al.*	1996
Increase renal pelvic contraction.	Kopp *et al.*	996
Increase substance P	Kopp *et al.*	1999
Increase motility of renal pelvis & ureter	Thulesius *et al.*	1986
Increase ureteric contraction.	Cole *et al.*	1988
Contract detrusor muscles & relax urethra	Palea *et al.*	1998
Increase acetyle choline from nerves.	Palea *et al.*	1998
Activate capsaicin-sensitive afferent in urinary bladder.	Maggi	1992
Enhance voiding efficiency	Maggi	1992
Release tackykinines & cause micturition	Ishizuki*a et al.*	1995
Relax contracted urethra	Andersson *et al.*	1983
Reduce intraurethral pressure.	Andersson *et al.*	1981
Cause bladder instability	Schussler	1990
Provoke micturition	Konda *et al.*	1983
Increase intracellular calcium	Takaichi & kurokawa	1988
Release calcium from internal stores	Seniro et al.	1992
Increase calcium influx	Shimizu *et al.*	1998
Cause oedema and hyperalgesia	Whelan *et al.*	1991
Increase IL-6 production.	Portanova *et al.*	1996
Inhibit GABA	Ibrahim *et al.*	1999
Cause inflammatory pain	Bley *et al.*	1998

Table 1: The main actions of prostaglandins on urinary system

6.4.1.4. Prostaglandin and inflammation

The inflammatory process is a nonspecific complex, coordinated response of tissue to injury. This process involves vascular permeability, active migration of blood cells and passage of plasma constituents into the injuries tissues. The emigration cells initiate the complex reactions that are controlled by a multitude of intracellular messengers called mediators. Prostaglandin E2 plays a major role in tissue oedema, hyperalgesia and IL-6 production at site of inflammation (Portanova *et al.* 1996).

Prostaglandin and nitric oxide are important mediators of inflammation. Upon stimulation of cells, prostaglandins synthesis increased in the cells by direct interaction between nitric oxide and PGHS (Goodwin *et al.*1999).

Nitric oxide production is increased in inflammatory reaction (Stichtenoth *et al.* 1994). Prostaglandin are generated in response to injury and inflammation and can sensitise or directly activate sensory nerve endings of nociceptions (Smith et al. 1998).

Prostaglandin productions

Many conditions in the urinary system could increase production of prostaglandins which might contribute to pathopysiology of the diseases (Table 2).

6.4.2. Nitric oxide

NO regulates Na^+/K^+ ATPase, Na^+/H^+-exchange and para-cellular permeability of proximal tubular cells (Liang & Knox 2000). NO has important role in inhibition of Na^+ reabsorption (Hagnes *et al.* 1997). It mediates pressure natriuresis and diuresis (Noonan & Banks 1999). NO decreases antidiuretic hormone stimulated water and Na^+ ion transport in the cortical collecting duct and it has a direct effect on cortical collecting duct which may explain its natriuretic and diuretic effects (Garcia *et al.* 1996). The occurrence of relaxant activities in the detrusor attributable to NO seems to be controversial. The detrusor muscle has a low sensitivity to NO and agents acting by the cGMP system (Andersson & Persson 1995). Sodium nitroprusside fails to produce any relaxation (Wheeler *et al.* 1997). In the human bladder, sodium niroprusside was even found to produce contraction (Moon *et al.* 1997). Sodium nitroprusside as well as exogenous NO increased neurogenic detrusor contraction (Lin & Li-shian 1997). NO-mediated relaxation in response to nerve stimulation, which was clear in the trigone and urethra but not in the detrusor (Andersson *et al.* 1992). Nitroprusside and NO are effective in relaxing urethral muscle (Persson & Andersson 1998). Therefore, L-arginine / NO pathway may be one of several possible mechanisms contributing to the decrease in intraurethral pressure preceding micturition. NO stimulates uterine contractions by increasing COX products (Franchi *et al.* 1994). Sodium nitroprusside was able to induce myometrial contractions by stimulating prostaglandin synthesis (Franchi *et al.* 1994). Endogenous NO stimulates the synthesis of PGE & PGF2 alpha in uterine and ovarian tissue (Motta *et al.* 1997). Some of effects of NO on the urinary system are shown in the table 3.

Neuropeptide Y (NPY) and Bradykinin

NPY is a co-transmitter of the sympathetic nervous system. Systemic and intrarenal NPY administration lower renal blood flow, and causes diuresis and natriuresis (Bischoff *et al.* 1996; Bischoff *et al.* 1998). Bradykinin causes renal vasodilitaion, natriuresis and diuresis, smooth muscle contractions, inflammatory reactions, and increases prostaglandin and NO productions (Matsumura *et al.*1999: Couture *at al.* 2001; Rodriguez *et al.*2001).

Conditions	Sites	References
Diabetes, smoking, aging	Bladder	Tarean *et al.* 2000
Bladder nerve stimulation	Bladder	Tarean *et al.* 2000
ESWL	Urinary tract	Hasanoglu *et al.* 1994
Increased ureteral pressure	Renal pelvis	Kopp *et al.* 1996
Ureteral obstruction	Glomeruli	Yanagisawa *et al.* 1991
Nephrotics	Kidney	Ruilope *et al.* 1983
Acetyl chorine	Plasma	Garin & Richard 1984
Activation of renal sensory neurons.	Kidney & bladder	Salom *et al.* 1991
Bradykinin	Kidney	Kopp *et al* 1996
Nitric oxide	Kidney	Salvenmini *et al.* 1994
Stretching of detrusor & nerve stimulation	Bladder	Maggi 1992
Vesicoureteral reflex	Urinary bladder	Walker & Garin 1990

Table 2: Conditions and factors stimulate production of prostaglandins at different parts of urinary system.

Actions	References
Increases renal blood flow & glomerular filtration rat	Campo *et al.* 1996
Inhibits sodium reabsorption	Hagnes *et al.* 1997
Natriuresis & diuresis	Noonan & Banks 1999
Inhibits fluid reabsorption	Liang & Knox 2000
Decreases antiduretic hormone	Garcia *et al.* 1996
Increases neurogenic detrusor contraction	Lin & Lim 1997
Relaxation of trigone & urethra	Andersson *et al.* 1992
Stimulates prostaglandin synthesis	Motta *et al.* 1997
Enhances nocicephors and causes pain	Anbar & Gratt 1997
Urethral relaxation	Garacia-Pascula *et al.* 1996
Mediates inflammation	Salvermini *et al.* 1994
Increases in ureteric obstruction	Moridaira *et al.* 2000

Table 3 : Some effects of nitric oxide on the urinary system

6.5. Diseases of the Urinary System

6.5.1. Enuresis and nocturnal Frequency of Micturition

Detrusor instability commonly is associated with ageing and bladder outlet obstruction (Elbadawi 1995). Age-matched healthy men have an incidence of detrusor instability of 25 to 63%. Frequency, nocturia and urgency increased with age almost equally in men and women, and bladder capacity declined equally in both aged sexes. Aging causes increased lower urinary tract symptoms due to a smaller bladder capacity, increased detrusor instability, nocturnal polyuria and a less contractile bladder (Hald & Horn 1998). Nocturnal polyuria is defined as increased urine output during the night (Asplund 1995). The diurnal pattern of antidiuretic hormone secretion has been changed in the elderly, and plasma levels are often undetectable during night in the elderly with nocturia (Weiss & Blaivas 2000). Many patients with nocturia are found to have a combination of nocturnal polyuria and low nocturnal bladder capacity (Weiss & Blaivas 2000). Recently, other study showed that nocturnal urinary volume and nocturnal capacity were the significant determinants of nocturnal frequency in healthy older men (Kawanchi *et al.* 2000).

Enuresis is a common challenging problem. Conflicting data still exist regarding its aetiology and pathogenesis. Bladder dysfunction may play a role in enuresis. Enuretic children exhibited more frequent and more intense spontaneous evoked contractions of the detrusor muscle and also experienced greater bladder pressure (Scharf *et al.* 1987). Functional bladder capacity in enuresis may be less than 50% of the normal children (McLorie & Husmann 1987). Small functional bladder capacity results from inadequate cortical inhibition development delay or may be part of an allergic reaction in which the bladder is maintained in spasm which prevents it from accommodation large amounts of urine (Doleys & Dolce 1982).

Children with enuresis have been described as a deep sleepers (Wille 1994). Anatomical abnormalities were not usually found in cases of enuresis, but functional

bladder capacity may be reduced in-patient with enuresis (Mayo & Burns 1990; Weerasinghe & Molane 1993). Children with enuresis did not show a normal rise in nocturnal secretion of antidiuretic hormone (Norgaad *et al.* 1985; Ritting *et al.* 1989). Some studies showed a lower nocturnal secretion of antidiuretic hormone with nocturnal enuresis (Fefferman 1994; Eggert & Kuhn 1995). Enuretic children need significant higher antidiuretic hormone plasma levels to maintain constant plasma osmolality (Eggert *et al.* 1999). Na^+ and Mg^{2+} excretion is elevated not only during the night but also through out a 24-hour period in enuresis (Vurgun *et al.* 1998).

Children with enuresis have higher nocturnal Na^+ excretion but not higher nocturnal free-water clearance (Vurgun et al. 1998; Yuri et al. 1999). There is a decrease in the ion reabsorption in the thick ascending LOH (Kuzentsova *et al.* 1996). It has been suggested that there might be a difference in the mechanism of reabsorption of Na^+ and K^+ between enuretic and nonenuretic (Vurgun *et al.* 1998). There was markedly high nocturnal urine production on wet night (Hansen & Jorgensen 1997). Neurophysiological study of enuresis showed hypoexcitability of sphincter nuclei (Podnar *et al.* 1999).

6.5.2. Renal Colic and Urinary Obstruction

Renal colic typically caused by acute obstruction of the ureter by a calculus or by the passage of crystalline precipitate from the renal pelvis through the ureter. The renal colic, typically sudden and severe, manifests as waxing and waning pain in the flank, abdomen, and / or groin and genitalia.

Since the 1970s the role of prostaglandins in ureteral colic has been elucidated (Sjodin 1981; Holmlund 1983). Obstruction of the urinary tract is associated with an increase in pelvic pressure and decrease in renal blood flow, which is associated with increased TXA2 synthesis (Sheehan *et al.* 1994). A greater production of PGE2 and TXB2 was noted by glomeruli from the kidneys with unilateral obstruction (Fukuzaki *et al.* 1993). Increased ureteral pressure results in an increase in afferent renal nerve activity and release of substance P, which is facilitated by renal pelvic

release of PGE (Kopp *et al.*1996). The production of PGE2, PGF1 alpha and TXB2 by cortical and medullary tubules was significantly high in bilateral ureteric obstruction (Fukazaki et al. 1993). PGE2 may participate in calcium stone formation by regulating the renal tubular handling of calcium (Hirayama *et al.* 1988).

Patients with recurrent idiopathic urolithiasis had high level of urinary PGE2, which showed a positive correlation with urinary calcium excretion (Hirayama *et al.* 1988). Pain of acute renal colic might be related to higher pressure in the collecting system proximal to the stone (Holmlund & Sjodin 1978). Stones causing ureteric obstruction are a potent stimulus for renal blood flow and diuresis (Olsen *et al.1965).* In ureteral calculus causing uro-epithelial damage, urine can penetrate subepithelially and induced degranulation of mast cells with release of histamine and prostaglandins causing forceful peristaltic contraction (Ugaily & Thulesius 1988). The pathophysiology of renal colic is related to tension exerted on the excretory cavities by an obstruction, generally a stone, causing secretion of prostaglandin, which, in turn, increases the renal blood flow and glomerular filtration rate. NO is associated with an alteration in glomerular hemodynamics seen after the induction of ureteral ligation.

The expression of NO synthase was significantly greater in glomeruli with unilateral ureteric obstruction in both obstructed kidney and in contralateral non-obstructed kidney (Moridaira *et al.* 2000). Bradykinin stimulates PGE2 release in ureteral obstructed hydronephrotic kidney which is attenuated by NO inhibition (Salvenmini *et al.* 1994). Bradykinin causes renal vasodilitation, natriuresis and diuresis by NO and prostaglandin production (Matsumura *et al.*1999; Tadano *et al.*2001). Inhibition of NO and prostaglandin abolished renal effects of bradykinin (Rodriguez *et al.*2001). In addition, bradykinin causes smooth muscle contractions which depends on calcium and prostaglandin (Oriordan *et al.*2001). Bradykinin causes pain and inflammation (Couture *et al.*2001). Endogenous release of NO in the contralateral kidney and in the obstructed kidney results in increased release of prostaglandins (Salvenmini *et al.* 1994). Events occuring in the ureteric obstruction are illustrated in figure 9.

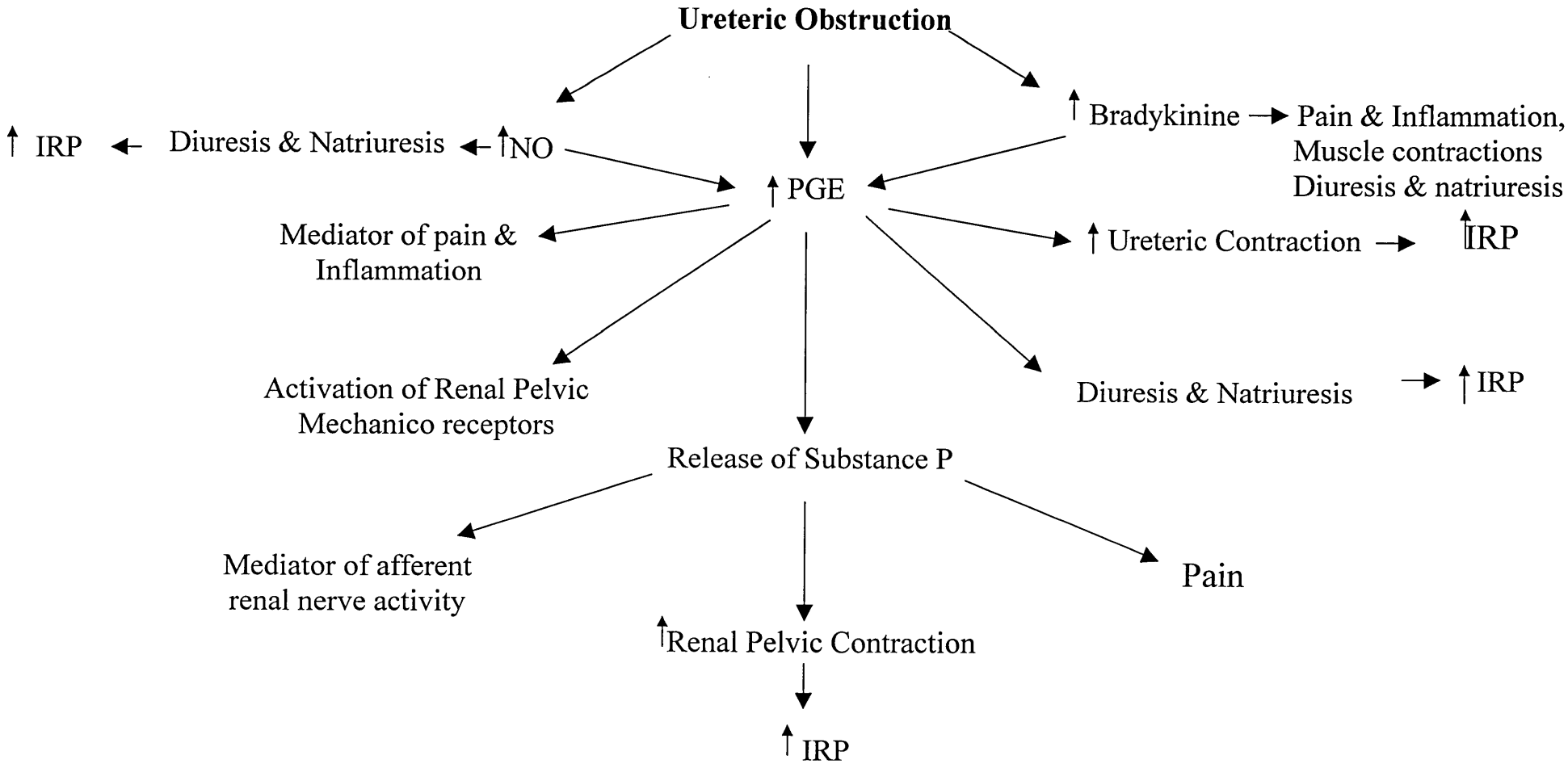

Figure 9 : Events Occuring in Ureteric Obstruction
IRP : Intra Renal Pressure

6.6 Pain

6.6.1 Types and Pathophysiology

Pain is unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage, according to definition by the International Association for the Study of Pain (IASP, 1986). Pain is multifactorial. 15-20% of population have acute pain and between 25-30% suffer from chronic pain (Aghabeigi 1992).

There are two types of pain:

1- Acute pain

It is associated with trauma or diseases and has a well defined location, character, and timing. It accompanied by symptoms of autonomic hyperactivity such as sweating, hypertension, tackycardia and mydriasis.

2- Chronic pain

This is lasting more than few months. There is no signs of autonomic hyperactivity and the patients experience physical, social, psychological, and functional deterioration. It is not necessarily associated with trauma or diseases and its location, character and timing are vague.

Another classification of pain showed that pain may be divided into:

1- Pathological pain associated with underlying diseases and arises from inflammatory response following tissue damage or direct damage of nervous tissue. It may divided into inflammatory and neuropathic pain (Woolf 1989)

2- Psychological pain which may be delusional or may be due to psychologically induced chronic psychological changes.

Physiologically pain may be divided into:

1- Nociceptive pain

It follows activation of nociceptores by noxious stimuli but is not associated with injury to the peripheral nerves or the CNS.

Nociceptors are specific pain receptors that have numerous different receptors such as GABA, bradykinin, histamine, serotonin and capsaicin receptors. The most fascinating aspect of pain perception in the periphery is that normally most of nociceptors lie dormant. Inflammation sensitizes nociceptors. This pain may be divide into:-

1- Somatic pain which is usually well localized pain and may be described as deeply located sharp or dull, stabbing, throbbing or pressure like.
2- Visceral pain which is not evoked by all viscera, is not liked to visceral injury, is referred to other location, is diffuse and poorly located and is accompanied by motor and autonomic reflex. Visceral pain is a prominent symptoms in the clinical setting and one of the main reason for patients seeking medical care. The pain is described as deeply located, aching, cramping or pressing, and may be accompanied nausea and vomiting. Nociceptive pain usually responds to treatment with analgesic.
3- Neuropathic pain

   It is resulted from damage or dysfunction of peripheral nerves/receptors or of the CNS. The pain covers deafferentation pain, sympathetically maintained pain including causalgia and reflex sympathetic dystrophy, painful conditions such as postherpetic and trigeminal neurologia, and diabetes' neuropathy. It responds poorly to analgesia.

There are two types of peripheral nociceptors:

1- Mechanical receptors have high stimulation threshold and respond to intense noxious stimuli. They are associated with rapidly conducting small myelinated A fibers and their stimulation result in sharp localized pain that serves to activate withdrawal reflexes.
2- Polmodal nociceptors respond to mechanical, chemical or thermal stimuli. They are also activated by cellular mediators that are released following tissue damage. They are associated with slowly conducting unmyelinated C types fibers and produce dull, aching and poorly localized pain.

Nerve fibers from nociceptors terminate in the dorsal root of spinal cord before transmission by ascending pathways to the brain. The main types of nociceptor nerve fibers are :

1- C- Fibers. They mediate second pain which is dull, itching or burning sensation. They form majority of sensory nerves (Ran *et al.* 1991)
2- A delta fibers mediate first pain which is sharp sensation. These fibers react to chemical stimuli like bradykinin (Cambell *et al.* 1989).

Primary hyperalgesia is characterized by a reduced pain threshold in damaged tissues to even non-noxious stimuli in which there are changes in the pain threshold within the area of injury, and it is due to sensitization of primary neurons (Ferreria 1981, Raja and Meyer 1988, Raja *et al.* 1988). However, secondary hyperalgesia is due to changes in the surrounding uninjured tissues and is considered to result from activation of NMAD receptors in the dorsal horn of the spinal cord (Woolf 1989, Woolf 1991).

6.6.2. Pain pathway

The following components are included in pain pathway

1-Peripheral receptors.

There are two response to a painful stimulus: a first pain which is well-localized and brief and second pain which is more diffuse. Visceral pain can be referred to a region of the body surface (Cervero 1994).

2-Neural pathway

Important fibers coming from the periphery into the dorsal horn includes

1-Unmyelinated C-fibers

2-Myelinated A delta fibers

3-A beta fibers that carry information about vibration and position sense.

3- Spinal pathway

There are two main pathways

1-Spino-reticulo-diencephalic tract pass to thalamus and from thalamus informations pass to cortex, mainly in the frontal lobe.

2-Neospinothalamic tract that passes to lateral thalamus and then informations pass to postcentral gyrus. GABA, CCK and NPY may play a role in pain transmission

4- Descending pathways

This originated from cortex, thalamus and brainstem. There are serotoninergic-based pathways and noreadrenergic-based pathways that inhibit incoming painful impulses.

6.6.3. Mediators of pain with specific references to prostaglandin and nitric oxide

Inflammatory mediators may exert their effects on nociceptive neurons either by direct coupling to membrane receptors (H+, K+, ATP, Serotonin) or by

indirect action mediated by intracellular second messengers (Prostaglandins, Bradykinin, Histamine). Many inflammatory cells express receptors for neuropeptide that are released from peripheral nerve terminals (Substance P and CGRP) (Besson *et al.* 1987). Stimulation of peripheral nociceptors increases the release of excitatory amino acid such as glutamate which acts at the NMDA receptors (Davis and Lodage 1987).

The nociceptive response to acute tissue injury can be divide into:

1- Release of sensitizing mediators. This includes K+ , H+, which activates the release of substance P, bradykinin, histamine and serotonin (Krishtal & Pidoplichko 1980). These mediators increase prostaglandin productions and lipoxygenase pathway products (Rang *et al.* 1991).

2- Peripheral sensitization of nociceptors by released chemical mediators causing primary hyperalgesia. The inflammatory mediators also stimulate release of stored neuropeptide from the peripheral nociceptors terminals like substance P and calcitonin gene-related peptide and thereby cause vasodilatation, increased vasopermeability, and extravasations of plasma protein and inflammatory cells including mast cells, neutrophils and macrophages (Levine *et al.* 1988).

3- Central sensitization. The synaptic transduction properties of the neurons in the dorsal horn of the spinal cord and other central neurons result in the release of NMDA (Kuraishi *et al.* 1989). The reflux of substance P and excitatory amino acid at the dorsal horn not only causes changes in the neurons with which C-fibers have a common synapse but also in the surrounding receptive field, which is the main reason for the development of secondary hyperalgesia (Woolf 1989).

4- Recovery of normal nociception.

Pain is experienced predominantly during the second and third stage of nociceptive response.

It has been demonstrated that prostaglandins, substance P, VIP, calcitonin gene-related peptide, histamine, serotonin, bradykinin, K+, H+ and ATP are important mediators either as neurotransmitters or senitizers of pain receptors (Helme 1990). Neurogenic inflammation leads to stimulation of C-fibers causing vasodilatation and increased capillary permeability. This is due to local release of substance P. K+, H+, histamine, and bradykinine which in turn cause prostaglandins and interleukienes productions. It has been found that

nerve growth factors, bradykinin and cannabinoids are responsible for primary hyperalgesia (Rice 1998). Nerve growth factor has a key role not only in the development of sensory and autonomic nerves but also in the presence of nociception (McMakon and Bennett 1997).

In general, neurotransmitters can be divided into;

1-Excitatory

This includes glutamate and tackykinin that act at the various neurotinin receptors as substance P. Other mediators that transmit pain impulse from incoming nerves in the dorsal horn including VIP, somatostatin and calcitonin gene-related peptide.

2-Inhibitory. Such as GABA.

3-Neurotransmitters involved in descending pain regulation which includes noradrenaline and serotonin.

Consequence of glutamate receptors activation include production of c-fos and spinal production of prostaglandin and NO (Herdegen and Leak 1998). Central C-fos expression correlates externally with painful stimulation. Noxious peripheral stimulation not only causes fos to appear in the spinal cord but also the inducible transcription factor that control mammalian gene expression.

Regarding prostaglandins and NO, there are abundant data indicating that inducible isofroms, COX-2, is important in inflammation and pain. The constituent isoforms, COX-1 has also been suggested to play a role in the pain and inflammation (Smith *et al.* 1998). Prostaglandins exert central as well as a peripheral hyperalgesic action (Ferreira *et al.* 1973, Van 1971, Ferreira e*t al.* 1978, Yaksh 1982). Prostaglandins did not activate directly but sensitize nociceptors to both mechanical stimuli and other chemical mediators of nociceptors such as bradykinin and histamine (Ferreira 1980, Higgs 1980). Prostaglandin acts with other mediators to sensitize receptors to affect nerve ending to produce inflammatory pain (Vane and Botting 1990).

Sensitizing effects of endogenous prostaglandins have been demonstrated on different indicator of sensory neuron function, including ion channel activation, neuropeptide release and second messenger level (Nicel *et al.*1997). IP receptors

plays a major role in the sensitization of sensory neurones (Jacqueline *et al.* 1998). Prostaglandins activate different second messenger pathway through intervals with several G-protein coupled receptors (Coleman *et al* 1994, Pierce *et al.* 1995). Prostaglandins sensitize the peripheral terminals of primary afferent nociceptors (Ferreira *et al.* 1974, Willis and Corelsen 1973). Prostaglandins contribute to the peripheral mechanism underlying hyperalgesia following nerve injury (Syriatowiz *et al.* 1999).

Peripheral irritation triggers the release of prostaglandin which in turn produces a release of CGRP from primary sensory afferent (Fries *et al.*1997). Prostaglandin E2 potentiated bradykinin-induced hyperalgesia and prostaglandin D2 potentiate oedema (Whelan *et al.* 1991). Acute and chronic peripheral inflammation, interleukienes and spinal nerve injury increase the expression of COX-2 and release of prostaglandin. Prostaglandins decrease firing threshold, increase firing rate and release of excitatory amino acid, substance P and CGRP (Vagegas and Schaible 2001).

It has been found that prostaglandins sensitize or activate nociceptors and elicit spontaneous pain and hyperalgesia when injected peripherally (Hong & Abbott 1994). Prostaglandins contribute to neuropathic hypralgesia (Syriatowicz *et al.* 1999). Nerve growth factor and mast cells were shown to contribute to hyperalgesia following nerve injury and nerve growth factor induces synthesis of prostaglandins by mast cells (Marshall *et al.* 1999; Ro *et al.* 1999). Prostaglandins act on mylinated and unmyelinated afferents (Patermoichelakis and Rood 1982; Birrell *et al.* 1991). Intradermal prostaglandin E2 produces hyperalgesia by descending the threshold of primary afferent nociceptors (Yaksh 1982,Yetunde *et al.* 1985).

Prostaglandin may also play a role in sensitization of central neurons (Willinale *et al.* 1997). After C-fiber stimulation prostaglandin may contribute to nociceptive processing in the spinal cord (Willingale *et al.* 1997). Substance P and neurokinin cause release of prostaglandin (Thorboll *et al.* 1998). Spinal substance P-induced thermal hyperalgesia is mediated by an increase in spinal PGE2 via activation of the neurokinin 1 receptors (Han *et al.* 1999). Prostaglandins act on a G-protein-coupled binding site on dissociated dorsal root

ganglion cells to induce a Ca2+ -dependent release of substance P (White 1996). Following peripheral injury and inflammation, NMDA, substance P and capsaicin significantly increase spinal prostaglandin E2 release in spinal cord and spinal prostaglandin E2 and NK-1 receptors activation play a role in development of hyperalgesia (Dirig and Yaksh 1999). Intrathecal administration of prostaglandin E produces hyperalgesia (Ferreira *et al.* 1978). Prostaglandin F2 alpha also produces hyperalgesia when injected into the spinal subarachnoid space (Yaksh 1982).

Prostaglandins and NO have been shown to be a key mediators involved in the induction and facilitation of spinal nociceptive transmission and central sensitization after peripheral tissue injury and inflammation. NO may act as a retrograde transmitters in the spinal cord (Vetter *et al.* 2001). In addition, NO may be involved in the generation and processing of pain signals (Stegmann *et al.* 2001). It has been shown that low level of NO facilitates cAMP-dependent prostaglandin E2-induced hyperalgesia, whereas higher level of NO produces a cGMP-dependent hyperalgesia (Aley *et al* 1998). Skin hypothermia caused by regional vasodilatation is induced by extravascular NO. NO enhances the sensitivity of peripheral nociceptros (Aubar and Gratt 1997).

6.6.4. Pain in the Kidney and Ureter

Kidneys are insensitive to all forms of stimulation so that no sensation can be evoked by even the most damaging stimuli. Ureters are very sensitive to distension of lumen or inflammation of mucosa (Cervero 1994). Pain sensation in ureter can be evoked by irritation of the mucosa, ischemia of the organ, overdistension and enhanced motor activity (Cervero 1994). Pain is only sensation that can be evoked from ureter and the kidneys. Picking, cutting heating or cooling the outer surface and parenchyma of the kidneys did not elicit any sensation, whereas distension of the kidney, renal pelvis and ureter evoked server pain (Cervero 1994). Electrical stimulation of the organ evoked intense pain (McLellan and Goodell 1943).

Uretral pain in human is usually referred ipsilaterally to a location that follows approximately the lateral edge of the rectus muscle of the abdomen. If

the pain is due to the passage of kidney stone, the area of referral extends progressively toward the supra public region and can reach the scrotal or labial skin and even the medial thigh (Bonica 1990). The most common form of renal and ureteric pain is that produced by acute urinary obstruction due to passage of renal stones. Inflammatory or ischemia of the kidney and subcapsular haematoma can also evoke pain.

Basically two types of renal sensory receptors are recognized:

1-Mechanoreceptors

The activities of these receptors are to trigger regulatory reflexes concerned with the control of the renal blood follow and body fluid (Dibona 1982, Stella and Zanchetti 1991). Some of these can be activated by large pressure increase in the kidney and pelvis (Beacham and Kunze 1969).

2-Chemoreceptors

These are sensitive to chemicals released by the hypoxic kidney and may play a role in renal pain (Moss 1989). They trigger regulatory reflexes to the control of body fluid.

Regarding the ureter, the sympathetic and parasympathetic innervations of the kidneys extend to the tope of the ureter. The bottom half received its own innervations from the hypogastric nerves and its parasympathetic innervations from the pelvic plexus and nerves (Semeneko and Cervero 1992). There are mechanoreceptors at either end of the ureter. They respond to increase in ureteral pressure and may be involved in the pain from pelvis and ureter. Mechanosensitive unites are classified into U-1 contain only 9% of the unites and U-2 contained the vast majority of the unit. The U-2 units could mediate the intensive pain sensation.

6.6.5. Assessment of the pain

Pain is subjective experience which can not be simultaneously shared by others. It is clinically important to accept the subjects description of the pain experience. However, pain is not only subjective but it also something that can be documented in objective fashion particularly after the discovery of gene C-fos which is rapidly expressed in the spinal cord in response to painful peripheral

stimulation (Cross 1994). Though there is no doubt about the physical component of pain, the psychological and social aspect should not be ignored particularly in the case of the chronic pain.

Each year emergency departments see millions of patients with moderate to sever pain. The use of valid, language-sensitive pain assessment method is a critical prerequisite to selection and evaluation of pain treatment. The nature of the patient's pain is one predictor of the response to treatment. It is mainly characterized by its location, intensity, extent, timing and types as well as patterns of radiation, onset of duration and alleviating and aggravating factors. Pain assessment could be multidimensional process and emphasis is on the patients self-report as the major indictor of pain. The multiple components of the pain experiences include:

1-Physiological component. This includes the organic aetiology of the pain

2-Sensory component. How the pain actually feels to the individual who has it (intensity, location, and quality of pain) (Melzack and Wall 1965).

3-Affective component. This is related to how the pain makes the patients fell. Pain has effects on mood, emotional states, and sense of well-being. This component include anxiety, depression and fear.

4-Cognitive component. This includes the manner in which the pain effects person thoughts.

5-Behavioral component. This includes physical activity, medication and treatment (Fordyce 1986)

6-Sociocultural dimension of pain (Snelling 1990; Greenwald 1991)

However, using a variety of instruments allowing the patients to select one that is most meaningful. Despite the growing interest of developing multidimensional scales, the use of uni-dimensional scales in assessing clinical pain is popular for its simplicity, efficiency and ease of use. Pain intensity rating scale must be appropriate for the patients population. When it is not possible to take direct measurement, it is often possible to grade individual in some way. Patients may be asked to assess their degree of something unmeasurable like pain. As pain assessment is subjective, the scales and measurements are of most values when looking at changes within individuals, e.g. before and after intervention.

A questionnaire can be regarded as an instrument in its own right. It may try to measure personal attributes such as level of pain. There are two major types of questions (Altman 1999)

1- open question in which respondents are asked to reply in their won words
2- Closed question in which the possible responses are given

More than 40 potential instruments or tools for pain assessment were used such as McGill- Pain Questionnaire (Melzack 1975), Wiscosin Brief Pain Questionnaire (Daut 1983), Memorial Pain Questionnaire (Fishman *et al.* 1987), Integrated Pain Score (Ventafridda *et al.* 1983), Pain assessment Maps and simple rating scales such as Verbal Rating Scales (VRS) or Visual Analogue Scales (VAS). The McGill Pain Questionnaire (MPQ) is used to specify subjective pain experience using affective, sensory and evaluating word descriptors. The MPQ was developed to indicate the extent of change in pain quality and intensity as a result of an intervention. Patients with acute pain displayed a greater use of sensory word groups while patients with chronic pain used affective and evaluative groups (Reading 1982). The MPQ takes 5-10 minutes to administer. VAS and VRS are widely used and considered as a standardized tools exist for daily assessment of pain intensity (Altman 1999). It has been found that numerical rating scale and a word descriptive scale were equally preferred by patients whether they spoke English or Spanish. Patients in acute pain were able to use both ways of communicating their pain to doctors and thereafter patients could be offered their choices of either of these simple pain rating scales to evaluate pain and the effectiveness of pain-relieving interview (Puntillo and Neighbor 1997). However, some patients have difficulty with expressing their pain by use of numbers. Adults patients are encourage to use the 0-10 scale and if they can not understand or are unwilling to use it, the VRS is used. VRS was found to improve measurement of pain intensity in cancer patients (Au 1994). It was found that a VRS has its value in the measurement of pain intensity with culture relevancy (Chung *et al.* 1999). In VAS, the patient is shown a straight line (often 10 cm long), the ends of which are labeled with no pain in one end and very severe pain in the other end. They are asked to mark the point on the line which represents their perception of pain. It has been found that no significant difference between the horizontal and the vertical VAS-values were found in the assessment of pain (Dreivik and Skoglund 1998). It has been

demonstrated that a difference in VAS pain score of less than 20 mm is unlikely to be clinically meaningful when the patients with acute pain marked the level of their pain on 100 mm VAS and gave a verbal rating of their pain (Kelly 2001). However, in comparison of VAS and other tools of pain assessment, it was found that patients had some difficulty competing the paper and pencil VAS during the procedure (Jensen *et al.* 1998). Berthior *et al.* 1998 reported that in a hospital emergency department both scales were used successively for acute pain assessment in 290 patients. VAS and VRS were used to assess the pain intensity after injection of morphine and it was found that there was no significant difference between the assessment of pain using both tools and the results obtained for both instruments are similar (Billion *et al.* 1994). Moreover, in a series of 255 patients with acute pain, it has been found that pain scales such as VAS and VRS are used easily and convenient for the assessment of pain intensity (Ricard-Hibo *et al.* 1997). In other study, Soyannwo *et al.* 2000 found that VAS and VRS constitute useful tools for pain assessment in patients with acute pain.

Briggs and Closs 1999 studies 417 patients with postoperative pain. Fifty-nine patients (14.2%) did not complete VAS and two patients did not complete VRS (0.05%). It was found that the VRS was more suitable for use. The scores generated from VAS and VRS correlated well. In addition to pain, VAS and 4-point VRS were used for assessment of postoperative nausea (Boogaerts *et al.* 2000). In acute pain , VAS or VRS were used in most of studies reporting the affects of intervention on the patients pain. MPQ may be useful during the initial evaluation and when the person s condition permits. However, in acute pain like severe acute renal colic, some patients are quite ill and only simplest description of pain intensity can be obtained from their evaluation. Moreover, repeated clinical measurements of acute pain must be short and concerns sensory component and pain intensity. In chronic pain , measurement of many component of pain like psychological functions , behavioral dimension, or sociocultural components of pain may be important in evaluation of patients.

6.6.5.1. Choice of pain assessment methods

In section 6.6 we saw that there were many methods for pain assessment. However, recent a review stated that VRS and VAS represent useful tools for acute

pain measurement. In acute renal colic, VSA and VRS were used widely for assessment of pain intensity (Jonsson *et al.* 1987; Cordell *et al.* 1996; Aybek *et al.* 1998). They are easy for quick answering and suitable for patients with acute crisis. In earlier observations, I found that there were no differences in expressing of acute pain intensity using either of the scales (Al-Waili 2001). Prof. Melzack stressed that the VRS and VAS would be valid for our work on acute renal colic and they correlate very highly with other measures of MPQ (Personal communication). Therefore, using either VRS or VAS is valid and acceptable in our studies. We used VRS in four studies and VAS in one study. We selected VAS in one study because patients were able to express their pain intensity using such scale. In other studies most of the patients found some difficulty using the paper and pencil VAS during the attacks. This might be partly related to fact that most of these patients came from villages. Hence, we mainly depend on VRS to measure pain intensity though both scales are valid.

6.6.6. Management of pain

Several approaches to manage pain have been applied (Justin 1993, Justines 1994, Rouveix *et al.* 1999). These are:

1- Inhibition of transmission of pain impulses to the brain.

1- Pain may be managed at a peripheral level as in the use of ice packs or NSAIDs to inhibit local response to trauma or prevent stimulation of nociceptors. Nerve blocks or cryoanalgesia can be used.

2- At spinal level, intervention of pain can be accomplished using stimulation techniques or spinal injections of opioids, local anesthetics. Opioids and psychotropic agents can alter centeral processing of pain impulses. In case of opioids-insensitive pain, many drugs can be used such as corticosteroids, antihistamine, antiemetics, muscles relaxant, anti psychotics phenothiazines and calcium regulatory agents. These are used in bone pain, nausea, vomiting, and pain due to increase intraocular pressure.

2- Physiotherapy, nervous system stimulation, surgery, acupuncture and radiation could be used for management of chronic pain.

In general, analgesic drugs for treatment of pain can be divide into 1-Non-opioids analgesics included NSAIDs which are suitable for use in acute and chronic pain (APS, 1990).

2- Opioids analgesics like morphine which is strongest opioid of choice. It has short half-life with many side effects particularly respiratory depression and dependence.

6.6.7. NSAIDs analgesia

It has been shown that the most frequent prescribed treatment for pain is NSAIDs (Gurwitz *et al.*1994). NSAIDs have been used widely for treatment of various types of pain such as musculoskeletal pain and visceral pain. In addition, they relieve pain in post-herpetic neurolgia, reflex sympathetic dystrophy, chronic neurogenic pain and mechanical hyperalgesia induced by capsaicin (King 1988, Farah 1993, Tharison and Bhattachrgi 1997). The increase use of NSAIDs to treat pain is due to:

1- Lack of unwanted affects of opioids on CNS like respiratory depression and addiction (Cohen 1980)

2- NSAIDs may desensitize the nociceptors indirectly by inhibition of prostaglandin synthesis or by a direct action on the nociceptors (Conory *et al.* 1991).

3- NSAIDs have prophylactic effects of pain (Mattila *et al.* 1983).

The analgesic and anti-inflammatory potencies of NSAIDs are not simply the reflection of a common mechanism, namely inhibition of peripheral prostaglandin synthesis but also through many other peripheral and central mechanisms of actions (Dahl and Kehlet 1993). NSAIDs decrease significantly substance P and NKA response (Thorboll *et al.* 1998). Inhibition of COX-2 represents the most likely mechanism of action for NSAIDs-mediated analgesia and all NSAIDs inhibit neutrophil function such as cell aggregation (Ku *et al.* 1982, Minta and Williams 1985). NSAIDs inhibit phosphodiesterase, resulting in an increase in intracellular cAMP and reducing release of known mediators contributing to inflammatory response (Dahl and Kehlet 1991).

There is increasing evidences that NSAIDs have central mechanism of action that augments the peripheral mechanism which may be result of interference with formation of prostaglandin in CNS (Cashman 1996). NSAIDs prevent the rise in CSF prostaglandin after activation of the NMDA receptors (Bjorkman 1995). It has been found that spinally administered NSAIDs has antinociceptive effects (Wang *et al.* 1995). NSAIDs inhibit prostaglandin synthesis in the CNS mainly in the thalamus (Abdel-halim *et al.* 1978, Attal *et al.* 1988). NSAIDs may suppress the synthesis of prostaglandin because they easily cross the blood-brain barrier (Bannwarth *et al.* 1990). In addition, NSAIDs reduce both brain stem and spinal cord serotonin levels and activate descending serotoninogenic pathways to elicit antinociception (McCormack 1994). Pretreatment with NSAIDs has been shown to reduce hyperalgesia induced by NMDA activation as well as antagonize the hyperalgesia induced by spinal substance P and glutamate receptors (Malmberg and Yaksh 1992, Bjorkman 1995). It has been found that spinal NMDA receptors activation resulted in enhanced biosynthesis of NO from arginine and the anticiptive effects of NSAIDs may in part attributed to interference with endogenous NO activity at spinal cord (Bjorkman 1995). Moreover, NSAIDs may ameliorate or even abolish excitatory amino acid-directed gene expression by reducing NMDA induction of C-fos messenger RNA (McCormack 1994). Steroselective interference of G-protein-induced signals transduction by some NSAIDs may from the basis of an analgesic mechanism unrelated to inhibition of prostaglandin synthesis (Brune *et al.*1991).

In general, NSAIDs have the following actions regarding pain relief:-

1-They have antipyretic, analgesic and anti-inflammatory actions.

2-NSAIDs have antinociceptive action and anti-inflammatory effects (Huskaar *et al.* 1986)

3-The anti-inflammatory action is peripheral while the antinociceptive action is also centrally mediated (Malmberg and Yaksh 1992)

4- NSAIDs inhibit release of noradrenaline from sympathetic nerves ending and may inhibit the development of sympathetic pain (Hedqvist and Brundin 1969).

5- NDAIDs increase beta-endorphines (Martini *et al.* 1982)

6.7. Pharmacokinetics and Pharmacodynamics of Prostaglandin Synthesis Inhibitors

6.7.1. Basic Pharmacology

Pharmacokinetic is the study of what the body does to a drug. Pharmacodynamic is the study of what a drug does to the body. A constant fraction of the drug in the body is eliminated per unit time. The rate of elimination is proportional to the amount of drug in the body. The volume of distribution (Vd) is the amount of drug in the body divided by concentration in the blood. The Clearance (CL) of a drug is the volume of plasma from which the drug is completely removed per unit time. Elimination half-life (t1/2) is the time taken for plasma concentration to reduce by 50%. After 4 half, elimination is 94% complete. The rate of elimination is the clearance times the concentration in the plasma. Bioavailability is the fraction of the administered doses that reaches the systemic circulation. Thus one plot plasma concentration against time, and the bioavailability is the area under the curve. The maintenance dose is equal to the rate of elimination at steady state (at steady state: rate of elimination=rate of administration). Many drugs are metabolized by the liver. The rate of elimination depends on

1-The liver ability to metabolize the drug

2-The amount of drug presented to the liver for metabolism

The drugs administered orally are delivered from the gut to the portal vein to the liver. Higher dose is needed when drug was delivered orally than intravenously.

Drug distribution depends on blood flow and protein binding. More highly bound drugs have a longer duration of action and a lower volume of distribution. An unbound drug is generally considered responsible for pharmacological effects.

6.7.2. Types of the investigated drugs

Drugs investigated in the thesis are listed in the figure 10. The drugs have inhibitory effects on prostaglandin synthesis and activities. In addition, they have effects on NO and neuropeptide production, calcium influx, smooth muscle contraction, antidiuretic hormone activity and water metabolism besides their central effects. The importance of these properties are discussed in relation to their

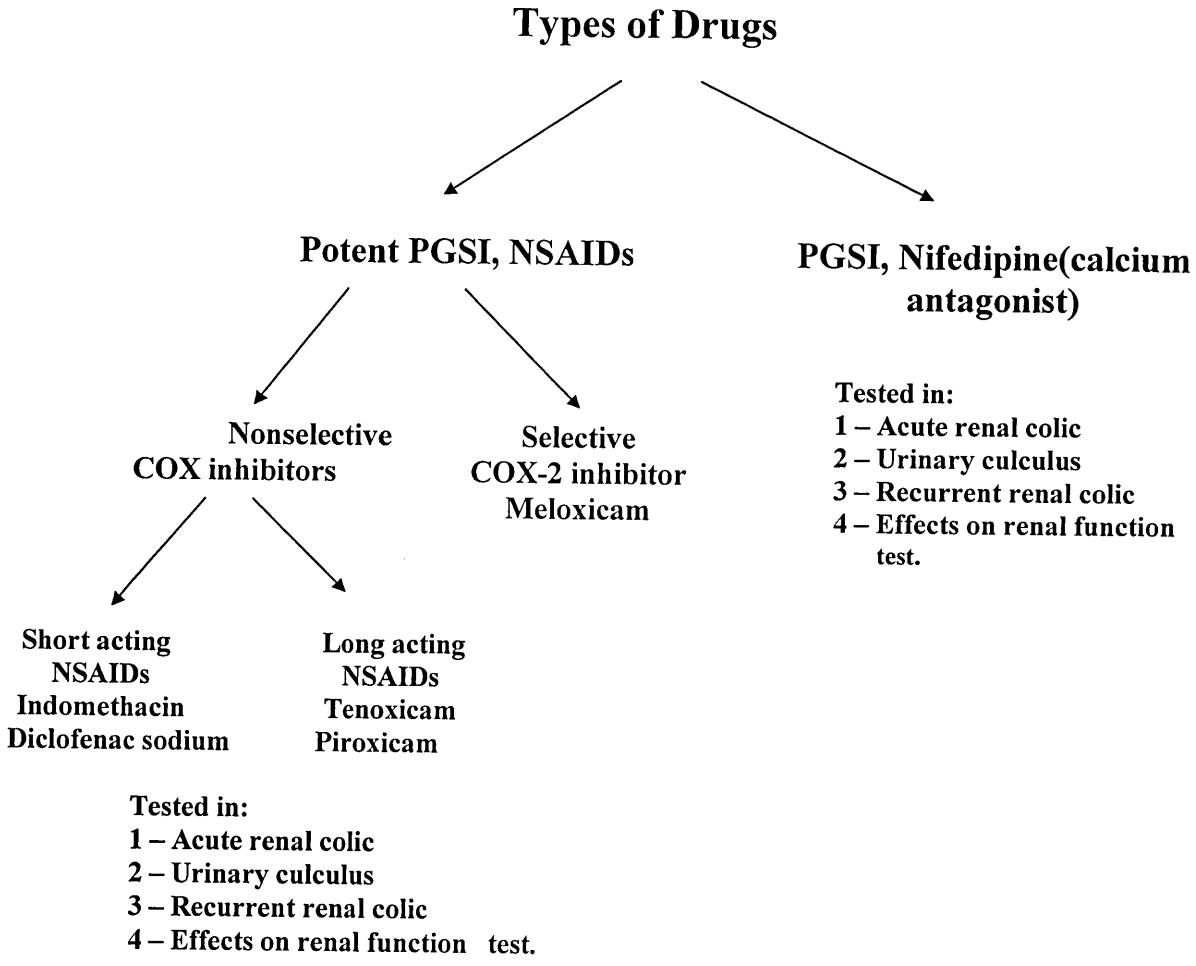

Figure 10; ***Drug tested in renal colic and urinary calculus, PGIS: Prostaglandin synthesis inhibitor***

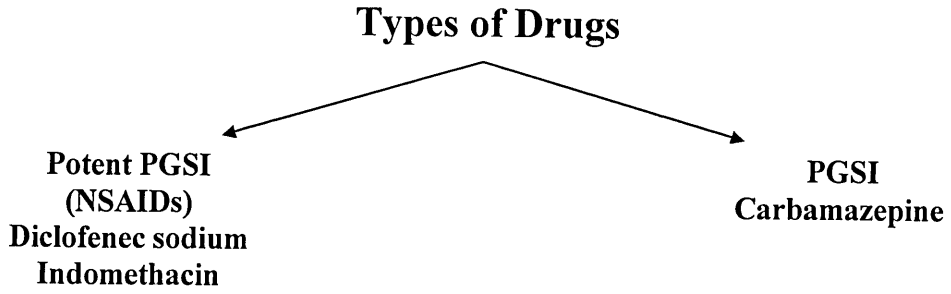

Figure 11; ***Drugs tested in primary enuresis and frequecy of micturition. PGSI: Prostaglandin Synthesis Inhibitor.***

therapeutic effects in primary enuresis, frequency of micturition, pain of renal colic, pain recurrence and urinary calculus.

6.7.3. NSAIDs

6.7.3.1 Classification of NSAIDs

The currently available NSAIDs can be grouped in six major chemical classes (Table 4). However, based on recent studies, it has now become possible to classify NSAIDs on the basis of their relative selectivity for two isoforms of COX enzyme. Older NSAIDs such as indomethacin, piroxicam, tenoxicam, mefenamic acid are non-selective inhibitors of COX enzyme. Recently, number of new agents have been discovered which selectively inhibit the activity and / or gene expression of COX-2. These agents include nemsulide, meloxicam, and celecoxib. Moreover, NSAIDs can be classified into long acting or short acting NSAIDs according to their half-life.

6.7.3.2. Phamacokinetics

NSAIDs are among the most frequently prescribed medication (Roth *et al.* 1988). Among NSAIDs users, 40% to 60% are over 60 years of age (Gurwitz & Avorn 1991). Absorption of NSAIDs is generally complete after oral administration and they are absorbed via passive diffusion (Kean and Buchanan 1987). H2 antagonist, antacids and proton pump inhibitors will elevate gastric pH, altering gastric absorption of NSAIDs. They are weakly acidic, lipophilic and bound extensively to plasma albumin. Most NSAIDs are metabolized by hepatic oxidation, hepatic conjugation or both. Their plasma elimination half-life varies widely from 0.25 to 70 hr. No correlation has been found between NSAIDs adverse effects and half-life (Albengers *et al.* 1988). In case of short half-life NSAIDs, an increase in administration frequency could be expected. Some NSAIDs undergo enterohepatic re-circulation and some experimental evidence identifies biliary excretion as important in the pathogenesis of NSAIDs entropathy (Wax *et al.* 1970). A summary of pharmacokinetics of NSAIDs used in our studies is illustrated in the table 5.

Salicylic acids and esters :
Aspirin , salicylates , salicylamide , salsalate , diflunisal , benorylate.
Propionic acids:
Ibuprofen , fenoproten , naproxen , ketoprofen , piprofen , flubiprofen , oxaprozin, carprofen , suprofen.
Acetic acids:
Indomethacin , tolmetin , sulindac , diclofenac , etodolac , zomepirac
Fenamates:
Meclofenamate , mefenamic acid , flufenamic acid
Enolic acids:
Oxyphenbutazone , phenylbutazone , piroxicam , sudoxicam , isoxicam , tenoxicam, droxicam
Naphthylkanones, nonacidic compounds:
Nabumetone , proquazone , bufexamac

Table (4): Classification of NSAIDs.(Wen,S.(1997) Nephrotoxicities of nonsteriodal anti-inflammatory drugs. J Formos Med Assoc, 96, 157-171).

Drugs	Bound in Plasma (% of plasma total)	t ½ B (h)	Vd (L/kg)	CL/F (L/h/kg)	Renal exccretion (% unchanged)	Primary metabolic Pathways	Biliary excretion (% of total drug)
Diclofenac	99.7	1-2	0.12	0.22	< 1	Oxidation	10-20
Indomethacin	> 90	4.5-6	0.12	0.0024	60-70	Oxidation, conjugation	Extensive
Tenoxicam	98.5	60	0.12	0.102/10kg	Insignificant	Oxidation	0
Piroxicam	> 99	30-86	0.12	0.0024	< 5	Oxidation	0
Meloxicam	99	13-20	0.1-0.2	0.0072	< 0.25	Oxidation	Extensive
Carbamazepin	74	15	1.4	0.076	1	conjucation	0
Nifedipine	96	1.8	0.42	0.78	0	Oxidation	0
CL/F= oral clearance;t ½ B = elimination half-life ; Vd = volume of distribution.							

Table 5: The pharmacokinetic properties of the drugs used in the study.
(Brater1988, Verbeeck 1988, Verbeeck 1990, Sorkin 1995, Holford and Benet 1998, Martindela 1998, Davies & Skjodt 2000).

6.7.3.4. Pharmacodynamics

1- Mode of Action

(1) All NSAIDs appear to inhibit prostaglandin synthesis by blocking COX activity, both COX-1 and COX-2, by binding reversibly or irreversibly to the enzymes (Sharma & Sharma 1997).

(2) Part of the action of NSAIDs may be related to a decrease in the generation of superoxide and hydroxyl free radicals (Ikeda *et al.* 2001).

(3) NSAIDs are antihyperalgesic through a direct action on the spinal cord or inhibition of prostaglandin synthesis in CNS (Cashman 1996).

(4) Interference with G-protein-mediated signal transduction by NSAIDs may form the basis of an analgesic mechanism unrelated to inhibition of prostaglandin synthesis (Cashman 1996).

(5) Epidural application of NSAIDs affects hyperalgesia produced by NO and dose-dependently suppressed nitroglycerine-induced thermal hyperalgesia (Masue 1999).

(6) Inhibition of calcium influx is another mechanism of action of NSAIDs, which is not related to inhibition of prostaglandin synthesis (Kankaaranta 1996).

(7) Inhibition of neutrophil activation might represent another mechanism of action of NSAIDs (Altman 1990).

2- Anti-inflammatory effects

The cardinal signs of inflammation develops as an acute response to a local inflammatory mediators such as prostaglandins, NO, bradykinins, histamine and complement (Garrison 1990, Moncada *et al* 1991). Prostaglandin is produced during inflammatory responses, and increased levels of prostaglandins help mediate some of cardinal signs of inflammation such as pain, oedema, fever and erythemia (Coleman *et al.* 1994).

NSAIDs inhibit prostaglandin productions, interfere with chemical mediators of kallikrienes system, inhibit NO, inhibit granulocytes adherence to damaged vascular tissues, stabilize lysosomes and inhibit migration of leukocytes and macrophages into the site of inflammation (Katzung and Furst 1998). Therefore, NSAIDs possess strong anti-inflammatory properties. It has been shown that a selective COX-2

inhibitor attenuated prostaglandin and thromboxane production in a skin inflammation (Smith *et al.* 1998).

3- Antipyretic effects

NSAIDs reduced elevated temperature. Elevated temperature is due to production of prostaglandin in the CNS, and effect of interleukiene-1 on the hypothalamus. NSAIDS inhibit interleukiene-1 and prostaglandins.

4- Analgesic effects

NSAIDs have a potent analgesic action in different types of pain. They have been used for treatment of acute and chronic pain, somatic and visceral pain. The mechanism of action was discussed in the section 9. More recently, it was suggested that the analgesic actions of NSAIDs in inflammatory pain, especially visceral stimuli, are mediated to a significant degree by inhibition of signaling through EP1 receptors (Stock *et al.* 2001).

5- Platelet effects

NSAIDs, particularly aspirin, might affect homeostasis. Single dose of aspirin produces a slight prolonged bleeding time. This is due to inhibition of thromboxane synthesis (Katzung and Furst 1998).

6- NSAIDs Effects on Renal Functions

NSAIDs have many effects on the kidney functions (Table 4). NSAIDs may possess receptor-mediated mineral corticoid activity to account for their salt-retaining effect (Feldman & Couropmitree 1976). The most efficacious NSAIDs seem to inhibit renal prostaglandin synthesis by only 60 to 80%, a large amount of renal prostaglandin synthesis remains intact (Patrono & Pieruccii 1986). NSAIDs treatment reduces the hyperfiltration, hyperperfusion and vascular glomerular lesions associated with hypertension and diabetes mellitus (Zambraski 1995). NSAIDs were used successfully to reduce urinary protein excretion in proteinuric renal diseases (Ganservoor *et al.* 1992; Remuzzi & Remuzzi 1995). Inhibition of endogenous prostaglandin production by several COX inhibitors caused a reduction of inducible NO synthase (Minghetti *et al.* 1997).

Prostaglandins mediate chronic inflammatory processes and increased synthesis of these compounds may contribute to the pathogenesis of the progressive nephropathy associated with renal mass reduction (Fujihara e*t al.* 1998). Abnormal high synthesis of prostaglandins is seen in renal interstitial inflammation (Vriesendrop *et al.*1986). Chronic treatment with specific thromboxane inhibitors ameliorates glomerular injury (Zoja *et al.* 1990). Chronic NSAIDs treatment may ameliorate progressive nephropathies, glomerular proteinuria and tubular defects such as Fanconi syndrome and Batters syndrome (Usberti *et al.* 1985; Fujihara *et al.* 1998). NSAIDs with short or long half-life do not decrease renal functions in individuals without renal impairment (Lang *et al.*1991). They aided in amelioration of cyclosporin toxicity and in prevention of explanted kidneys being prepared for transplantation (Winchester 1996).

Aspirin has beneficial effects in treatment of some glomerulonephritis such as diabetic nephropathy, pregnancy-induced hypertension and renovascular hypertension and it ameliorates cyclosporin toxicity in transplanted kidney (Winchester 1996). NSAIDs reduce hyperfiltration, hyperperfusion and vascular glomerular lesions associated with the hypertensive state (Zambraski 1995). Thromboxan inhibitors decreased significantly macroalbuminuria in diabetic patients (Tajiri *et al.*1990). NSAIDs-nephropathy including acute nephritis, minimal change nephropathy, membranous glomerulonephritis, may be caused by hypersensitivity (Ravnskov 1999).

7- Other effects

In addition to the main uses of NSAIDs in musculoskeletal disorders, gout, rheumatic diseases, NSAIDs, particularly aspirin, are showing promise in the chemoprevention of colorectal and oesophageal cancer (Morgan 1999). Recently we demonstrated that tenoxicam is safe and effective to treat biliary colic and to prevent complications, particularly cholecystitis (Al-Waili 1998). In paediatrics, NSAIDs are used in the treatment of childhood rheumatic diseases and other chronic inflammatory conditions, symptomatic treatment of fever, or musculoskeletal pain, and in induction of patent ductus arteriosus (Lindsley 1993). We and others found that NSAIDs are useful in the treatment of menstrual disorders, migraine,

postoperative pain, polyhydraminos, premature labour, chorionic carcinoma and skin cancer (Al-Waili *et al* 1985, Al-Waili and Subhi 1988, Al-Waili and Khalaf 1990, Al-Waili and Saloom 2000, Al-Waili 2001, Al-Waili 2001).

6.7.3.5. USES OF NSAIDs

1- Fever
2- Gout
3- Headache
4- Hypersensitivity such as conjunctivitis and rhinitis
5- Malignant disorders. Regular use of aspirin may reduce the risk of development of fatal cancer of the esophagus, stomach, colon or rectum (Thun 1993). We used NSAIDs to treat skin cancer and chorionic carcinoma (Al-Waili *et al.*1985, Al-Waili 1988)
6- Menstrual disorders such as dysmenorrhoea, menorrhagia, premenstrual syndrome. We have used NSAIDs to treat severe primary dysmenorrhoea (Al-Waili and Khalf 1990, Al-Waili 2001).
7- Migraine and menstrual migraine. We used NSAIDs to treat acute attacks of classical migraine or menstrual migraine (Al-Waili and Saloom 2000, Al-Jabouri and Al-Waili 2001,).
8- Orthostatic hypotension
9- Musculoskeletal and joints disorders.
10- Pain due to renal or biliary colic and postoperative pain. We used NSAIDs to treat acute biliary colic and postoperative pain (Al-Waili and Saloom 1998, Al-Waili 2001)
11- Kidney disorders
    1- Use for control of proteinuria due to nephrotic syndrome. We used indomethacin to treat steroid-dependent nephrotic syndrome (Al-Waili 1988).
    2- Use as anti-platelet aggregation agent in mesangiocapillary glomerulonephritis.
12- Attenuation of suxamethonium-induced myalgia (Naguib *et al.* 1987).
13- Partner drug for antibiotics to inhibit the inflammatory response to bacterial death caused by antibiotics (Qualiarello and Schield 1992)
14- Prophylaxis of thromboembolic complications (Schroder and Schror 1992).

6.7.3.6. Side effects of NSAIDS

1- The most common side effects during treatment are gastrointestinal disturbances such as gastrointestinal ulcer and bleeding (Cryer and Feldman 1992)

2- CNS-related side effects such as headache, dizziness, depression and insomnia.

3- Hypersensitivity reaction as rash, fever or asthma. The later may be due to block of the lipo-oxygenase pathway and more leukotrienes released (Schror 1984).

4- Haematological side effects such as anemia, thrombocytopenia or neutropenia.

5- Some NSAIDs cause nephrotoxicity mainly phenacetin. High doses of NSAIDs like indomethacin (10 mg/kg) decrease glomerular filtration rate and renal blood flow (Beilin and Bhattacharga 1975). However, the effect of inhibition on renal prostaglandins is slight in normal situation (Dunn 1984). In stress like hypovolaemia, hypotension or cardiac failure in which high concentration of catacholamines and angiotensin causes vasoconstriction, renal blood flow is dependent on prostaglandin (Dunn 1984). Patients with such stress are at risk from NSAIDs side effects in addition to patients with dehydration, cirrhosis or sepsis (Harris 1992, McDonald 1994). NSAIDs cause salt and water retention particularly when there is preexisting hypertension or sodium depletion (Harris 1992). NSAIDs may cause acute interstitial nephritis, perhaps involving an allergic response (Whelton and Hamilton 1991). General precautions to be obtained include administration to patients with acute peptic ulcer, asthma, history of hypersensitivity to NSAIDs, impaired renal, hepatic and cardiac functions. NSAIDs enhance the effects of oral anticoagulant and reduce the antihypertensive effects of bet-blockers and diuretics.

Some of the effects of NSAIDs on the urinary systems are demonstrated in the table 6.

Decrease renal blood flow, glomerulr filtration rate, and sodium excretion	Tannenbanum *et al.*	1996
Decrease aldosterone	Whelton & Hamilton	1991
Increase antidiuretic hormone.	Whelton & Hamilton	1991
Increase chloride uptake by loop of Henle.	Kirchner	1985
Inhibit calcium mobilization.	Jermy *et al.*	1982
Inhibit spinal nitric oxide & reduce hyperalgesia	Masue *et al*	1999
Decrease proteinuria	Remuzzi & Remuzzi	1995
Decrease urinary stone recurrence	Schlichter & brudig	1990
Inhibit nitric oxide.	Sakitani *et al.*	1997
Inhibit isoproterenol-induced bladder contraction	Bolle *et al.*	1994
Decrease urinary bladder response to Ach	Meggi *et al*	1984
Cause smooth muscle relaxation	Perez vallina *et al*	1995
Cause sodium retention	Zambrski	1995

Table 6: Some actions of NSAIDs on urinary system.

6.7.3.7. Nonselective Prostaglandin Synthesis Inhibitors

6.7.3.7.1. Short Acting NSAIDs

6.7.3.7.1.1. Indomethacin

Pharmacokinetics

Indomethacin, an indole acetic acid derivative (1-(p-chlorobenzoyl)-5-methoxy-2-methylinedole-3-acetic acid), is one of the strongest inhibitors of COX pathways like diclofenac sodium (Menasse *et al.* 1978). It inhibits COX in a competitive reversible manner (Stanford *et al.* 1977).

Indomethacin is a NSAID that was introduced into clinical practice in the early sixties. It is readily absorbed from the gastrointestinal tract in adults and the peak plasma concentration is reached a bout 2 hour after a dose. Absorption may be slowed by food or aluminum or magnesium containing antacids. The bioavailability of rectal suppositories in adult has been reported to be comparable with or slightly less than the bioavailability of indomethacin after oral dosage forms. The bioavailibility of indomethacin after oral or rectal use is about 80% (Martindale 1996). The time until maximum concentration after oral or rectal application varies between 30 min and 4 hours (Turakka and Airaksinen 1974, Hellberg 1981, Moller and Grenabo 1985). The main terminal half-life of indomethacin is 5-7 hours after oral, i.v., i.m., or rectal administration (Hellberg 1981, Moller and Grenabo 1985). Plasma clearance of indomethacin is 1-2.5 ml/min (Helleberg 1981). Indomethacin is metabolized in the liver. Up to 100% of indomethacin is entrohepatically recycled (Helleberg 1981). Excretion of indomethacin and its metabolites is predominantly in the urine (60%) and in the faeces (40%) (Helleberg 1981). About one sixth of indomethacin is excreted into the urine in the unchanged form (Baber *et al.* 1979). About 99.7% of indomethacin is bound to plasma protein, especially albumin (Martindale 1996). Indomethacin is easily cross blood brain-barriers and can be detected in CSF 30 min after i.m injection (Bannwarth *et al.* 1990). It has been found that peak plasma concentrations of indomethacin occurred 20 min after administration of rectal solution, 40 min after intramuscular and 60 min after suppositories. The availability after the two rectal forms was found to be almost the same, 80% (Jensen and Grenabo 1985). Rectal administration is associated with

earlier peak plasma concentration. Watanabe *et al.* 1993 found that plasma reached the maximum level at 30 min after rectal administration. No histological changes of the rectal mucosa were found with multiple treatment with indomethacin suppositories (Ogiso *et al.* 1984). The total daily combined dose by mouth or rectum should be not exceeding 200 mg.

Uses of Indomethacin

Indomethacin is used widely in musculoskeletal and joints diseases and in disease other than musculoskeletal disorders and pain. It is used in the treatment of fever, gout, headache, hypersensitivity, malignant neoplasm, othostatic hypotension, patent ductus arteriousus, eye disorders, polyhydraminos, premature labour (Searle 1990, Johnson 1993, Murphy and Medlry 1993, Merchant and Sakhalkar 1994, Al-Waili and Khelood 2001, Al-Waili and Al-Jabouri 2001). Others and we have found that indomethacin suppository is effective in inhibiting uterus contractions and delaying delivery in-patients in preterm labour (Johnsson 1993; Al-Waili 2001). We have used indomethacin to treat advance chorionic carcinoma and basal cell carcinoma (Al-Waili *et al.* 1984; Al-Waili 1989). Indomethacin has been used to treat patients with glomerulo-nephritis and the treatment proved effective in 65% of the patients (Doreskyi 1991). It has been shown that normotensive patients with chronic glomerulonephritis, but with preserved renal function, have no increased risk of acute deterioration of renal function during administration of indomethacin compared with healthy individuals (Nielsen *et al.* 1994). Improvement in diurnal and nocturnal frequency was obtained with use of indomethacin in patients with detrusor instability (Cardozo & Stanton *et al.* 1980). The use of indomethacin in children with daytime urinary frequency was associated with significant increase in urine osmolality and urine pH, and decrease in urine sodium and potassium levels (Luo 1992). Indomethacin suppository is considered to be favorable agent in reducing polyuria in diabetes insipidus (Fujii *et al.* 1985).

Pharmacodynamic

Indomethacin is a non-specific COX1 / COX-2 inhibitor (Catella-Lawson *et al.* 1999). It reduces PGE2 urinary excretion (Stockes *et al.* 1997; Angnoli *et al.*

1999). Indomethacin inhibits IL-1 and NO production (Du & Li 1999). This explains the beneficial effect of indomethacin on Alzheimer's diseases.

Indomethacin prevents intrathecal PGF2 alpha–induced hyperalgesia (Taiwo & Levine 1986). In the kidney, indomethacin blocked the increase in afferent renal nerve activity and release of substance P and prostaglandin produced by increased ureteral pressure (Kopp *et al.* 1996). Indomethacin stimulates circulating antidiuretic hormone levels and enhances peripheral antidiuretic hormone effects (Walker *et al.* 1994). It also inhibits renin release (Lijnen *et al.* 1991; Olsen *et al.* 1999). Indomethacin decreases mean urinary excretion of PGE2 by 73% and 80% and excretion of sodium (Prescott *et al.* 1990).

Indomethacin reduces arterial natriuretic peptide-induced sodium excretion and creatinine clearance by 75% (Villarreal *et al.* 1997). It decreases fractional Mg^{2+} and calcium excretion (Dai *et al.* 1998). Indomethacin completely abolishes NPY-induced diuresis and natriuresis (Bischoff *et al.* 1998). It reduces the smooth muscle activity of human renal pelvis and upper urinary tract (Zwergel *et al.* 1990). Indomethacin stops spontaneous rhythmic human ureteric contraction that was reactivated by PGF2 alpha (Sahin 1993).

Indomethacin i.v. reduces renal pelvic pressure (Zwergel *et al.* 1991). Motility of isolated ureteral preparation obtained from patients at surgery was dose-dependently inhibited with indomethacin (Angelo-Khattar *et al.* 1985). Indomethacin causes significant reduction of calcium excretion (Hirayma *et al.* 1988). Indomethacin decreased proteinuria, glomerular filtration rate, plasma renin activity and renal PGE2 excretion in nephrotic syndrome. The effects might be due to inhibition of renal prostaglandin synthesis and by lowering transcapillary glomerular hydraulic pressure (Vriescendorp *et al.*1986). Indomethacin potentiates the antiproteinuric effect of blocking angiotensin 11 without impairment of renal function (Perico *et al.* 1998).

Some effects of indomethacin on the urinary systems are demonstrated in the table 7.

Actions	References	
Inhibits COX-1/COX-2	Catella-Lawson *et al.*	1999
Decreases renal blood flow and angiotensin II.	Frokiaer *et al.*	1993
Causes mesangial contraction.	TerBorg *et al*	1989
Decreases renal pelvic pressure.	Zwergel *et al.*	1991
Decrease polyuria	Fujii *et al*	198
Decreases frequency of micturition	Luo	1992
Decreases proteinuria	Vriescendrop *et al.*	1986
Decreases calcium & magnesium excretion	Dai et al.	1998
Decreases sodium excretion	Prescott *et al.*	1990
Inhibits rennin release	Lijnen *et al.*	199
Decreases atrial natriuretic factor induced sodium excretion	Villarreal *et al.*	1997
Stimulates antidiuretic hormone	Walker *et al.*	1994
Decreases urinary prostaglandin excretion	Stockes *et al.*	1997
Inhibits NPY-diuresis & natriuresis	Bischoff *et al.*	1998
Decreases renal pelvic pressure	Zwergel *et al.*	1991
Decreases calcium excretion	Buck *et al.*	198
Blocks release of substance P	Kopp *et al.*	1996
Blocks ATP-bladder contraction	Husted *et al.*	1980
Stops ureteric contraction	Sahin	1993
Inhibits bradykinin & bladder contraction	Nakahata *et al.*	1987
Decreases histamine release from ureter	Nakata *et al.*	1998
Inhibits nitric oxide & IL-1	Du & Li	1999
Inhibits calcium channel	Sawdy *et al.*	1998
Inhibits renal hypoxic damage.	Kim *et al.*	2000

Table 7: Some effects of indomethacin on the urinary system

Side effects

The main side effects of indomethacin are gastro-intestinal disturbances, headache, vertigo, drowsiness, tinnitus, skin rash, stomatitis, and rectal irritation. Renal and hepatic lesions have been reported in patients given indomethacin. Other side effects were occasionally reported such as pruritis, skin rash, alopecia, hypersensitivity reaction, syncope or psychiatric disorders (Boiskin 1987, Sheehan 1989, Weir 1991).

6.7.3.7.1.2. Diclofenac Sodium

Pharmacokinetics

Diclofenac sodium (sodium (O-(2,6,-dichorophenol)-amin0)-phenyl)-acetate) is one of the strongest inhibitors of the COX pathway in clinical use. It is as potent as indomethacin and many times stronger than acetylsalicylic acid (Menasse *et al.*1978). Diclofenac is rapidly absorbed when given as an oral formula, i.m. injection or rectal suppository. 99% bound to plasma proteins. The terminal plasma half-life is about 1 to 2 hours. Peak plasma concentration is 3 h after oral administration as compared to 20-30 min after intramuscular injection of 75 mg. (Kurowski 1988). The peak plasma concentration is reached within 0.6 h after rectal administration (Landsdrop *et al.* 1990). Two hours after intramuscular of 75 mg of diclofenac sodium it could be detected in CSF (Zecca *et al.* 1991). After intravenous infusion, terminal half-life was 78 min (Willis *et al.* 1979). It is subjected to first pass metabolism after oral administration so that about 50 % of the drug reaches circulation in the unchanged form. The main metabolites of diclofenac sodium which account for 40% of all products of biotransformation, displays as antioedematous effect about 30 times less that that of the diclofenac sodium (Mensass *et al* 1978). Diclofenac sodium is excreted in the form of glucuronide and sulphate conjugate, mainly in the urine, about 65%, and also in the feces, about 35% (Fowler 1983). The mean clearance in children, 7.7 ml/kg/min, was twice as long as in adults (Korpela and Olkkola 1990).

Pharmacodynamics and Uses

It inhibits prostaglandin synthetase competitively and irreversibly (Ku *et al.* 1975). Diclofenac is used mainly as the sodium salt for the relief of pain and inflammation in various conditions, gout, eye diseases, fever, pain. We found that diclofenac sodium 75 mg intramuscularly could alleviate post-caesarean pain and reduce the use of opioids (Al-Waili 2001). In addition we have used diclofenac sodium to treat tonic clonic epilepsy (Al-Waili 1988). Diclofenac sodium has been used for treatment of renal and biliary colic (Grossi 1986, Lundstam 1987, Hetherington and Philp 1986; Sanahuja 1990). It is available in a number of administration forms, which can be given orally, rectally or intramuscularly.

Diclofenac sodium decreases the spontaneous phasic activity of renal pelvic smooth muscle (Lundstam *et al.* 1985). Diclofenac as indomethacin, abolish almost completely the contractile response of ureteric muscle to electrical field stimulation (Cole *et al.* 1988). Diclofenac sodium as well as indomethacin exerts a direct protective effect against the hypoxia/ re-oxygenation induced renal cell injury (Kim *et al.* 2000). The usual dose by month is 75 to 150 mg of diclofenac sodium daily in divided doses. It may be also given by deep i.m. injection into gluteal muscle in a dose of 75 mg once or twice daily. When administered intramuscularly it is at least comparable to, and frequently superior to, many narcotic and spasmolytic in conditions such as renal and biliary colic. It is suggested that i.m injectable diclofenac sodium provide fast drug liberation suitable for acute analgesic treatment (Kurowski 1988). It is well tolerated compared to other NSAIDs and rarely produced gastrointestinal ulceration or other serious side effects (Todd and Sorkin 1988). It has no effects on carbohydrate metabolism, insulin levels or tolbutamide metabolism. It does not affect the individual clotting factors (Fowler 1979).

Side effects

The most frequently reported adverse effects were gastrointestinal, CNS-related side effects, allergy or local reactions (Small 1989). Gastrointestinal side effects were reported in 7.6% of patients. CNS adverse effects were reported in 0.7 %, and allergy or local reaction in 0.4% (Willkens 1985). The side effects of diclofenac sodium are usually mild and transient (Small 1989). At higher

concentration, diclofenac sodium also reduces the formulation of products of lipoxygenase like leukotrienes (Ku *et al.* 1986).

6.7.3.7.2. Long Acting NSAIDs

6.7.3.7.2.1. Tenoxicam

Pharmacokinetics

Tenoxicam is a thienothiazine derivative of the oxicam class of NSAIDs, which is a piroxicam analogue. It is a weak acid. It is entirely ionized at physiological pH, has minimal lipophilic properties, high plasma protein binding, and does not accumulate in fatty tissues and skin. Tenoxicam disposition is not influenced by age, sex or diseases (Guentert *at al.* 1987). The pharmacokinetic behaviour of tenoxicam after oral, i.m or i.v administration does not differ, with exception that higher plasma concentration was reached during the first 2 hours after the parental dose. After both i.m and i.v applications, tenoxicam showed a rapid onset of action and reliable improvement of pain states (Jenuet *et al.* 1989). It is well absorbed following oral administration and peak plasma concentrations occur in 1 to 2 hours. The bioavailability of oral tenoxicam was 97% (Heinz *et al.* 1984). Intake of food delays absorption. It has been found that peak plasma concentration occurred in 1 to 2 hrs in fasting patients and in 4 to 6 hrs when tenoxicam is given with food (Guentert 1994, Nilsen 1994). 98.5% of tenoxicam is protein bound. Plasma elimination half-life is about 60 to 75 hours. Tenoxicam is completely metabolised to inactive metabolites, which are excreted in the urine. The two main metabolites, the inactive 5-hydroxy and 6-0-glucurnidated forms, are excreted in urine and bile respectively. Urinary and fecal excretion of unchanged form is less than 1% of the administered dose (Dell *et al.* 1984). No significant differences have been demonstrated in either single or multiple dose pharmacokinetics of tenoxicam in healthy individuals, patients with renal or hepatic failure, or elderly (Crevoisier *et al.* 1989b, Al-Ghamdi *et al.* 1992). No dosage adjustments seem justified for those patients on basis of pharmacokinetics (Heintz 1995). Tenoxicam has a low potential to interact with diuretics, hypoglycaemic drugs, anticoagulants and H2-antagonist (Heintz and Gunter 1987). No clinical or pathological evidence of haematological impairment following intravenous administration of tenoxicam was recorded (Jones 2000). After intravenous of 20 mg, the plasma clearance was low with values from

1.3 to 4.2/min and the volume of distribution was small averaging 20-40% of the total body weight. The median half-life of elimination from the body was 72 hrs (Heintz *et al.* 1984). Administration of 20 mg intravenously, intramuscularly or orally revealed no difference in the half-life of tenoxicam (Jeunet *et al.* 1989). Stebler and Guentert found that after i.m administration, tenoxicam was more rapidly absorbed compared to the oral dose while peak concentration was similar. It is completely absorbed after i.m administration and slowly eliminated (Scaglione *et al.* 1993).

Pharmacodynamic and Uses

Tenoxicam has anti-inflammatory, analgesic and antipyretic properties. It also inhibits platelet aggregation and neutrophil activation and may act as scavenger for active oxygen radicals at site of inflammation (Maffei-Facina *et al.* 1996). The principal pharmacodynamic effect of tenoxicam appears to be related to inhibition of COX and subsequent prostaglandin production (Bradshaw *et al.* 1984; Konig *et al.* 1987). Tenoxicam inhibits a number of leukocyte functions including phagocytosis and histamine release and inhibits also leukotrienes B4 and C4 and PGE2 release (Konig *et al.* 1987; Todd & Clissold 1991).

It is indicated for musculo-skeletal disorders (Caughey & Waterworth 1989; Marcolongoz & Fioravanti 1991). Recently, others and we found that parental tenoxicam is a potent for postoperative pain, acute biliary colic and prevention of acute cholecystitis (Elhakim and Nafie 1995; Al-Waili 1997; Al-Waili & Saloom 1998).

Side effects

The majority of side effects of tenoxicam relates to gastrointestinal tract, nervous system or skin (Todd and Clissold 1991).

6.7.3.7.2.2. Piroxicam

Pharmacokinetics

Piroxicam is well absorbed after oral administration, reaching levels with about 2-3 hours and 5-6 hours after a single rectal dose (Schaintarelli *et al.* 1981,

Richardson *et al.* 1985). Food slows the rate of absorption after oral administration (Hobbs and Twomey 1979). Piroxicam has long half-life of 30 to 60 hours permitting administration once daily (Hobbs 1986). Piroxicam is highly bound to plasma protein; approximately 99% plasma protein bound, and has a volume of distribution of about 8 liters (Hobbs and Twomey 1979). Piroxicam is metabolized by hydroxylation and conjugation in the liver and no more that 5-10% of the dose is excreted as intact piroxicam in the urine (Hobbs 1993). Piroxicam levels are not elevated in patients with renal impairment and renal disease does not appear to alter pharmacokinetics of piroxicam (Woolf *et al.* 1983; Darragh *et al.* 1985). In addition, the pharmacokinetic profile of piroxicam does not increase the risk of adverse reaction in the elderly (Hobbs 1986).

Pharmacodynamics and Uses

Piroxicam is prostaglandin synthesis inhibitors. Piroxicam is indicated for long-term use in the relief of signs and symptoms of the musculo-skeletal diseases. It is given in a usual dose of 20 mg by mouth daily as single dose and some patients require daily doses of 30 mg in single or divided doses (Martindale 1998). 40 mg of piroxicam was used for treatment of acute gout by oral, recta or i.m injection (Lee and Balfour 1994). Piroxicam can be used for treatment of dysmenorrhoea or postoperative pain (Saltveit 1985, Hutchison 1990). Piroxicam was reported to be superior to diclofenac and ketorolac to reduce post-operative pain following laporoscopy (O'Hanlon *et al.* 1996).

Side effects

Side effects are as for NSAIDs in general, and the most frequent adverse effects are gastro-intestinal. Piroxicam like diclofenac and indomethacin do not decrease renal function in individuals without renal impairment (Lang *et al.* 1991).

6.7.3.8. Selective COX-2 Inhibitor (Meloxicam)

Pharmacokinetics

Meloxicam is a new NSAID derived from enolic acid. Single and multiple dosing via oral, intravenous and rectal routs showed that meloxicam is almost

completely absorbed and is bound to plasma protein by more than 99.5% (Turck *et al.* 1995). The highest concentration of meloxicam was seen in the kidneys and liver (Busch *et al.* 1998). Elimination half-life is around 20 hrs, which is, reflected in a total plasma clearance of 7 to 8 ml/min. This indicates that meloxicam is suitable for once-daily administration (Turck *et al.* 1997). Intramuscular meloxicam have a more rapid onset of action than oral meloxicam in acute pain and local tolerance of i.m meloxicam was good and incidence of adverse effects was low (Euller-Zeigler *et al.* 2001). Following i.m administration meloxicam was rapidly and completely absorbed while i.v administration resulted in higher plasma concentration than i.m injection (Najrjes *et al.* 1996). Meloxicam is excreted in feces and urine and urinary excretion of unchanged is negligible (Schmid *et al.* 1995). The metabolites detected in urine are biologically inactive (Poulsen Nautrup and Hortermann 1999). The pharmacokinetic of meloxicam was not substantially altered in patients with mild renal impairment (Boulton-Jones *et al.* 1997). Neither renal adverse effects nor further deterioration in renal function test were reported (Boulton-Jones *et al.* 1997).

Dosage adjustment is not required in the elderly patients (Davis and Skjodt 1999).

Pharmacodynamics and Uses

Meloxicam has potent anti-inflammatory activity, together with good gastrointestinal and renal tolerability (Engelhardt *et al.* 1996). Meloxicam is prostaglandin synthesis inhibitor and it causes selective COX-2 inhibition (Furst 1997). COX-2 is the inducible isoenzyme implicated in the inflammatory response, whereas COX-1 has cytoprotective effects in the gastric mucosa. Meloxicam was well tolerated by patients with renal impairments (Boulton-Jones *et al.* 1997). Meloxicam has high anti-inflammatory potency and it inhibits swelling, bone and cartilage destruction and systemic signs of arthritis (Engelhardt 1996). It inhibits leucocytes migration and shows long-lasting anti-inflammatory and analgesic effect on inflammatory pain. Intramuscular meloxicam has rapid onset of analgesic action in arthritis, sciatica and lumbago (Euller-Ziegler *et al.* 2001). Meloxicam was much better tolerated than diclofenac sodium in the treatment of acute pain associated with osteoarthritis (Valat *et al.* 2001). COX-2 inhibition reduced motility index (amplitude multiplied by frequency) in the upper urinary tract in a concentration-dependent manner (Davidson *et al.* 2000).

6.7.4. Carbamazepine

Pharmacokinetics

Carbamazepine is a complex drug that also possesses anticholinergic, antidiuretic, antiarrhythmic, muscle relaxant, antidepressant and neuromuscular-blocking proprieties. It administered orally. Absorption from gastro-intestinal tract is slow. Oral carbamazepine achieves therapeutic total carbamazepine level within 5 hrs and was well tolerated by patients (Colen *et al.* 1998). Mean maximum plasma concentration, time to reach maximum plasma concentration and half life for carbamazepine were 2.17 +/- 0.42 mcg/ml, 2.72 +/- 1.8 h and 11.67+/- 6.37 h respectively (Renaskar *et al.* 1999). Estimation of plasma half-life of carbamazepine is 10-20 hr (Bertilsson and Tomson 1986). It is widely distributed throughout the body and is extensively bound to plasma protein (75%). Carbamazepine is metabolized in the liver. It is excreted in the urine in the form of its metabolites, carbamazepine 10,11-epoxide, 72% as unconjugated and only 3% as unchanged drug. The remainder is excreted in the feces. Carbamazepine appeared in beast milk, and is excreted in the urine and faeces and extensively bound to plasma protein. The mean half-life of carbamazepine on repeated administration is about 10 to 20 hr.

Pharmacodynamics and Uses

Carbamazepine is chemically similar to tricyclic antidepressants. By blocking postganglionic parasympathetic receptors, it exerts a potent anticholinergic effect on the detrusor muscles (Bissada *et al.* 1979). Since carbamazepine is chemically similar to imipramine, it may increase bladder outlet resistance and enhance the tone of the internal urethral sphincter by blocking parasympathetic norepinephrine re-uptake (Merrill and Markland 1972). In addition, it is a central nervous system depressant and can interfere with the spinal micturition reflex (Wein 1984). Carbamazepine promotes antidiuretic hormone secretion (Smith *et al.* 1977). During carbamazepine treatment, the ability to excrete the oral water load was decreased, the urine / plasma osmolality ratio was higher, and free water clearance was lower (Soelberg & Hammer 1984). The use of carbamazepine was found to induce urinary retention in long-standing diabetes mellitus (Steiner & Bimanns 1993).

Carbamazepine has water retaining propriety mediated by increased renal sensitivity to normal plasma concentration of arginine vasopressin and resetting of osmoreceptors (Stephens *et al.* 1978). Others reported that carbamazepine induced antidiuresis by release of antidiuretic hormone and impaired excretion of a water load (Perucca *et al.* 1978). Plasma osmolality and sodium concentrations were lower during carbamazepine administration (Soelberg, Sovernsen and Hammer 1984). Review states that although hyponatremia occurs in 10-15 % of patients taking carbamazepine, it is seldom symptomatic or severe enough to cause fluid retention (Mucklow 1991)

Carbamazepine increased bladder capacity (Anders *et al.* 1985). Because of its antidiuretic effect, carbamazepine has been used successfully to treat diabetes insipidus centralis. It caused considerable antidiuresis and altered sensitivity to serum osmolality by the hypothalamic osmoreceptors and increased sensitivity of renal tubules to circulating antidiuretic hormone (Rado *et al.* 1973; Vimla *et al.* 1983). In multiple scleroses, carbamazepine could suppress attack of urinary incontinence (Yoshimura *et al.* 1997). On the other hand, carbamazepine dose dependently reduces inflammatory exudates, substance P and PGE2 and it reduced hyperalgesia and oedema (Bianchi *et al.* 1995). In addition, it causes dose-dependent inhibition of both prostaglandin and NO (Matoth *et al.*2000). It has been found that carbamazepine inhibited prostaglandin-induced hyperalgesia (Nakamura-Craig & Follenfant 1995). Carbamazepine induces hepatic microsomal enzymes and can accelerate its own metabolism or metabolism of other drugs. Drugs that can be potentially affected included prazequental, anticoagulants, corticosteroids, antifungal and cyclosporin (Hansan 1971, Bonay 1993, Quinn and Day 1995).

Carbamazepine is used in the management of epilepsy, neuralgia, manic depression, multiple sclerosis pain such as trigeminal neurologia, tinnitus, withdrawal syndromes, and psychiatric disorders (Murphy 1989; Guthrie 1989; Osterman 1976; Skelton 1988).

The suggested initial oral dose is 100 to 200 mg once or twice daily, gradually increased at weekly intervals. The usual oral dose in children is 10-20 mg per kg body-weight and suggested daily doses for children are: up to 5 to 10 years

400 to 600 mg and 10 to 15 years: 600 mg to 1 gram daily (Martindale 1998). It has been used to promote ADH secretion (Seck 1989).

Side effects

The common side effects of carbamazepine are dizziness, drowsiness and ataxia. Gastro-intestinal side effects are less common which included dry mouth, nausea, vomiting, diarrhea and abdominal pain.

6.7.5. Nifedipine

Pharmacokinetics

Nifedipine is a dihydropyridine calcium-channel blocker with peripheral and coronary vasodilator properties. It is rapidly and almost completely absorbed from the gastro-intestinal tract after oral, rectal or sublingual administration (Kelly and Malley 1992). Following administration by mouth peak blood concentrations are reported to occur after 30 to 60 minutes with a half-life of 2 to 5 hours (Ruemsch and Sommer 1982). Peak plasma nifedipine concentrations were reduced when nifedipine capsules were given after a meal (Hirasawa 1985). 92 to 98% of nifedipine bound to plasma proteins and it goes extensive hepatic first-pass metabolism. Nifedipine undergoes complete hepatic oxidation to three pharmacologically inactive metabolites which are excreted in urine, and 30 to 40% of the amount absorbed is metabolized during the first pass through the liver (Sorkin 1985).

Bioavailability after oral administration is between 45 to 75 % and 70 to 80 % of a dose is excreted in the urine almost entirely as inactive metabolites. During sublingual administration of nifedipine, the peak plasma concentration was larger than data obtained following swallowing administration (Palm-Aguirre *et al.* 1989).

Pharmacodynamics and Uses

It has been found that calcium antagonists have inhibitory effects on phospholipase activity and prostaglandin synthesis (Danon *et al.*1986). Nifedipine, a calcium antagonist, could inhibit phospholipase, prostaglandins and leukotrienes (Chang *et al.*1987). It inhibited prostaglandin or leukotrienes in a dose-dependent

manner (Levine 1983). In addition, nifedipine has anti-inflammatory properties and could attenuate inflammatory oedema and pain (Briukhanov *et al.*1994; Sanchez *et al.*1998). In renal tissues, it has been shown that prostaglandin synthesis in response to different stimuli is a calcium dependent process, which could be inhibited by nifedipine (Scharschmidt & Dunn 1983; Wuthrich & Vallotton 1986). Nifedipine exerted an antioxidant action and reduced blood serum PGF2 alpha in asthmatics (Amatuni *et al.* 1992). Nifedipine decreased plasma TXB 2 and PG1 alpha concentrations in both smokers and non-smokers (Nakashima *et al.* 1990). Oral nifedipine attenuated development of inflammatory oedema in dose dependent manner (Briukhanov *et al.* 1994). Nifedipine suppressed carageenan-induced inflammation, an effect, which was potentiated when nifedipine was administered together with indomethacin (Madan *et al.* 1989). Nifedipine, verapamil and indomethacin stop spontaneous rhythmic contractions of human isolated ureter (Sahin *et al.* 1993). The effect of a single 20 mg sublingual dose of nifedipine on function of proximal tubule of nephrone in patients with essential hypertension was studied. It induced an increase in diuresis, natriuresis and excretion of uric acid (Papek-Musialik 1994).

Nifedipine is a peripheral and coronary vasodilator and has little or no effect on cardiac conduction and negative inotropic effect is rarely seen. Its administration results in vasodilatation with reduced peripheral resistance, blood pressure and increased coronary blood flow, and a reflex increase in heart rate (Anonymous 1986). Nifedipine is usually given by mouth. Liquid-filled capsules with a rapid onset, but short duration of action have sometimes been used for sublingual or buccal administration (Storkin 1985). In the management of hypertension nifedipine may be given up to 20 to 100 mg once daily. In angina pectoris, nifedipine may be given in a dose of 10 to 40 mg twice daily or 30 to 60 mg once daily. The liquid-filled capsules may be given in an initial dose of 10 to 20 mg three times daily. The pharmacological effect of intranasal or sublingual was superior. For clinical usage, nifedipine capsules in which a hole is made with a needle, administered sublingually, can be effectively and safely used for rapid management of elevated blood pressure (Kubota *et al.* 2001). 20 mg of nifedipine sublingually was used for long time to treat patients with achalasia, 30-60 min before each meal (Bortolotti 1999). It has been found that sublingual nifedipine resulted in significant lowering of blood pressure without hypotension in pregnancy and it was

concluded that sublingual nifedipine was effective, easy to administer and without serious complication (Gallery and Gyory 1997). Sublingual nifedipine was used to treat hypertension in children and found to be effective for rapid control of severe hypertension (Kumar 1996). Sublingual nifedipine was used in pediatric patients with renal diseases and acute severe hypertension. An initial and rapid response was evident as early as 3 min post administration. The greater hypertensive effect was seen during first 30 min (Marror Arroyo *et al.* 1991). Moreover, 20 mg sublingual nifedipine induced an acute improvement of left ventricular diastolic dysfunction (Grandi *et al.* 1996).

Basically, nifedipine is used in the management of hypertension, angina pectoris and Raynaud's syndrome. It has also been tried in numerous non-vascular disorders. It has been shown that nifedipine 10 mg sublingually has achieved a rapid reduction in blood pressure without causing dangerous hypotension (Angeli *et al.* 1991; Al-Waili & Hasan 1999). We found that sublingual nifedipine was effective in the treatment of severe essential hypertension and in pregnancy-induced hypertension (Al-Waili 2001). I have demonstrated that concurrent treatment with nifedipine permitted a significant reduction in corticosteroid intake without worsening asthma scores and to abort acute asthmatic attacks (Al-Waili 1988 & 1999). Moreover, I have shown that nifedipine has a spasmolytic activity on intestinal muscles (Al-Waili 1990). Nifedipine has been used in the treatment of epilepsy, gastrointestinal spasm, dysmenorrhoea, cough, cramp, cardiomyopathies, hiccup, irritable bowel syndrome, migraine, myocardial infarction, esophageal disorders, myotonia, premature labour, phaeochromocytoma, and pulmonary hypertension (Rubin 1983, Read and Wellby 1986; Lenders 1985; Grigg and Wolfe 1991; Gifford 1991; Fogari 1992).

Regarding renal disorders, nifedipine has a protective effect on renal function and has also been reported to protect against cyclosporin-induced nephrotoxicity in renal transplant patients (Epstein 1992). It has been found that nifedipine and ACE inhibitor had similar effects on urinary excretion of albumin in diabetics (Demarie & Bakris1990). Nifedipine prevented increases in albuminuria in normotensive diabetic patients and decreased albuminuria in hypertensive diabetic patients (Melbourne Diabetic Nephropathy Study Group 1991). Improvement in renal function has been seen in patients with hypertension and moderate renal dysfunction given nifedipine

(Reama 1991). Nifedipine 10 to 30 mg by mouth has ability to inhibit detrusor contractions in women with urge incontinence (Rude 1979).

Side Effects

The most common side effects of nifedipine are associated with its vasodilator action such as headache, dizziness, flushing, palpitation, and peripheral oedema. Other side effects such as nausea, vomiting, gastrointestinal disturbances, lethargy, eye pain, skin rash and mental depression have also been reported (Martindale 1998).

6.7.6. Drugs selected for the studies

Drugs used in the studies were selected according their pharmacokinetics and pharmacodynamic properties (Section 6.7). The main purposes of the studies were to investigate effects of prostaglandin synthesis inhibitors on pain intensity of acute urinary colic, enuretic episodes in patients with primary enuresis and frequency in patients with primary nocturnal frequency of mictrution, besides their effects on renal functions (Figure 12,13). Prostaglandin inhibitors belong to NSAIDs and to other groups were used. Nonselective prostaglandin inhibitors were used in acute renal colic, primary enuresis and frequency of micturition and COX-2 inhibitor was used in acute renal colic. Indomethacin and diclofenac sodium are nonselective short acting prostaglandin inhibitors belong to NSAIDs. They were used for treatment of acute renal colic, primary enuresis and frequency of micturition. Tenoxicam and piroxicam are nonselective long acting prostaglandin synthesis inhibitors used for treatment of acute renal colic (Figure 10,11). Meloxicam, a selective COX-2 inhibitor, was used for treatment of acute renal colic. Nifedipine was selected for treatment of acute renal colic since it has prostaglandin inhibitory action as well as spasmolytic properties. Carbamazepine used for treatment of enuresis because it has antidiuretic action and it inhibits prostaglandin synthesis (Figure 11)

7. Hypotheses and purposes of studies

7.1 Prostaglandin and Primary Enuresis

It is clear that prostaglandins play an important role in the pathogenesis of many diseases of urinary tract, including; natriuresis and diuresis, inhibit antidiuretic

hormone, lower aldosterone secretion, increase renal blood flow, urine output, arterial natriuretic peptide and micturition pressure, and decreased bladder capacity and micturition volume. In enuresis, there is a reduction of functional bladder capacity, typical unstable detrusor contraction or low compliance. In addition, urinary electrolyte excretions are elevated and there is high nocturnal urine production. Therefore, it is logical to hypothesize that prostaglandins may play a role in the pathogenesis of primary nocturnal enuresis.

In order to test this hypothesis, prostaglandin synthesis inhibitors, indomethacin, and sodium diclofenac (NSAIDs) were used to treat subjects with primary nocturnal enuresis. Carbamazepine, another prostaglandin synthesis inhibitor, was also tested in enuretic patients.

7.2 Prostaglandin and Nocturnal Frequency of Micturition

There are common suggested pathophysiological mechanisms for both primary enuresis and frequency of micturition (such as increased bladder irritability, nocturia, decreased bladder capacity and low level of nocturnal antidiuretic hormone). Therefore we hypothesised that nocturnal frequency of micturition, in otherwise normal individuals, might be due to over production of prostaglandins or the action of renal prostaglandins.

In order to test this hypothesis, indomethacin was used to manage healthy subjects with primary nocturnal frequency of micturition. Indomethacin was chosen because it is a potent prostaglandin synthesis inhibitor and it inhibits natriuresis, urinary flow rate, NPY, bradykinin-induced smooth muscle contraction, atrial natriuretic peptide-induced Na^+ excretion and NO production and it stimulates antidiuretic hormone secretion.

7.3 Nitric oxide and enuresis

Similarly to prostaglandin, NO plays a role in the pathophysiology of urinary diseases, including; increases renal blood flow, glomerular filtration rate and causes diuresis and natriuresis. In addition, NO inhibits sodium and fluid reabsorption and decreases antidiuretic hormone secretion. Relaxation of trigone, bladder neck and urethra was mediated by NO during micturition. Therefore, we hypothesized that NO might play a role in the pathogenesis of enuresis and frequency of micturition besides

prostaglandins. Urinary nitrite excretion was measured in enuretics and compared with normal control subjects. Indomethacin, which inhibits both prostaglandins and NO, was used to treat enuretics in whom nitrite excretion was measured before and after treatment.

7.4 Prostaglandin and Urinary Calculus

Prostaglandins cause inflammation and oedema, which may possibly contribute to stone impact. Therefore, I hypothesised that inflammation and oedema around the stone might impact the stone in the urinary tract. Therefore, prostaglandin synthesis inhibition by NSAIDs and the calcium antagonist, nifedipine, might facilitate passage of urinary calculus by inhibition of inflammation and oedema around the stone and also cause relaxation of urinary smooth muscle. In order to test this hypothesis, indomethacin was used in patients with renal or ureteric calculi awaiting surgical removal. Nifedipine was used for long-term management of recurrent renal pain and urinary calculus.

7.5 COX-2 and Renal colic

It has been suggested that renal prostaglandin production in normal kidneys is driven by the activity of constitutive COX-1, while at sites of inflammation, such as hydronephrotic kidney, there is induction of COX-2 (Seibert *et al.* 1996). Urinary calculus stimulates the synthesis of prostaglandin that contributes to increases intra-renal pressure and local inflammation, increases peristalsis and activation of renal sensory nerves. I hypothesised that renal COX-2 may be increased during ureteric obstruction and renal colic due to urinary calculus, which causes increased production of prostaglandin.

7.6 Purposes of the Studies

The objectives of the present studies are to highlight the following topics and questions:

1- Do NSAIDs reduce nocturnal frequency of micturition in otherwise healthy individuals?
2- Do prostaglandin synthesis inhibitors given through oral or rectal routs reduce bedwetting in children not responding to antispasmodics, imipramine

or fluid restriction? And do enuretic patients not responding to NSAIDs respond to higher doses of these drugs?

3- Does carbamazepine improve primary enuresis and can NSAIDs improve patients not responding to carbamazepine?

4- Does urinary nitrite excretion increased in primary enuresis?

5- Does indomethacin which inhibits both prostaglandins and NO affects urine volume, urine osmolality, urine electrolytes, serum osmolality, serum electrolytes, clearance of free water, fractional sodium excretion, filtered sodium, creatinine clearance and 24 hrs urinary protein in patients with primary enuresis in normal and small functioning bladder capacity.

6- Do short acting NSAIDs given through rectal or sublingual routs relieve acute renal colic and renal colic resistant to antispasmodic/analgesic interventions and facilitate urinary calculus expulsion?

7- Do long acting NSAIDs relieve acute renal colic or prevent pain recurrence?

8- Are there differences between long and short acting NSAIDs and between long acting NSAIDs and spasmolytic/analgesic in the treatment of acute renal colic concerning efficacy, pain recurrence, side effects and cost of the treatment?

9- Does COX-2 inhibitor relieve acute renal colic?

10- Does nifedipine relieve acute renal colic and possess prophylactic effect in recurrent renal colic and facilitate passage of urinary calculus?

11- Do NSAIDs, nifedpine or carbamazepine affect renal function tests?

8. Trial Design

8.1 Steps and objectives of the studies

Two kinds of studies were conducted in relation to the urinary tract diseases concerned in the thesis.

8.1.1. Studies on primary nocturnal enuresis and frequency of micturition.

Primary nocturnal frequency of micturition and primary enuresis are common and controversy still exists regarding their aetiology and management. I suggested in my theories that there might be a correlation between prostaglandin and NO and pathogenesis of these challenging urological problems. This based on the effects of prostaglandins and NO on physiological functions of the kidney, urinary bladder, urethra and autonomic nervous system and on the pathophysiological changes occurred in enuresis and frequency of micturition such as reduced bladder capacity, irritable detrusor and nocturia. If this is true, inhibition of prostaglandin might reduce bedwetting and frequency of micturition. Therefore reduction of prostaglandin biosynthesis might help patients with frequency and enuresis. To test this hypothesis seven steps were followed:

- Inhibition of prostaglandin production was obtained firstly with use of potent prostaglandin synthesis inhibitor, indomethacin suppository, which was used in patients with nocturnal frequency of micturition. The patients were treated with 100 mg of indomethacin suppositories administered before retiring. The patients were followed for number of micturition and any adverse effects. If the patients improved, we would move to the next step and applying same principle in the treatment of primary enuresis.

- As I stated that there might be common pathogenesis for enuresis and frequency as both have been shown to have small functioning bladder capacity, nocturia, irritable detrusor or abnormal antidiuretic hormone secretion and response. Therefore, I tested the possible efficacy and safety of potent prostaglandin inhibitor, diclofenac sodium, in children with primary enuresis. The drug was compared with placebo. 50 mg of diclofenac sodium once daily was first tested and the response as well as adverse effects was monitored.

- If there were no response regarding number of night wet to the 50 mg diclofenac sodium, the dose would be increased to 75 mg to test whether the response is dose-related. When I got favorable response from second and third step, I would move to the next step.

- This step is important since I tested another potent prostaglandin synthesis inhibitor, indomethacin suppository, in management of patients with resistant primary enuresis. The patients were selected randomly from large group of patients who showed no responses to fluid restriction, antispasmodics and imipramine. 50 mg/day of indomethacin was used firstly and the patients would be followed for number of night dry, adverse effects or development of nocturia.

- If there was no response to 50 mg of indomethacin, it was decided to treat the patients with higher doses of indomethacin to explore whether the response was also dose-related.

- In this step I tested whether another prostaglandin synthesis inhibitor drug, carbamazepine, could improve patients with primary enuresis. The patients were selected from large group of patients who showed no response to antispasmodics or imipramine. Carbamazepine belongs to different group, viz, not to NSAID group. In addition, carbamazepine was chosen since it possesses pharmacodynamic actions that made it suitable candidate for this study. It is chemically similar to imipramine and exerts a potent anticholinergic effect. In addition, it is a CNS depressant and promotes antidiuretic hormone secretion and inhibits prostaglandin and NO production.

- Patients who showed no response to carbamazepine were treated with potent prostaglandin synthesis inhibitor, indomethacin suppository. This would disclose whether the patients not responding to carbamazepine might respond to potent prostaglandin inhibitor from NSAIDs group. According to similarity of actions of prostaglandins and NO and their interaction in many biological systems, we hypothesized that NO might play a role in the pathogenesis of primary enuresis and frequency of micturition. Hence, we conducted study, which is the 8^{th} step.

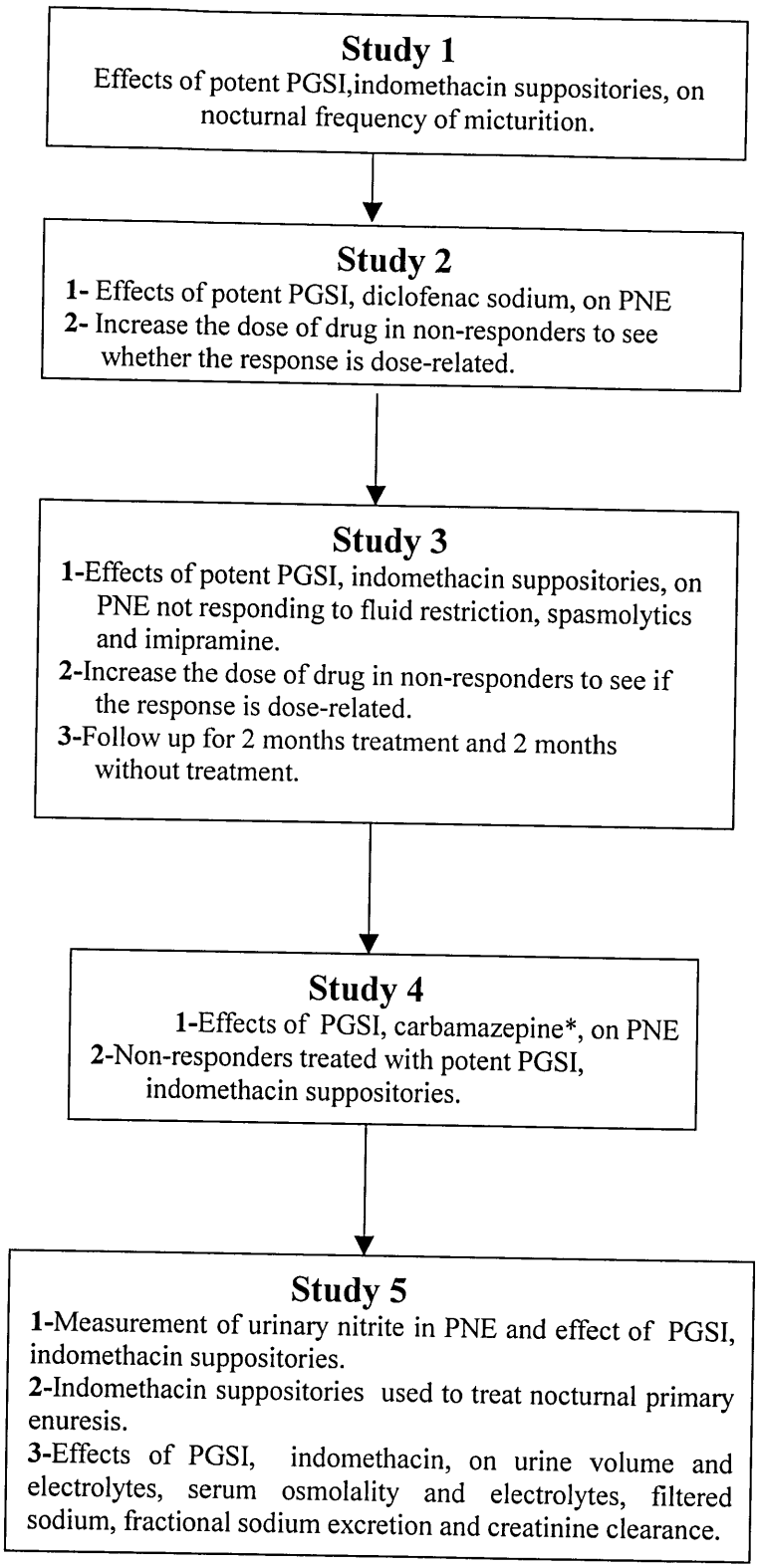

Figure (12) : Steps of studies on nocturnal frequancy of micturition and primary nocturnal enuresis. PGSI : Prostaglandin Synthesis Inhibitor, PNE : Primary Nocturnal Enuresis. * (Bianchi *et al.* 1995; Nakamura *et al.*1995; Matoth *et al.*2000)

- Urinary nitrite excretion was measured in patients with primary enuresis and compared with normal control. The patients were treated with indomethacin and urinary nitrite was measured before and after treatment and its level was discussed with the responses of the patients. To investigate the mechanism of action of indomethacin on patients with enuresis, a 9th step was carried out.

- Enuretic subjects were treated with indomethacin suppositories. Urine volume, urine electrolytes and osmolality, clearance of free water, osmolar clearance, filtered sodium, fractional sodium excretion, creatinine clearance, 24 hrs urinary protein, serum electrolytes and osmolality and functional bladder capacity were measured before treatment and at day 15 during treatment.

8.1.2- Studies on the acute renal colic and urinary calculus.

According to the review of the literatures regarding pathophysiological role of prostaglandins and NO in the urinary system and pain we could summarized that the pain of renal colic may be attributed to:

- Local ischemia due to ureteric and pelvic wall distension, stone impacting and local oedema.
- Prostaglandins stimulate and facilitate calcium influx, which triggers smooth muscle contraction, and increases peristalsis.
- Ureteric obstruction stimulates increases in renal blood flow, diuresis and high atrial natriuretic peptide and prostaglandin production, which in turn contributes to increased intra-renal pressure and activation of renal sensory nerve.
- Ureteral damage by stone causes release of histamine, bradykinin and prostaglandin which contribute to local inflammation and increase peristalsis.
- Prostaglandins facilitate release of substance P from renal pelvic sensory nerve by calcium-dependent mechanism.
- Prostaglandins sensitise nociceptors and elicit hyperalgesia.
- Production of NO in the obstructed kidney contributes markedly to increase prostaglandin release.

Prostaglandin synthesis inhibitors, NSAIDs and nifedipine, were used in eight consecutive studies to treat acute renal colic and urinary calculus. Two types of

NSAIDs were studied, short and long acting potent prostaglandin synthesis inhibitors, which are selective and nonselective COX inhibitors. In addition to their effects on prostaglandin biosynthesis, NSAIDs could inhibit NO production, significantly decrease substance P, desensitize nociceptors, inhibit release of noradrenaline from sympathetic nerve ending, increase beta-endorphins and have central and peripheral analgesic actions. They inhibited bradykinin-induced smooth muscle contraction. Calcium antagonist, nifedipine, inhibits prostaglandin production, attenuates development of inflammatory oedema and has anti-inflammatory activity. It inhibited bradykinin-induced smooth muscle contraction. Nifedipine inhibit phospholipase A2, PGE2 and LTC4 (Chang *et al.* 1987). Nifedipine has analgesic and antinoceptive action (Miranda et al. 1992). Previously we used nifedipine orally or sublingually to treat asthma, intestinal colic, post-partum hypertension, epilepsy, emergency hypertension and allergy (Al-Waili 1989, 1990, 2000 & 2001; Al-Waili & Hasan 2000).

Eight steps (Figure 13) have been followed consequently to investigate safety and efficacy of short and long acting prostaglandin synthesis inhibitors, NSAIDs and calcium antagonist, nifedipine in acute renal colic and urinary calculus:

- Short acting NSAID, indomethacin suppository, a potent nonselective prostaglandin synthesis inhibitor, was investigated in patients with renal colic not responding to analgesic/antispasmodics. Indomethacin decreases urinary prostaglandin, reduces pelvic pressure, reduces calcium excretion, inhibits NO production, inhibits renin release, blocks the increase in afferent renal activity and release of substance P, and stops spontaneous rhythmic human ureteric contraction. The patients with resistant renal colic were treated with 100 mg of indomethacin and they were observed for pain relief, side effects and destination of their urinary calculus. When there was pain relief or passage of urinary calculus, the second step would be conducted.

- Patients with urinary calculus awaiting surgical removal were entered for study. They were treated with 100 mg indomethacin suppositories twice daily and the patients were followed regarding expulsion of their urinary calculus and recurrence of renal pain. When there was pain relief and expulsion of urinary calculus it was decided to move to the next steps which involved using another prostaglandin synthesis inhibition, nifedipine, to treat acute renal colic and

urinary calculus (steps 3 and 4), and testing efficacy and safety of long acting NSAIDs for treatment of acute renal colic (step 5).

- Patients with acute renal colic were treated with sublingual nifedipine and they were followed regarding pain relief and side effects. It was decided to investigate efficacy of potent prostaglandin synthesis inhibitor, indomethacin suppositories, in patients not responding to nifedipine. If the patients responded well, they would be entered for fourth step.

- The nifedipine-responded patients were treated with oral nifedipine for long period and they were followed for renal pain recurrence, possibility of expulsion of renal calculus, renal function test and appearance of any side effects.

- This step was conducted to investigate the possible efficacy of long acting non-selective NSAIDs in patients with acute renal colic. Tenoxicam and piroxicam were used in this step since they are long acting with long half-life, safe, potent prostaglandin synthesis inhibitors, and inexpensive. They could be delivered through i.m or i.v. routes. Their uses might reduce pain recurrence after initial responses. Recently, we have used i.m tenoxicam to treat visceral pain such as acute biliary colic and severe primary dysmenorrhoea (Al-Waili and Saloom 1998; Al-Waili 2001). Tenoxicam and piroxicam were used for treatment of postoperative pain. Patients with acute renal colic were treated with 20mg i.m tenoxicam. The patients were observed for pain relief and any side effects. When there was no response the patients would be treated with pethidine. If the results of this trial were promising regarding the ability of tenoxicam to relief acute renal pain, another potent and long acting prostaglandin synthesis inhibitor would be investigated in acute renal colic to substantiate the results. A pilot study was conducted, showing that piroxicam 20-40 mg i.m was useful in patients with acute renal colic not responding to antispasmodics. After these encouraging results we moved to next steps, 6 and 7.

- Long acting NSAIDs and antispasmodics/analgesic were compared in patients with acute renal colic. Tenoxicam 20g i.v was used and compared with i.v. buscopan compositum (hyoscine butylbromide 20 mg and dipyrone 2.5 g). Patients with acute renal colic were treated blindly with one of either tested drug.

The efficacy, safety, and onset of action of both drugs were monitored and compared. Frequency of pain recurrence during the next 24 hrs after injection of either drug would be recorded and compared. The cost of each treatment was accounted and compared with each other. After this study we moved to the next step.

- This step was important and was planned to compare between short and long acting NSAIDs in treatment of acute renal colic. Diclofenac sodium injection was used as short acting NSAIDs. Diclofenac sodium was chosen since it was being used widely for treatment of acute renal colic and many studies reported its safety and efficacy. In addition, I found that i.m diclofenac sodium was safe and effective for treatment of pain following caesarean section and had opioids-sparing effects (Al-Waili 2001). Long acting NSAID piroxicam i.m, 40 mg was used and compared with 75 mg i.m diclofenac sodium. The comparison between the two drugs were carried out concerning number of improved patients, requirement for pethidine-rescue treatment, pain relapse after initial response, onset of analgesia and pain score one hour after injection. After investigating nonselective short and long acting prostaglandin synthesis inhibitors, I moved to the next step concerning the effect of COX-2 inhibitor in acute renal colic.

- I hypothesized that expression of COX-2 might be increased during ureteric obstruction and impacting of urinary calculus resulting in overproduction of prostaglandin that is played an important role in the cascade of renal colic pathogenesis. Accordingly, selective COX-2 inhibitor might be useful for treatment of acute renal colic. This is important regarding the adverse effects that might arise with use of nonselective NSAIDs. Meloxicam is prostaglandin inhibitor with highly selectivity for COX-2. It has high anti-inflammatory potency and it inhibits swelling, leukocytes migration and shows long lasting anti-inflammatory and analgesic effects and has long half life. Meloxicam is well tolerated in the treatment of acute pain. Different routs were used such as oral, i.m and rectal with well analgesic action. In our trial, I used 15 mg meloxicam tablet delivered sublingually for patients with acute renal colic who were followed for pain intensity and adverse effects.

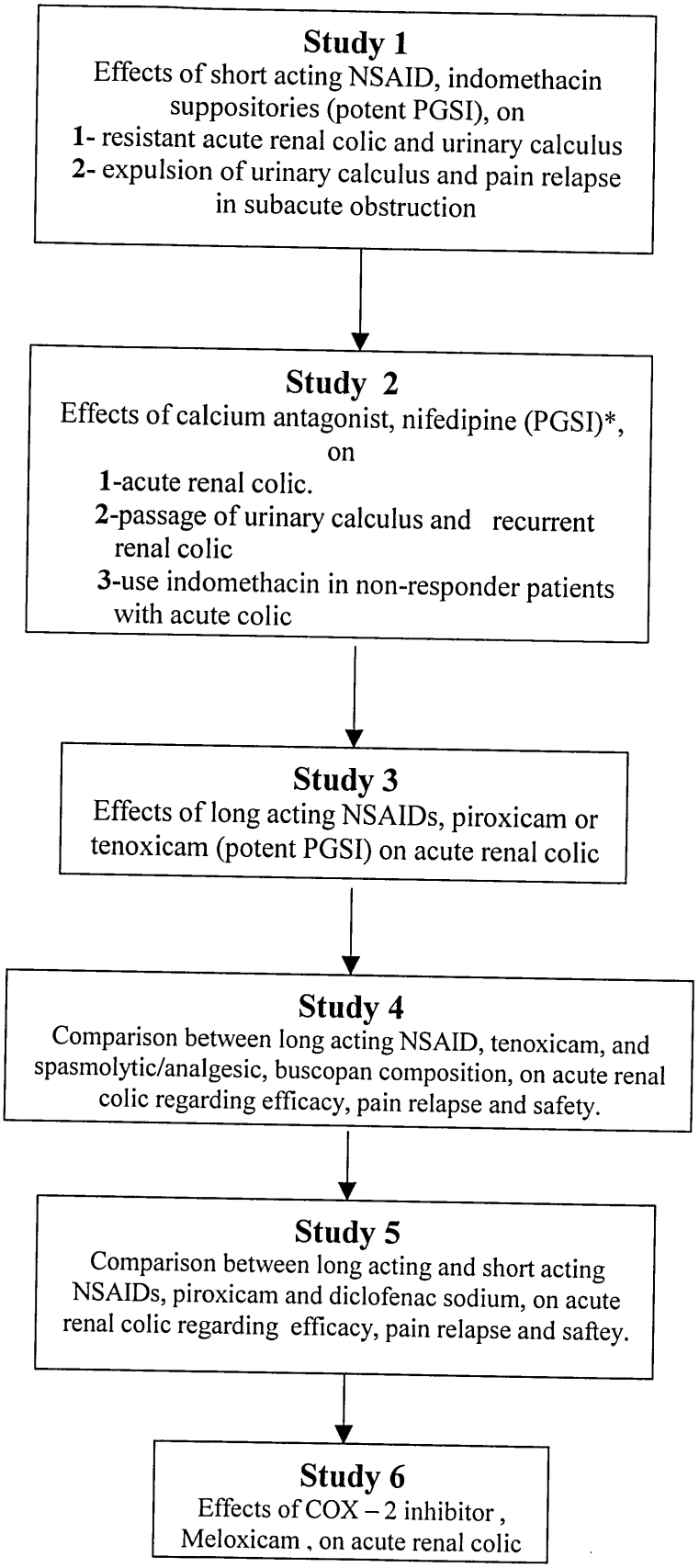

Figure (13): Steps of studies on acute renal colic and urinary calculus.* (Levine 1983; Danon *et al.* 1986; Chang *et al.* 1987; el Din & Malik 1988), PGSI:Prostaglandin synthesis inhibitor.

8.2. Assessment of Acute Renal Pain

Our patients suffered from acute renal colic, which is one of the most common and aggressive pain experienced by humans. The pain is due to passage of kidney stone, which causes irritation of the mucosa, ischemia, over distension, acute urinary obstruction and elevation of intrarenal pressure, and enhances motor activity of renal pelvis and ureter. As for patients with acute pain, our patients were suggested to display a greater use of sensory pain component. There are many instruments applied for assessment of acute or chronic pain. During severe renal colic, after initial pain assessment repeated clinical measurements of pain must be short and concerns with sensory component and pain intensity since the patients are quite ill.

Recent review stated that visual analogue scale (VAS) and verbal rating scale (VRS) constitute useful tools for acute pain measurement. In acute pain states, as renal colic, VAS or VRS were used for assessment of pain intensity in most of the studies reporting the effects of intervention on the acute renal colic (Jonsson *et al* 1987, Cordell *et al.* 1994, Villoria-Muriel 1995, Cordell *et al.* 1996, Stein 1996, Supervia *et al.* 1998, Aybek *et al.* 1998). I found that there was no difference in expressing of acute pain intensity using VAS and VRS (Al-Waili 2001). However, patients with acute renal pain had some difficulty using the paper and pencil VAS during the attacks and some had difficulty with expressing the pain by use of numbers.

Many studies found that VRS was more suitable for use and could also be used for assessment of postoperative nausea. In our patients, we used VRS in four studies and VAS in one study. In discussing these measures with Prof. Melzack, the author of McGill Questionnaire, he said that the VRS and VAS would be valid for our studies and they correlate very highly with other measures of the MPQ (Personal communication). We observed that using VRS was easy and convenient for pain measurement. Self-assessment was made by asking the patients to indicate the occurrence and severity of their pain (no pain, mild pain, moderate pain, severe pain and very severe pain) and number was assigned for each grading. All the patients had severe to very severe pain and satisfactory pain relief was achieved when the pain became none or mild. In one study that compared between piroxicam and diclofenac sodium in treatment of renal colic, we used VAS. The patients were asked to mark point on horizontal line (10 cm) which represented the level of pain they are experiencing. The left-hand end of the line representing no pain, the right-hand end,

unbearable pain. A cm rule has been used to measure the distance of the marked point from the left hand end.

In the initial assessment of pain, which was part of the diagnosis, beside pain intensity measurement other pain characters including, location, radiation, aggravating and relieving factors, timing, and type were also assessed.

8.3. Assessment of renal functions

8.3.1 Studies on acute renal colic and urinary calculus

8.3.1.1 Studies on acute renal colic.

After clinical examination and initial assessment of pain, renal function tests were performed. These included blood urea, serum creatinine, serum uric acid, serum sodium, serum potassium, serum chloride, general urine examination and urine culture. The same parameters were repeated 24 hrs after treatment.

8.3.1.2 Studies on urinary calculus and recurrent renal pain

We had two groups of patients:

1 Patients with urinary calculus awaiting surgical removal treated by indomethacin suppositories 100 mg twice daily for one month. Renal function tests were performed before the trial and at days 10, 20 and 30 during indomethacin treatment.

2 Patients with acute renal colic who showed response to nifedipine were entered long-term follow up with use of oral nifedipine. Renal function tests were performed before the trial and repeated during the treatment.

8.3.2 Studies on nocturnal frequency of micturition and primary enuresis

8.3.2.1 Study on frequency of micturition

Renal function tests were performed before the trial and repeated at after 15 days of using indomethacin suppositories. Comparison between results was done before and after the treatment.

8.3.2.2 Studies on primary enuresis

- Studies using diclofenac sodium or indomethacin for treatment of primary enuresis. Renal function tests were performed before commencement of treatment and repeated 30 days during the treatment.

- Study using carbamazepine for treatment of enuresis. Renal function tests were performed before the trial and repeated at day 30 during therapy. In addition, 24 hrs urinary protein and creatinine clearance test and measurement of urinary output were also performed. However, since all our patients wetted the bed each night, may be more than one attacks, it was difficult to obtain accurate collection of urine for 24 hrs. The parents were asked to awake the child each 3 hrs at night to pass voluntarily urine. However, out of 26 patients enrolled in the study, 9 patients could collect 24 hr urinary output accurately. Therefore, the same tests were repeated for these nine patients after 30 days for comparison.

- In attempt to find out the mechanism of action of indomethacin suppositories in patients with primary enuresis, measurements of urine volume, urine osmolality, serum electrolytes and osmolality, filtered sodium, creatinine clearance, 24 hr urinary protein excretion, blood urea nitrogen and general urine examination were performed before treatment and at day 15 during the treatment.

8.4 Methods of Drug Administration

In basic pharmacology, there are various routs for drug administration. These include oral, i.v, i.m, subcutaneous, intradermal, sublingual, rectal and transdermal. Intravenous rout has most rapid onset of action. In oral rout the first pass effect may be significant which is less with rectal rout. The hepatic first-pass effect can be avoided to a great extent by use of sublingual rout and transdermal preparations and to a lesser extent by use of rectal suppository. Bioavailability, which is fraction of unchanged drug reaching systemic circulation after administration, is 100% for i.v while for i.m is equal or less than 100% and for other routs is less that 100% (Katzung and Furst 1998).

In our studies, we used oral diclofenac sodium and carbamazepine for primary enuresis, indomethacin suppository for primary enuresis, frequency of micturition and renal colic, i.m and i.v tenoxicam and piroxicam for acute renal colic and sublingual nifedipine and meloxicam for acute renal colic.

Regarding indomethacin suppository, it has been shown that indomethacin suppository was found to be well tolerated by patients with rheumatic diseases and dyspepsia, and it relieved joints pain and alleviated dyspepsia (Wright and Hopkins 1979). Lauza *et al.* 1982 found that endoscopic evaluation of the gastric mucosa showed that indomethacin capsule caused significantly more gastric irritation than

indomethacin suppositories. The maximum plasma indomethacin concentration after administration of suppository was found after one hour (Alvan *et al.* 1975, Jonkman *et al.* 1984).

More recently, Watanabe *et al.* 1993 found that plasma reached the maximum level at 30 min after rectal administration. No histological changes of the rectal mucosa were found with multiple treatment with indomethacin suppositories (Ogiso *et al.* 1984). In renal colic we used indomethacin suppository since nausea and vomiting are common association with acute renal colic. In addition rectal rout would eliminate the upper gastro-intestinal side effects frequently associated with NSAIDs and reduced hepatic first pass effect. Other advantage of suppository is that the patients appeared less scared to return home at an early stage since the pain could be adequately and rapidly alleviated at home. This is explained the importance of self-administration of indomethacin suppository to achieve rapid release of colicky pain prior to hospitalization. In addition, patients with suspected ureteral colic must have nothing by mouth until accurate diagnosis of the attack was settled. Indomethacin suppository can be used as outpatient treatment for pain relapse because most of patients with acute renal colic discharge home from emergency department.

We used i.m and i.v. tenoxicam and i.m piroxicam for treatment of acute renal colic. Review of 19 articles comparing parenteral NSAIDs with placebo or analgesic agents showed that parenteral NSAIDs are more effective than placebo and analgesic drugs in the treatment of renal colic (Labrecque *et al.* 1995). The use of parenteral piroxicam or tenoxicam was common in patients with musculoskeletal disorders and extra-articular diseases. We found that i.v tenoxicam was safe and effective to treat biliary colic (Al-Waili and Saloom 1998). In addition, i.v tenoxicam was well tolerated and effective for postoperative pain (Chin and Lin 1998; Roelofse *et al.* 1993, Eggers *et al.* 1999, Jones *et al.* 2000). It has been found that the extent of i.m administration was complete and tenoxicam was more rapidly absorbed compared to the oral dose (Scaglione *et al.* 1993; Stebler and Guentert 1993). After both i.m and i.v application, tenoxicam showed a rapid onset of action and reliable relief of acute pain states (Jenuet *et al.*1989). Administration of tenoxicam i.m, i.v., or orally showed no difference in the half life (Jenuet *et al.*1989). In our studies we firstly tested the possible therapeutic effects of i.m tenoxicam on renal colic then i.v. tenoxicam was compared with i.v buscopan compositum for pain relief, safety and prophylactic effect for recurrent pain.

Intramuscular piroxicam produced comparatively higher piroxicam plasma concentration up to 45 minutes after 40 mg dose than oral piroxicam (Fourtillan 1987). Intramuscular piroxicam was compared with i.m diclofenac sodium to identify whether long acting NSAID relieved acute renal pain and prevent pain relapse. Diclofenac sodium was chosen for comparison because it is short acting NSAID and has been widely used for treatment of acute renal colic (Vignoni *et al.* 1983, el-Sherif *et al* 1995, Laervum *et al* 1996).

Nifedipine and meloxicam were used sublingually for treatment of acute renal colic. Sublingual administration of drugs has several advantages: (i) Sublingual mucosa is rich with mucosal network of systemic veins and lymphatics which give rises to quick absorption and rapid onset of action. (ii) This route is suitable in patients with swallowing difficulties, malabsorption or postoperative ileus. (iii) The drug will be absorbed to the systemic circulation and avoid first-pass hepatic or intestinal metabolism.

Nifedipine has been used increasingly by sublingual rout for the management of acute hypertension crisis and used for long-term treatment of achalasia (Motwani and Lipworth 1991, Bortolotti 1999). It has been found that sublingual nifedipine was effective, easy to administer and without serious side effects in patients with pregnancy-induced hypertension (Gallery and Gyory 1997). We have reported safety and efficacy of sublingual nifedipine in the treatment of hypertensive crisis and pregnancy-induced hypertension (Al-Waili and Hasan 1999, Al-Waili 2001). It has been demonstrated that sublingual, oral or rectal nifedipine is rapidly and almost completely absorbed (Kelly and Malley 1992). During sublingual rout, the peak plasma concentration was larger than that following oral administration (Palm-Aguirre *et al.* 1989). An initial and rapid response was seen after 3 minutes post-administration in children with renal diseases and hypertension (Kumare 1996).

As for rectal route, we chosen studying the effectiveness of sublingual rout in the treatment of acute renal colic which is characterized by its recurrence, because this route is easy to use, could be self-administered and is useful when there is contraindications for oral rout or parenteral preparations were not available or there is no sophisticated monitoring with use of intravenous line. Self-administration is good advantage that make sublingual or rectal rout useful for patients familiars with their symptoms of acute renal colic and also in hospitals, general practice and busy emergency words.

9- Papers on primary enuresis and primary nocturnal frequency of micturition with original data on renal function tests

Pages 103-133

Pages 104-133 have been removed due to copyright restriction. Provided below are the citations for those publications.

Al-Waili, N.S. (1986) 'Indomethacin suppositories: an alternative treatment for nocturnal frequency of micturition', IRCS Journal of Medical Science, 14, pp. 322-323.

Al-Waili, N.S. (1986) 'Diclofenac sodium in the treatment of primary nocturnal enuresis: double-blind crossover study', Clinical and Experimental Pharmacology &Physiology, 13, pp. 139-142.

Al-Waili, N.S. (1989) 'Indomethacin suppository to treat primary nocturnal enuresis: double-blind study', Journal of Urology, 142(5), pp. 1290-1292.

Al-Waili, N.S. (2000) 'Carbamazepine to treat primary nocturnal enuresis: double-blind study', European Journal of Medical Research, 5(1), pp. 40-44.

Al-Waili, N.S. (2002) 'Increased urinary nitrite excretion in primary enuresis: effects of indomethacin treatment on urinary and serum osmolality and electrolytes, urinary volumes and nitrite excretion', BJU International, 90(3), pp. 294-301.

10. Brief Results of the linked studies on Frequency of micturition and primary enuresis

Indomethacin suppository significantly reduced the frequency of micturition in all the 15 patients treated. Mean frequency was decreased from 71.4 +/- 23.6 to 16.8+/-10.4 during a period of 15 days of the treatment. All the patients showed more than 60% reduction in the frequency of micturition.

Regarding primary enuresis, diclofenac sodium was used to treat primary enuresis. Out of 20 patients treated, 15 had more than 50% reduction in the wet nights. Three of the five non-responders showed better responses when the dose of the drug increased to 75 mg. The total number of responders to either dose was 18 patients (90%). This revealed that the response is dose-dependent.

In resistant primary nocturnal enuresis, 14/19 patients had more than 18/30 dry nights with use of 50 mg of indomethacin suppository, another potent prostaglandin inhibitor. The other five non-responders were re-treated with 100 mg of indomethacin and three of them showed better responses. This demonstrated that the response was dose-dependent. A total of 17 indomethacin-responders (89.4%) continued to take indomethacin for 2 more months, of them 6 maintained complete dryness and 11 wet minimally. After stopping treatment, 5 remained dry and 6 return to daily wetting during 2 months of follow-up.

With use of another prostaglandin inhibitor, carbamazepine, which belongs to different drug family, 20 out of 26 patients had more than 50% reduction in the episodes of bedwetting (76.9%). The other six patients were retreated with potent prostaglandin inhibitor, indomethacin suppositories, and four of them showed better responses.

In the other study, indomethacin suppository (50 mg) given daily to 10 patients with primary enuresis caused a significant reduction in the frequency of bed-wetting, from daily bed-wetting to 0-4 wet nights during a period of 15 days. Urinary nitrite, the end product of NO, was significantly elevated in the patients with enuresis and was reduced markedly at day 15 during indomethacin treatment.

Renal function tests and side effects.

Treatment of patients with primary enuresis by prostaglandin inhibitors NSAIDs, diclofenac sodium or indomethacin, and carbamazepine did not cause significant changes or deterioration in the renal function tests regarding blood urea nitrogen, serum creatinine, serum uric acid and serum electrolytes (see details tables of the results in the sections 10, and 11). In addition, with use of carbamazepine, 24 hr urine volume could be collected only from nine patients before treatment, of them six showed significant improvements and urine volume was measured at day 30 during the treatment. Mean 24 hrs urine volume was 835+/-121 ml before treatment which was decreased to 492.8 +/- 228 ml during treatment ($p< 0.05$). Mean 24 hrs absolute urine sodium excretion was 82.9 +/- 49.2 mmol that was changed slightly to 78.5+/- 55.9 mmol. Creatinin clearance was decreased from 105.6 +/- 28.5 to 85.9 +/- 20.98. Blood osmolality decreased significantly from 283+/-3.44 mOsmol/kg to 277.2 +/-2.87 mOsmol./Kg. Mean blood sodium concentration slightly decreased from 142.8+/-1.47 mmol/l to 140.2 +/-2.04 mmol/l. These results showed that carbamazepine reduced urine volume which might explain its effectiveness in primary enuresis. In addition, urinary excretion of nitrite was significantly increased in patients with enuresis which was decreased markedly by indomethacin treatment. This reduction was associated with significant reduction in frequency of wetting. Indomethacin caused reduction of urine volume by 41.3%. It decreased clearance of free water, osmolal clearance, filtered sodium, fractional sodium excretion, creatinine clearance, and urinary protein excretion. No significant change was seen in serum osmolality. Indomethacin decreased bed-wetting in normal and small functioning bladder capacity.

Summary

The results showed that inhibition of prostaglandin synthesis by NSAIDs, indomethacin rectal suppository and diclofenac sodium oral tablet, and by carbamazepine might widen therapeutic lines for treatment of primary enuresis and frequency of micturition. This indirectly supports the hypothesis that prostaglandin might play a role in the pathogenesis of primary enuresis or nocturnal frequency of micturition. Moreover, the result substantiate our hypothesis that in addition to prostaglandins, NO might have place in the pathogenesis of enuresis. Therefore, the

results highlighted new concept for aetiology and pathogenesis of these urological problems in relation to prostaglandins and NO. The mode of action of indomethacin could be contributed to reduction of urine volume, clearance of free water, urine electrolytes, filtered sodium, and fractional sodium excretion.

Brief results of studies on primary nocturnal frequency and primary enuresis are illustrated in the tables 8. The subsequent sections include original papers discussing in details the results on frequency of micturition, episodes of bed-wetting, side effects and renal function tests and the possible modem of action.

Studies	Diseases	Drugs	Doses mg/day	Treatment Duration (Days)	Number of Patients Studied	Responses	
						Number of patients with significant response *	%+
1	Primary nocturnal frequency of Micturition	Indomethacin Suppositories	100	15	15	15	100
2	Primary Enuresis	Diclofenac Sodium	50 -75	30	20	18	90
3	Primary Enuresis (Resistant)	Indomethacin Suppositories	50 -100	30	19	17	89.4
4	Primary Enuresis	Carbamazepine	200	30	26	20	76.9
5	Primary Enuresis	Indomethacin Suppositories	50	15	10	10	100

Table 16 : Brief results of studies conducted on primary enuresis. * Number of patients who showed more than 50% night dryness with use of the treatment ($p<0.05$). + Percent of responders out of treated patients.

11.CRITICAL APPRAISAL OF THE PUBLISHED PAPERS ON FREQUENCY OF MICTURITION AND PRIMARY ENURESIS

11.1.Frequency of micturition

All the patients with primary nocturnal frequency of micturition showed considerable responses to indomethacin suppository. Although this is an open study, marked reduction in the number of nocturnal micturition was obtained with use of 100 mg of indomethacin suppository given before retiring. The mode of action of indomethacin might be the result of inhibition of prostaglandin biosynthesis at renal, vesical, urethral and nervous system levels. The inhibition might cause reduction in urine output, increase in the threshold volume of micturition, lowering of intravesical pressure, elevation of urethral pressure and lowering of inhibitory action of prostaglandins on adrenergic transmission in the bladder and urethra.

Diseases of the cardiovascular and nervous systems and endocrine and metabolic disorders could cause nocturnal frequency of micturition. However, there is a group of patients having nocturia without any obvious causes as in our patients. The cornerstone of management of nocturnal frequency of micturition is the treatment of the underlining pathology, but this is not always possible or successful. It has been suggested that nocturnal polyuria might be due to low antidiuretic hormone (Asplund 1995; Weiss & Blaivas 2000). There is increase Na^+ excretion in nocturnal frequency of micturition (Mathiesen *et al.* 1996). Decreased nocturnal bladder capacity was found in old patients with nocturnal frequency of micturition (Kawanchi *et al.* 2000). Therefore, antispasmodics, fluid restriction and antidiuretic preparations may be helpful (Hundballe *et al.* 1997; Weiss 2000). However, antidiuretics are expensive and may cause severe side effects. We found some similarity between despmopressin and indomethacin regarding reduction of urine output. Hence, indomethacin suppository could be a suitable alternative in the management of nocturnal frequency of micturition. On the other hand, it has been shown that patients with nocturnal polyuria and primary enuresis have higher nocturnal sodium excretion but no higher nocturnal free-water clearance and using vasopressin to induce water retention in elderly with nocturnal polyuria is illogical and potentially hazards (Mckeigue & Reynard 2000). Polyuria with nephrogenic diabetus insipidus is associated with elevated urinary PGE2 and 6-ketoPGF1

(Hochberg *et al.* 1998). Prostaglandin synthesis inhibitors are used to treat bladder overactivity and urinary incontinence and urgency and indomethacin was used to treat nephrogenic diabetus insipidus (Weinstock & Moses 1990; Dagues & Costa 1995; Andersson 2000). Oral indomethacin was shown to improve daytime urinary frequency in children (Luo 1992). These studies support our hypothesis that prostaglandins might also be the cause for nocturnal frequency of micturition. Moreover, it was found that misoprostal induces urinary incontinence and a deficiency in urethral resistance (Bergman *et al.* 1991).

11.2. PRIMARY ENURESIS

11.2.1. Prostaglandin and prostaglandin inhibition

Drugs used to inhibit prostaglandin biosynthesis in patients with primary enuresis are NSAIDs, diclofenac sodium or indomethacin suppositories, and carbamazepine. The results demonstrated that indomethacin, diclofenac sodium and carbamazepine reduced significantly nocturnal bedwetting. This suggests indirectly that prostaglandins may play a role in the pathogenesis of primary nocturnal enuresis. In addition to inhibition of prostaglandin biosynthesis these drugs have other biological effects that might contribute to their efficacy in the management of enuresis.

11.2.1.1. NSAIDs Effects

Human bladder mucosa produces large amounts of prostaglandin, which were shown to be liberated into the blood stream during vesical distension and after pelvic nerve stimulation (Gilmore & Vance 1971; Khalaf *et al.* 1979). Indomethacin and diclofenac might cause depression of the smooth muscles of the bladder in enuretic children. Such effects might be ascribed to prostaglandin synthesis inhibition and its known calcium antagonistic responses (Jeremy 1982).

At the urethral level prostaglandins caused a significant urethral pressure decrease at basal condition and during micturition, and reduced urethral resistance Konda *et al.* 1983; Schussler 1990). These effects might be a result of direct action of prostaglandins on the smooth muscle of the urethra or through inhibitory effects of prostaglandins on the adrenergic transmission (Andersson *et al.* 1983).

Prostaglandins are a potent inhibitor of noradrenaline release (Hedqvist 1977). Therefore, inhibition of prostaglandin with diclofenac sodium or indomethacin might result in elevation of urethral pressure and resistance and lowering of inhibitory action of prostaglandin on adrenergic transmission in the bladder and urethra. Generally, the frequency of bedwetting in enuretic patients could be reduced with use of indomethacin or diclofenac sodium by inhibition of prostaglandin biosynthesis and release at different sites of the urinary tract:

1- At renal level, results in reduction of diuretic and renal vascular effects of prostaglandin and glomerular filtration rate
2- At bladder level, results in reduction of the maximum intravesical pressure and increased threshold volume of micturition
3- At urethral level, results in elevation of urethral pressure and resistance
4- At nervous system, results in reducing the inhibitory action of prostaglandin on adrenergic transmission in the bladder and urethra.

The inhibition of prostaglandin synthesis might cause decreased urine output, an increase in the effect of antidiuretic hormone, increased threshold volume of micturition, and decreased inhibitory action of prostaglandins on adrenergic transmission in the bladder and urethra. Other action of diclofenac sodium and indomethacin might help enuretic patients, such as analgesic effect, which may be responsible for more restful sleep.

Indomethacin inhibits not only COX but also the mobilization of Ca^{2+} linked prostaglandin synthesis in the urinary bladder (Jeremy *et al.* 1982). It decreased plasma renin concentration, increased antidiuretic hormone and osmotic water permeability and abolished natriuresis (Lijnen *et al.*1991; Walker *et al.* 1994; Rouch & Kudo 1997). Indomethacin reduced atrial natriuretic peptide-induced sodium excretion (Villarreal *et al.* 1997). It inhibits sodium dependent adenosine transport in brush-border membrane (Gonzalez-Gastillo *et al.* 1997) and completely eliminated neuropeptide induced diuresis and natriuresis (Bischoff *et al.* 1998).

To describe the possible mechanism of action of indomethacin, urine volume, urine electrolytes and osmolality, serum electrolytes and osmolality, creatinine clearance, urinary protein, fractional excretion of sodium and filtered sodium were measured before and during indomethacin suppository treatment. Indomethacin caused reduction in the total 24 hr urinary volume, night urine volume and day-time urine volume. Daytime urine volume decreased by 25.4% during indomethacin treatment. The reduction was significant at night (39.9%) and throughout 24 hour urinary volume (41.3%). Same results were obtained when urine was measured per min / kg. body weight . In addition, day to night urine volume ratio increased from 0.982 +/- 0.395 to 1.521 +/- 1.1. Indomethacin decreased also clearance of free water by 46.4%. Indomethacin increased 24 hr urine osmolality by 54.89%, night urine osmolality by 86.2% and daytime urine osmolality by 29.25%. The absolute amount of calcium, phosphorus, magnesium, glucose, urea, and creatinine excreted in the urine decreased after indomethacin treatment. Indomethacin decreased osmolal clearance. No significant changes were seen in serum osmolality, serum glucose, blood urea nitrogen, creatinine, calcium, magnesium, and phosphorus concentrations during indomethacin treatment. Sixty percent of the patients had less than 70% predicted bladder capacity and the other patients had more than 70 %, up to 100%. However, maximum functional bladder capacity increased slightly from 200 +/- 52.4 ml to 210 +/-73.4 ml at day 15 after commencement of indomethacin treatment. The absolute amount of sodium and chloride excreted in daytime urine, night urine and 24 hr urine was decreased by indomethacin. Insignificant changes were seen in serum sodium or chloride after indomethacin treatment. Fractional excretion of sodium and filtered sodium also were decreased by indomethacin. In addition, fractional excretion of potassium and the absolute amount of potassium excreted in the urine collected at night, day or during 24 hrs were decreased by indomethacin though this change was statistically insignificant. Serum potassium concentration was not altered significantly by indomethacin. Indomethacin decreased creatinine clearance by 19.91% and 24 hr urinary protein excretion from by 47.25%.

The apparent action of indomethacin is mainly related to reduced urine output, fractional excretion of sodium, filtered sodium and electrolytes excretions. In addition, indomethacin could stimulate antidiuretic hormone, modulate tubular actions, suppress bladder contractility and increase urethral tone by inhibition of both NO and prostaglandin productions. Central effects of indomethacin on prostaglandin

and NO productions in CNS might affect sleep pattern or central and neuronal control of bladder function. Moreover, it has been shown that neuropeptide Y caused diuresis and natriuresis and increased prostaglandin production in renal tissue (el Din & Malik 1988). Indomethacin could abolish neuropeptide Y-induced diuresis and natriuresis (Bischoff *et al.*1998). Therefore, indomethacin might exert its effects by inhibition of prostaglandins, NO or neuropeptide Y. More investigations are needed.

11.2.1.2. Carbamazepine Effect

It has been found that carbamazepine dose dependently inhibited prostaglandin E2 activity and prostaglandin E2-induced hyperalgesia (Bianchi *et al.*1995; Nakamura-Craig & Follenfant 1995; Matoth *et al.*2000). The results showed that nocturnal bedwetting could be also reduced significantly with use of carbamazepine 200 mg tablet. Many studies reported other effects of carbamazepine such as its effects on antidiuretic hormone and water metabolism. Carbamazepine has water-retaining property mediated by increased renal sensitivity to normal plasma concentration of antidiuretic hormone and resetting of osmoreceptors (Jien *et al.* 1977). Others reported that carbamazepine induced antidiuresis by release of antidiuretic hormone and impaired excretion of water load (Perucca *et al.* 1978; Soelberg *et al.* 1984). It decreases the ability to excrete water load and causes lower free water clearance and higher urine / plasma osmolality ratio (Soelberg *et al.* 1984).

Because of its antidiuretic effect, carbamazepine has been used successfully to treat diabetes insipidus centralis. It caused considerable antidiuresis and altered sensitivity to serum osmolality by the hypothalamic osmoreceptors and increased sensitivity of renal tubules to circulating antidiuretic hormone (Kimura *et al.* 1974; Stogmann 1975; Vimla *et al.* 1983; Yoshimura *et al.* 1997). Some studies reported increased plasma antidiuretic hormone by carbamazepine (Stephens *et al.* 1978). In combination with chlorpropamide, carbamazepine has been used to treat diabetes insipidus in childhood (Stogmann 1975).

The mechanism of action of carbamazepine is not clear, but it might be related to its antidiuretic effects, increased bladder capacity or reduction of prostaglandin-like activity. Recently, it was found that carbamazepine inhibited NO production (Matoth *et al.*2000). Therefore, its possible inhibitory effects on NO

production in the urinary system, as we suggested with NSAIDs, might play a role in the mechanism of action. This needs further investigations. However, the main first goal of our study was to find whether carbamazepine has any clinically therapeutic effects on patients with primary enuresis besides its possible effects on renal function tests. The patients wetted the bed each night once or more. To study the effects of carbamazepine on urine volume, we needed to collect urine at night and day, which would be used also to measure creatinine clearance. However, accurate collection of nocturnal urine production from children with daily enuresis is not an easy task. Invasive methods like transurethral catheterization or external catheter have been used to collect urine at night. Spontaneous voiding at 2-3 hrs interval by repeated waking patient also was used. Diapers has been used but could not absorb all the urine and the amount of urine at each enuretic episodes could not be determined as diapers could contain urine form more than one episodes. These measures could decrease patient's compliance and it was decided that it was not necessary to stress on urine collection at that stage, viz before knowing the effect of carbamazepine on enuresis. However, we have asked the parents to a wake the child at night for spontaneous voiding. Accurate urine collection was obtained from nine patients. After treatment with carbamazepine, six patients showed dryness and urine collected from them at day 15 during treatment for comparison. Urine volume, urine osmolality, creatinine clearance, urine sodium and serum electrolytes were measured. The results demonstrated that carbamazepine significantly reduced urine volume and increased urine osmolality. It decreased blood osmolality to a lesser extent. Mild lowering of serum sodium was encountered. Though the number of the patients was small, it seems that the main action of carbamazepine is the marked reduction of urine volume. Further studies are needed to substantiate this possible mode of action.

11.2.2. Nitric oxide and enuresis

NO has an important role in the renal physiology and micturition (see Introduction). Renal vasoconstrictor and antinatriuretic effects of COX inhibitors are enhanced when NO synthesis is reduced (Gonzalez *et al.* 1998). It inhibits fluid and Na^+ reabsorption by proximal tubules (Hagnes *et al.* 1997; Liang & Knox 2000). Sodium nitroprusside and NO increased neurogenic detrusor contraction and they are effective in relaxing urethral muscle (Persson & Andersson 1994; Lin & Lin 1997). It has been demonstrated that inhibition of NO alone causes antidiuresis and

antinatriuresis and decrease in renal blood flow and glomerular filtration rate (Sirajy *et al.* 1997). NSAIDs and carbamazepine inhibited NO production (Cirino *et al.* 1996; Du & Li 1999; Matoth *et al.*2000). Indomethacin inhibits both the release of prostaglandin and NO and reduced COX-2 activity irreversibly (Du & Li 1999; Motta *et al.* 1999; Harback *et al.* 2001). Inhibition of endogenous prostaglandins by COX inhibition caused reduction of inducible NO synthesis (Minchetti *et al.* 1997). Therefore, NSAIDs or carbamazepine might help patients with enuresis and frequency of micturition by inhibition of prostaglandins, and NO.

NO has been identified in nerve fibres of the detrusor, trigone and urethra. NO is the major neural inhibitory regulator of urethral tone and considered to be a mediator for the neurogenic dilator of the bladder neck and urethra during micturition reflex (Parlani *et al.*1993; Bennett *et al.*1995). NO caused reflex urethral smooth muscle relaxation (Vizzard *et al.*1994). A drop in urethral pressure immediately precedes an elevation in bladder pressure causing urethral relaxation as the first part of micturition (Low *et al.*1989). It has been found that fluid passing through urethra could facilitate detrusor activity (Suk *et al.*1999). Involuntary detrusor contractions were proceeded by a fall in urethral pressure (Low 1977). Moreover, urethral instability is a common finding in detrusor instability (Sorenson *et al.*1986). Intraurethral administration of NO donors caused decreased urethral pressure (Suk *et al.* 1999). Inhibition of NO synthase blocked urethral relaxation to parasympathetic nerve stimulation (Fraser *et al* 1995).

It has been suggested that there is a major interaction between NO and prostaglandin in mediating renal response to various situations (Salazar *et al.* 1995). In addition to prostaglandin, NO production in the urinary system may be involved in the pathophysiology of enuresis. Over production of NO mainly at renal, bladder neck and urethral levels may increase urine production, solutes excretion and drop urethral pressure. The latter might allow passage of little urine in the urethra and initiate bladder contraction, which is exaggerated by high prostaglandin production encountered in enuresis. Therefore, we might hypothesize that both prostaglandin and NO are involved in the pathogenesis of enuresis. The present study presents for the first time the amount of nitrite in urine samples of enuretics, which was found to be significantly higher than normal control.

NO and prostaglandin have similar action on renal water and electrolyte excretion and bladder neck and urethral contraction. Inhibition of NO and prostaglandin caused antidiuresis, antinatriuresis, decreased renal blood flow, glomerular filtration rate and bladder excitability and increased intra urethral pressure. NSAIDs and carbamazepine inhibit NO and prostaglandin production. Inhibition of prostaglandin itself resulted in reduction of inducible NO synthesis. In enuresis, it was found that both urinary prostaglandin and NO concentrations increased, which might be the main reason for enuretic episodes. Therefore, inhibition of prostaglandin, NO or both might reverse their effects on renal, ureteral, vesicle or urethral level and consequently improved frequency of bedwetting.

11.2.3. Supported studies

The differences between enuretic patients suggest different aetiology, probably related to an increase prostaglandins and antagonistic mechanism of action of antidiuretic hormone or desmopressin (Medel *et al.* 1998). Our results demonstrated that prostaglandin might be a possible cause for primary nocturnal enuresis and nocturnal frequency of micturition. This is either due to higher production of prostaglandins in the urinary tract, increased sensitivity of urinary tract tissues to prostaglandins or dominance of prostaglandin effects. Recently, subsequent studies by others confirmed our works and hypothesis. Natochin and Kuzenetsora (1997) found that the enuretic children had a high night diuresis and free water reabsorption and increased in nocturnal excretion of sodium, calcium and magnesium ions. Inhibition of prostaglandin leads to normalization of diuresis and natriuresis and elimination of nocturnal enuresis. The evidence has been obtained that nocturnal enuresis is accompanied by an increased production of autocoids in the thick ascending LOH which causes saluresis and diuresis. Study by Kuzenetsova *et al.* (2000) suggested that change in the renal function in primary enuresis are due to dominance of prostaglandin effects as compared to other physiologically active substances that simultaneously act on the renal tubular cells, and there is a correlation between sodium ion and renal excretion of prostaglandin. In addition, it has been found that the mean serum and urine PGE2 concentration in enuretics were higher from control serum and urine PGE2 (Sener *et al.* 1998). 100 mg of indomethacin was shown to be effective in the treatment of primary enuresis, which

confirms our hypothesis (Sener *et al.* 1998). The study showed also that significant decrease in serum and urine PGE2 concentrations was seen after indomethacin treatment. Medel *et al.* (1998) found desmopressin non-responder enuretics had overnight mean PGE2 level greater than in normal subjects or desmopressin-responder. Diclofenac sodium was also found to be effective in the treatment of children with primary enuresis and it could restore ions and water transport in the kidney (Batislm *et al.* 1995; Natachin & Kuzenetsova 2000). In addition, other investigators showed that diclofenac sodium suppository was superior to placebo in the treatment of enuretic children (Metin & Agkel 1992). These results confirm our published findings and hypothesis. Moreover, prostaglandin synthesis inhibitors are useful to treat urinary incontinence and bladder instability (Wall 1990). These studies give further evidences for the validity of our hypothesis. Regarding the implication of NO in the aetiology of enuresis, our findings reported elevation of NO production in primary enuresis also substantiates our hypothesis on possible relation between nitric oxide and enuresis.

In general, many theories on the aetiology of primary nocturnal enuresis have been suggested, including psychological and behavioural factors, a small capacity and unstable bladder, and anatomical abnormalities of the urinary tract (Ullom-Minnich 1996; Hansen & Jorgensen 1997). Management with psychotherapy, fluid restriction, antispasmodics, tricyclic antidepressants and antidiuretic preparations is used but is not always effective (Miller *et al.* 1992; Chiozza *et al.* 1997). Our patients showed good response with use of prostaglandin synthesis inhibitors.

11.2.4. Pathogenesis of enuresis, indomethacin and desmopressin effects

Primary enuresis is a diseases of complex pathogenicity with accumulative of conflicting data. Most patients have either normal bladder function and capacity and large urine volume production at night or slightly increased micturition frequency during the day, and small bladder capacity at night-time (Djurhuus 1999). Rare enuresis subtypes included nighttime natriuresis with or without polyuria, calciuria and air way-induced enuresis.

It has been found that in primary enuresis, patients nocturnal urine production was greater than that of the control subjects and less concentrated (Hunsballe *et al.* 1997). This result in increased urine production, which in turn exceeds bladder capacity (Steffens *et al.* 1993; Eggert *et* al. 1995). Patients with nocturia showed increase urine production associated with increase nocturnal sodium excretion (Matthiesen *et al.* 1996). Enuretic patients had significantly higher fractional excretion of sodium and fractional excretion of potassium values than normal (Vrgun *et al.* 1997). There are significant correlation between fractional excretion of sodium and fractional excretion of potassium and frequency of bedwetting among enuretic (Vrgun *et al.* 1997). It has been found that diuresis during the night was 58.7% higher and the solute excretion 48.8% higher in enuretics than in healthy children (Natachin and Kuzenetsova 1999). This was mainly due to increase sodium and magnesium ions. The excretion of these ions is elevated not only during night but also throughout a 24 hour period in children with enuresis (Natachin and Kuzenetsova 1999). In response to fluid restriction, enuretics had significantly higher increase in plasma antidiuretic hormones than in comparable control (Eggert *et al.* 1999). Therefore, enuretic children showed higher secretion of antidiuretic hormone and do not show an antidiuretic hormone deficiency (Eggert *et al.*1999; Jonat 1999). There is a defect at the AVP receptor level rather than AVP deficiency that has to be supplemented. The success rate with desmopressin has been reported to range from 10% to 91% (Moffat *et al.* 1998). The basis for using desmopressin is that a missing circadian rhythm of antidiuretic hormone secretion result in nocturnal hormone deficiency in enuretics (Ritting *et al.* 1998). On the contrary, it has been shown that patients with primary enuresis do not have an increased nocturnal urine production when compared with a control group (Eggert & Kuhn 1995). There were no differences between the two groups regarding plasma osmolality and rhythm of antidiuretic hormone secretion. Enuretic children need significantly higher antidiuretic hormone to maintain constant plasma osmolality (Eggert *et al.*1999).

Other investigators showed that no difference between enuretics and normal control was found in the total diurnal urinary volume, osmolality or tubular capacity for reabsorption of water (Vurgun *et al.*1997). Moreover, no difference between enuretics and control were found for urine production, antidiuretic hormone levels during day and night or plasma osmolality (Eggert *et al.*1995). Therefore,

controversy is still existing regarding the aetiology of enuresis and the changes that might occur in the tubular function, water and electrolytes excretion and bladder capacity and physiology. According to the role of prostaglandins and NO in the physiology and pathophysiological events in the urinary system, we have hypothesized that primary enuresis and frequency of micturition might be a results of prostaglandins and NO interaction and accordingly we and others have confirmed that inhibition of prostaglandin and probably NO production in the urinary system could improve bedwetting.

With our studies, indomethacin provided marked reduction in the frequency of micturition in 100% of the patients treated, and it reduced significantly number of bedwetting in 100% of the patients with enuresis and in 89.4% in patients with resistant enuresis. Diclofenac sodium provided significant improvement in 90% of the cases. The responses were apparently dose-related. Carbamazepine provided improvement in 76.9% of the case and indomethacin could improve 66.6% of carbamazepine-non-responders. In addition, indomethacin improved patients with small and normal predicated functional bladder capacity. Seventeen patients were treated with indomethacin for 2 months, of them 29.4% returned to daily bed wetting after stopping the treatment.

Desmopressin is used widely to treat enuresis which caused a reduction in the number of wet nights and a decrease in nocturnal urine production, even though non of the children become totally dry during treatment with desmopressin (Hasen and Jorgensen 1997). It has been found that 61% response could be achieved with desmopressin and it was highly effective when used in combination with other treatments including alarm and oxybutinin (Hjalmas 1999). Some patients who showed resistant to desmopressin treatment responded well to anticholinergic drug (Neveus *et al.*1999). Enuretics with elevated nocturnal urination and electrolytes excretion had 85% response with desmopressin (Natachin and Kuzenetsova 2000). The most likely to be permanently dry with desmopressin treatment are older children and who do not wet frequently and who had only wet episode during night (Kruse *et al.* 2001). Desmopressin led to a reduction of nocturnal enuresis and to a decrease in osmolar clearance and excretion of sodium (Natachin and Kuzenetsova 2000). Lysine-8-vasopressin induced a significant reduction of creatinine clearance, urinary flow rate and of prostanoid excretion (Angnoli *et al.* 1989). Recently it has

been found that desmopressin responder produced larger amount and less concentrated urine than other children, while desmopressin non-responders had smaller bladder capacity than others (Neveus *et al.* 2001). In our patients, 60% had small predicted functional bladder capacity (<70%) and showed marked improvement with indomethacin while other found that patients with functional bladder capacity more that 70% predicated bladder capacity were more likely to respond to desmopressin (Rushton *et al.* 1999). Desmopressin like diclofenac sodium recovered renal function in enuretics and caused decreases in diuresis, osmolar clearance and excretion of calcium, sodium and magnesium (Natachin and Kuzenetsova 2000). Desmopressin might cause nasal irritation and nose bleeds and there is risk of water intoxication (Glazener and Evans 2000).

The action of indomethacin might be similar to desmopressin. Desmopressin and indomethacin reduced prostaglandins in urine and plasma in enuretics (Sener *et al.* 1998). It has been demonstrated that desmopressin-non-responders patients have overnight mean prostaglandin E2 level greater than in normal subjects or desmopressin-responders (Medel *et al.* 1998). However, indomethacin not only reduced water excretion, but also reduced absolute sodium excretion and improved patients with normal as well as small functioning bladder capacity. In addition, some of our patients become totally dry during indomethacin treatment.

Reduction of urine volume alone as it has been proposed with use of desmopressin may not be enough to avoid bed-wetting or to achieve total dry. So we might suggest that reduction of urine output by indomethacin might not be the only mechanism of action in the treatment of enuresis. It could stimulate antidiuretic hormone, decreased filtered sodium, modulate tubular actions, suppress bladder contractility and increased urethral tone by inhibition of both NO and prostaglandin productions. Central effects of indomethacin on prostaglandin and NO productions in central nervous system might affect sleep pattern or central and neuronal control of bladder function (Murphy *et al.* 1994; Naito *et al.* 1988). These need further investigations.

Prostaglandin synthesis inhibition with indomethacin decreased episodes of bedwetting by reduction of urine volume and electrolytes excretion and decreased bladder contractility and excitability. This is clear in our patients who had small predicted functional bladder capacity and showed marked response with indomethacin. However, this is opposite to what has been found with desmopressin treatment which revealed no significant effects on patients with small bladder capacity. Henze, prostaglandin inhibition might have superiority to desmopressin which showed its effects mainly in patients who produced large amount of and less concentrated urine.

According to the similarity of some actions between indomethacin and desmopressin, we suggest that using a combination of both drugs in management of primary enuresis might have synergistic effects and might result in better improvement and reduction of doses, and ultimately side effects. Other controlled studies are needed to substantiate this possibility.

12- Papers on renal colic and urinary calculus with original data on renal function tests

Pages 151-189

Pages 152-186 have been removed due to copyright restriction. Provided below are the citations for those publications.

Al-Waili, N.S. (1986) 'Prostaglandin synthetase inhibition with indomethacin rectal suppositories in the treatment of acute and chronic urinary calculus obstruction', Clinical and Experimental Pharmacology & Phyiosology, 13(3), pp.195-199.

Al-Waili, N.S. (1988) 'Letters to the editor: clinical usefulness of nifedipine in acute and recurrent ureteric colic,' Medical Science Research, 16(23) pp. 1245-1246.

Al-Waili, N.S. (1996) 'Intramuscular tenoxicam to treat acute renal colic', British Journal of Urology, 77(1), pp. 15-16.

Al-Waili, N.S., and Saloom, K.Y. (1998) 'Intravenous tenoxicam to treat acute renal colic: comparison with buscopan compositum', Journal of Pakistan Medical Association, 48(12), pp. 370-372.

Al-Waili, N.S., and Saloom, K.Y. (1999) 'Intramuscular piroxicam versus intramuscular diclofenac sodium in the treatment of acute renal colic: double-blind study', European Journal of Medical Research, 4(1), pp. 23-26.

Al-Waili, N.S. (2001) 'Letter to the editor: sublingual meloxicam for renal colic', Urologia Internationalis, 67(1), pp. 119-120.

13. Brief results of linked studies on renal colic and urinary calculus

Renal colic

Fifty-five patients with resistant renal colic treated with short acting potent prostaglandin synthesis inhibitor, indomethacin suppository 100 mg. Of them, 47 got pain relief within 30 min and other eight patients within 60 min.

Other twenty patients with acute renal colic were treated with prostaglandin synthesis inhibitor and calcium antagonist, nifedipine. Sixteen patients (80%) responded to sublingual nifedipine within 2 hrs. No pain relapse occurred with use of 20 mg of oral nifedipine six hourly. Four non-responders were treated with indomethacin suppositories, all showed marked improvement within one hour. The responded patients treated with 10 mg of nifedipine eight hourly. The patients showed no pain relapse with use of nifedipine.

Regarding the effects of long acting prostaglandin synthesis inhibitor, 24 out of 30 patients of acute renal colic (80%) treated with 20 mg i.m tenoxicam showed marked pain relief within one hour, 15 patients relieved within 30 min and nine patients within 60 min. Four patients showed pain relapse within 24 hrs. They were treated successfully with indomethacin suppositories.

In comparison between long acting prostaglandin synthesis inhibitor tenoxicam and antispasmodic/analgesic, buscopan compsoitum, twenty-five patients with acute renal colic were treated with 20 mg tenoxicam i.v., of them 20 patients (80%) showed significant responses. At 30 min, 16 patients got pain relief and at 60 min another 4 patients got pain relief. No relapse was encountered during 24 hrs follow-up. Twenty-two patients were tread by buscopan compositum i.v, of them 10 patients relived at 30 min and 6 patients relived at 60 min after injection, total 16 patients (72.2%). Of the 16 patients, 10 developed pain relapse during next 24 hrs. Patients developed dryness of mouth and dizziness. It seems that tenoxicam is better than buscopan compositum regarding the onset of analgesia, frequency of pain relapse, cost of the treatment and the analgesic efficacy.

In comparison between long acting and short acting prostaglandin synthesis inhibitors in renal colic, the results showed that complete pain relief was achieved within 30 min in 25/34 patients and within 60 min in seven patients (total 32/34 patients, 94.1%) when the patients were treated with long acting piroxicam 40 mg i.m. No pain relapse was seen within 24 hrs. Another comparable 30 patients with acute renal colic were treated with short acting prostaglandin inhibitor diclofenac sodium, of them 15 patients completely relieved at 30 min and 11 patients at 60 min, total 26 patients (86.6%). Nine patients showed pain relapse within 24 hrs which was relieved with use of another injection of diclofenac sodium.

Regarding COX-2 inhibitor, sublingual long acting and selective COX –2 inhibitor, meloxicam was used in the treatment of three patients with acute renal colic. The patients showed complete pain relief within 60 min and no patient got pain relapse during the next 24 hrs.

Urinary calculus

Fifty-five patients with resistant renal colic and urinary calculus were treated with indomethacin suppositories 100 mg twice daily for one month after their initial pain relief of acute renal colic with use of indomethacin suppositories. Fifteen patients passed their stones and none showed pain relapse. Another 30 patients with sub-acute obstruction and small urinary calculus were treated with 200 mg of indomethacin suppositories per day, of them 21 passed their stones within one month and none showed pain relapse. Another ten patients having small urinary calculus were treated with prostaglandin synthesis inhibitor and calcium antagonist, nifedipine (10 mg three times daily) after their initial pain relief of acute renal colic with use of sublingual nifedipine. Three patients passed their stones within one week and no pain relapse was encountered with use of nifedipine.

Renal function tests and side effects

Treatment of renal colic and urinary calculus with NSAIDs or nefidipine did not deteriorate renal functions during short and long period of the treatment. All the treated patients had normal functioning kidneys before treatment.

Summary

Regarding renal colic and urinary calculus, the results demonstrated that short acting potent prostaglandin inhibitor, indomethacin, which belong to NSAIDs group could relive pain in patients with resistant renal colic, facilitated passage of urinary calculus and prevent pain relapse in sub-acute obstruction. In addition, the results showed that calcium antagonist nifedipine which has prostaglandin inhibitory action could relive pain in acute renal colic, facilitated passage of urinary calculus in 30 % and prevent pain relapse. Patients not responding to nifedipine responded well to indomethacin. A combination of both drugs might have better effect. It seems that long acting piroxicam has faster onset of action, better analgesic efficacy and absence of pain relapse when compared with short acting diclofenac sodium.

In general, Long and short acting NSAIDs have significant analgesic effects on pain of acute renal colic due to urinary calculus including resistant renal colic, and either no or fewer episodes of pain relapse were seen with long acting during 24 hrs. Long acting prostaglandin synthesis inhibitor has better effects regarding onset of analgesia, side effects, episodes of relapse and analgesic efficacy when compared with combination of dipyrone and spasmolytics. Both nifedipine, calcium antagonist and prostaglandin inhibitor, and indomethacin, a potent prostaglandin inhibitor, could facilitate passage of urinary calculus and had prophylactic effects against renal colic relapse in patients with urinary calculus. Selective COX-2 inhibitor has also therapeutic effect in relieving pain of acute renal colic without pain relapse. The reported effects were seen when drugs were delivered rectally, sublingually, intravenously or intramuscularly. In addition, none of these drugs caused deterioration in renal function tests.

Brief results of studies on acute renal colic and urinary calculus are illustrated in the tables 9. The subsequent sections include original papers discussing in details the results on pain score, pain relapse, side effects and renal function tests and the possible modem of action.

Studies	Diseases	Drugs	Doses	Number of Patients	Responses+				Relapse	Side Effects
					30 min	60 min	Total	%*+		
1	Resistant acute renal colic	Indomethacin Suppostories	100 - 200mg	55	47	8	55	100	No	No
	Urinary calculus & pain	Indomethacin Suppostories	200 mg/day	30 (had small stone) **	21 Patients passed stones with in one month and all had pain relief, and no pain relapse			70	No	No
2	Acute renal colic	Sublingual nifedipine	30 mg	20	3	5	16 *	80	No	Headache (7 patients) and Dizziness (5 patients)
	Urinary calculus and renal pain	Nifedpine	10 mg / 8 hr	16 (10 had small stones)**	Three patients passed stone within one weekand all had pain relief and no relapse.			30	No	No
3	Acute renal colic	Tenoxicam i.m	20 mg	30	15	9	24	80	4 (16.6%)	No
4	Acute renal colic	Tenoxicam i.v	20 mg	25	16	4	20	80	No	No
		Buscopan Compositum i.v 1-Dipyrone 2-Hyocine –N Butyl bromide	2.5 g 20 mg	22	10	6	16	72.2	10 (62.5%)	Dryness of mouth and Drowsiness in all the patients
5	Acute renal colic	Piroxicam i.m	40 mg	34	25	7	32	94.1	No	No
		Diclofenac Sodium i.m	75 mg	30	15	11	26	86.6	9 (34.6%)	No
6	Acute renal colic	Meloxicam Sublingual	15 mg	3	1	2	3	100	No	No

Table 32 : Brief results of studies conducted on acute renal colic and urinary calculus .
(*) : Another eight patients responded within 2 hours. (**) : Small stones: size of the stone was one cm or less measured by radiography and ultrasound. (+): response (regarding pain of renal colic) when moderate, severe or very severe pain became none or mild ($p<0.05$). (*+) : Percent of the responders out of the patients treated.

14. Critical appraisal of the published papers on renal colic and urinary calculus

14.1. Short acting prostaglandin synthesis inhibitor, indomethacin.

14.1.1. Indomethacin and resistant renal colic

Regarding treatment of acute resistant renal colic by indomethacin, the results showed that indomethacin suppository might be an alternative analgesic of value for use in resistant renal colic not responding to spasmolytics / analgesics. This is the first study-proving efficacy of indomethacin suppository to treat resistant urinary colic. Indomethacin suppository has both a potent analgesic effect on acute urinary colic and a therapeutic value in the management of urinary calculus. However, the study was open since the design of a controlled study is difficult when rectal administration is being compared with standard analgesics, and it was thought unethical to use placebo because of the risk of possible complications. All the patients, who showed no response to analgesic/antispasmodics, responded to indomethacin suppository. No side effects were reported. 27% of the patients passed their stones within 30 days of using indomethacin. In addition, we used indomethacin suppositories to treat patients with acute renal colic who showed no response to sublingual nifedipine or tenoxicam. These patients showed better response to rescue indomethacin treatment after 1 h of using indomethacin. Therefore, indomethacin suppositories could relieve pain of acute renal colic resistant to spasmolytics/analgesics, calcium antagonist nifedipine and long acting prostaglandin synthesis inhibitor, tenoxicam.

Indomethacin stops human rhythmic ureteric contraction, which is reactivated by PGF2 alpha (Sahin *et al.* 1993). The mechanism of action of indomethacin in the relief of renal colic might be a result of inhibition of prostaglandin and NO synthesis since the pain may be related to elevated intrarenal pressure (see figure 9). Indomethacin may exert its effect not only as a result of inhibition of both renin activity and diuretic and renal effects of prostaglandins but by central analgesic

effects as has been suggested with other NSAIDs (Ferreira *et al.* 1978). In addition, possible inhibition of NO or bradykinin actions in ureteric obstruction might help in relieving renal colic. Intravenous indomethacin was first shown to have an effect in biliary and ureteric colic (Thornell *et al.* 1979). Moreover, intravenous indomethacin 100 mg is effective as intravenous pethidine in the treatment of acute renal colic (Al-Sahlawi & Tawfik 1996).

14.1.2. Indomethacin and urinary calculus

Of great interest is the apparent ability of indomethacin suppository to facilitate the passage of urinary stones in patients awaiting surgical removal. The mechanism facilitating the passage of stones needs to be investigated. Stones may cause urinary epithelial cell damage, which may result in the release of prostaglandin; these may increase vascular permeability and oedema around stones and cause pain with cumulative hyperalgesia (Moncada *et al.* 1973). Indomethacin might encourage the passage of stones by reducing the inflammatory reaction and oedema, particularly in the presence of urinary tract infections. In addition, indomethacin may dilate the urinary tract by inhibiting prostaglandin as prostaglandin may cause smooth muscle contraction in different organs (Nakano 1967).

14.1.3. Supported studies

Indomethacin suppositories were found effective to treat acute resistant renal colic, chronic renal pain, and urinary calculus in patients awaiting surgical removal, and they have a protective effect against recurrent renal colic due to urinary calculus. Recent studies confirming our findings showed that 73% of patients with urinary colic showed good pain relieve 30 min after receiving indomethacin rectally (Nissen *et al.* 1990). Rectal and intravenous indomethacin were also found effective to relieve pain of acute renal colic (Jonsson *et al.* 1987; Nelson *et al.* 1988). In addition, our findings regarding the efficacy of indomethacin in relieving resistant renal colic are also confirmed by recent study demonstrating that oral indomethacin is effective in the treatment of renal colic not responding to narcotics (Wolfson & Yealy 1991). Concerning urinary expulsion, our results are supported by other studies showing that NSAIDs could facilitate passage of ureteric stone (Friedman 1990; Ahmed *et al.* 1991).

The protective effect of indomethacin is confirmed by other study which showed that indomethacin suppository prevented recurrent ureteric colic and decrease use of narcotics in patients with ureteral stones (Kapoor *et al.* 1989). Other study showed that oral diclofenac sodium was used as prophylaxis for recurrent ureteric colic (Laerum *et al.* 1995).

14.2.Long acting prostaglandin inhibitor (NSAIDs) and antispasmodic/analgesic in acute renal colic

The results demonstrated that tenoxicam i.m or i.v was effective to alleviate acute renal colic. Tenoxicam i.v exhibits rapid onset of analgesia and prolong action as compared to buscopan compositum. Both i.v and i.m tenoxicam provided pain relief in 80% of cases of acute renal colic. 50% got relief within 30 min with use of i.m and 64% got pain relief within 30 min with use of i.v tenoxicam. 16.6% of patients showed pain relapse with i.m tenoxicam while no case of relapse was encountered with use of i.v tenoxicam. When comparable patients treated with buscopan compositum, 72.2% of the treated patients got pain relief, of them 62.5% showed pain relapse within 24 hrs. Within 30 min, 45.4% had complete pain relief. Therefore, it seems that tenoxicam i.v or i.m has faster onset of analgesia, better analgesic efficacy and no or fewer cases of pain relapse.

Tenoxicam is long acting NSAID and its half-life is 60 hrs. The results proved that long acting NSAID has rapid onset of action in cases of acute renal colic. Acute pain usually treated with short acting NSAIDs that have rapid onset of action, but they associated with high rate of pain relapse. In our study, long acting NSAIDs provided no or few cases of relapse.

Again the mechanism of action of tenoxicam might be due to its ability to inhibit prostaglandin synthesis. Other studies demonstrated that tenoxicam has both a good clinical effectiveness and a good bearing in long-term treatment and rarely causes gastrointestinal disturbances. It has fewer side effects than other anti-inflammatory agents and it is safe and well tolerated (Taglier *et al.* 1992). There was high percentage of relapse in patients receiving buscopan compositum which contains both dipyrone and hyoscine butylbromide. This drug can cause many side

effects such as dryness of mouth, thirst, tachycardia, urinary retention, mydriasis, constipation, dryness of skin, contact dermatitis, vomiting, drowsiness and psychosis (Gordon 1989).

The cost of single injection of tenoxicam is more than buscopan compositum. However, the number of patients responding to tenoxicam is higher than with buscopan compositum and the onset of analgesia is faster. Moreover, 67.2 % of patients who responded to buscopan compositum showed pain relapse and needed pethidine injection. Besides its side effects, pethidine is expensive in comparison to tenoxicam or buscopan compositum. Therefore, the overall cost of buscopan compositum therapy is higher than tenoxicam. We could conclude that long acting prostaglandin synthesis inhibitor i.v. and i.m tenoxicam will widen the alternative treatment for acute renal colic and also reduce the usage of opiates.

14.3. Long acting and short acting prostaglandin synthesis inhibitors (NSAIDs)

Two types of NSAIDs were compared in acute renal colic, which are short acting prostaglandin inhibitor, diclofenac sodium, and long acting prostaglandin inhibitor, piroxicam. Although there was no significant difference between piroxicam and diclofenac sodium regarding the number of the improved patients. piroxicam has rapid onset of analgesia as compared to diclofenac sodium and pain relapse was significantly higher with diclofenac sodium. Intramuscular piroxicam relieved pain of acute renal colic in 93.1% of the patients, of these 73.5% got relief within 30 min. 86.6% of the patients used diclofenac sodium had complete pain relief, of these 50% got relief within first 30 min. Vignoni *et al.* 1993 found that diclofenac sodium i.m provided relief of pain 25 min after injection in 59% of cases, while Laerum *et al.* 1996 demonstrated that significant reduction in pain intensity was achieved after 5 mins of diclofenac i.m.

Piroxicam is long acting NSAID and its half-life is 30-86 hrs while half-life of diclofenac sodium, short acting NSAID, is 1-2 hrs. The study proved that long acting NSAID could quickly alleviated acute renal colic, similar to short acting NSAID, with an excellent advantage of lower rate of pain relapse.

The mechanism of action of piroxicam in the relief of renal colic might be the result of inhibition of prostaglandin synthesis. Piroxicam may exert its effect not only as a result of inhibition of prostaglandins but by central analgesic effects as has been suggested with other NSAIDs. Piroxicam not only inhibits the synthesis of prostaglandin due to inhibition of COX enzyme, but also inhibits superoxide anion formation and release of lysosomal enzymes from polymorphonuclear leukocytes. Piroxicam was reported to be superior to diclofenac and ketorolac to reduce post-operative pain following laporoscopy (O'Hanlon *et al.* 1996). Moreover, piroxicam has long half-life, which results in the maintenance of relatively stable concentration throughout the day. This may explain that none of our patients showed relapse over 24 h. Although this study showed that diclofenac sodium has high therapeutic effect to overcome renal colic the rate of relapse is higher than piroxicam.

The advantages of using piroxicam over diclofenac are related to the findings that piroxicam has higher analgesic effect to reduce pain intensity, rapid onset of analgesia and prolonged effects with no relapse during 24 h following drug administration. In earlier observation we found that i.m. piroxicam 20 mg was effective to relieve acute renal colic and renal colic not responding to antispasmodics (Al-Waili 1997). More recently, 40 mg of sublingual piroxicam was found to be effective to treat acute renal colic and allover efficacy of treatment was 81% (Supervia *et al.* 1998).

14.4. Sublingual nifedipine in acute renal colic

Sublingual nifedipine, a calcium channel blocker and prostaglandin synthesis inhibitor, was used to treat acute renal colic. The results showed that nifedipine caused marked improvement in 16 out of 20 patients with acute urinary colic. The other four patients failed to respond to nifedipine and were successfully treated with indomethacin suppository. We found that sublingual nifedipine is effective to treat acute renal colic, prevents recurrent ureteric pain and facilitates passage of ureteric stone. These finding are in agreement with others who showed that nifedipine could relieve pain in acute renal colic in 44% of the cases (Lioret *et al.* 1986). More recently, Porpiglia *et al.* (2000) found that 30 mg of nifedipine daily caused stone expulsion in 79% of the patients and reduced pain recurrence due to ureteric stone.

Nifedipine limited calcium phosphate stone formation and it facilitates ureteral stone passage (Strohmaier *et al.* 1994; Berghi *et al.* 1999).

We suggested that a combination of both calcium channel blocker and prostaglandin synthesis inhibitor might be more effective in the treatment of renal colic. This is recently confirmed by others who found that addition of nifedipine to NSAIDs combined with oxycodeine caused higher stone passage rate and fewer emergency visits and surgical intervention (Cooper *et al.* 200). Many studies showed safety and effectiveness of nifedipine in urinary diseases. Nifedipine plus methylprednisolone are effective in facilitating ureteral stone in 87% of cases (Borghi *et al.* 1994). Nifedipine exhibited a protective effect on high emergency shock wave induced renal damage (Li *et al.* 1995).

It has been found that prostaglandin synthesis in response to different stimuli in renal cortical tubular cells is a calcium dependent process (Wuthrich & Vallotton 1986). Calcium antagonists enhance analgesic effects of analgesic drugs and antipyretics and have inhibitory effects on phospholipase activity and prostaglandin production (Danon *et al.*1986; Hrisen 1995). It has been found that nifedipine abolish effect of neuropeptide Y to promote prostaglandin synthesis (el Din & Malik 1988). Moreover, nifedipine could inhibit phospholipase A2 activity, prostaglandin and leukotrienes activity (Chang *et al.*1987). Levine 1983 has found that nifedipine inhibited synthesis of prostaglandins, leukotrienes and 12-hydroxyeicosatetraenoic acid. Calcium channel blockers, including nifedipine, inhibit thromoxan A2 and have antithrombogenic activity (Onoda *et al.*1984). Nifedipine blocked arginine vasopressin or angiotensin 11-stimulated prostaglandin production in the kidney (Scharshmidt & Dunn 1983). In addition, nifedipine could inhibit tumour cells to produce prostaglandins (Snoek & Levine 1983).

Recently, it was found that nifedipine has anti-inflammatory activity and attenuating the development of inflammatory oedema (Briukhanov *et al.*1994). Sanchez *et a.*1998 found that nifedipine has anti-inflammatory properties which are dose and time-dependent. Nifedipine has antinociceptive effect (Miranda *et al.* 1992; White & Consins 1998). It induced a dose-dependent analgesic action in mice and reduced oedema (Brinkhanor *et al.* 1994; Al-Hamayyd 1995). Nifedipine could enhance epidural morphine-induced postoperative pain relief (Pereria *et al.* 1993).

Nifedipine decreases thromboxan A2 in the kidney, which is increased in patients with glomerulonephritis (Tsygin & Kucherenko 2000; Dzgoeva & Kutyrima 2000).

Nifedipine reduces both proteinuria and acute interstitial nephritis and calcium antagonist has potential beneficial effects on kidney functions (Martin *et al.* 2000). Calcium antagonists have nephrone protective affected by reducing blood pressure, intraglomerular hydrostatic pressure and proteinuria and attenuation of ischemic effects of cyclophosphomide on the transplanted kidney (Deray 1999).

Nifedipine may inhibit the effect of prostaglandin on the cells of the ureteral and vascular wall since prostaglandin stimulate and facilitate calcium influx and movement across cell membranes, triggering and controlling smooth muscle contraction (Eagling 1972). In addition, nifedipine has a direct stabilising effect on the smooth muscle cell preventing contraction and also has an indirect action by stabilizing leucocytes and preventing mediator release such as prostaglandin, histamine, leukotrienes and vasoactive amines (Barnes 1985). Nifedipine stops spontaneous rhythmic activity of human ureter suggesting that in addition to prostaglandin synthesis, an influx of calcium is responsible for ureteric contraction (Sahin *et al.* 1993). Moreover, nifedipine caused a significant lowering of blood pressure and elevation of heart rate. These might result in reduction of intrarenal pressure. Renal blood flow failed to decline as blood pressure fell, which may be due to increased cardiac output, plasma renin activity and noradrenaline observed following acute nifedipine administration. A rise in renal blood flow may overcome any local ischemia resulting from a lodged stone. We have demonstrated that oral nifedipine has spasmolytic activity and could relieve intestinal colic (Al-Waili 1990).

The effects of nifedipine on acute renal colic, recurrent renal colic and urinary calculus might be ascribed to its ability to inhibit prostaglandin production, its anti-inflammatory activity, and its calcium channel blocker activity.

14.5. COX-2 inhibitor-meloxicam in acute renal colic

We used non-selective COX inhibitors to treat acute renal colic and urinary calculus with promising results. However, it has been suggested that renal prostaglandin production in normal kidneys is driven by the activity of constitutive

COX-1, while at sites of inflammation, such as hydronephrotic kidney, there is induction of COX-2 (Seibert *et al.* 1996). COX-2 inhibition reduced PGE2 excretion, urinary sodium excretion, urine flow rate and fractional lithium excretion (Rodriguez 2000). COX-2 inhibition reduced motility index (amplitude multiplied by frequency) in the upper urinary tract in a concentration-dependent manner (Davidson *et al.* 2000).

Meloxicam has selectivity for the inducible COX-2 (Furst 1997). It has greater *in vitro* and *in vivo* inhibitory action against the inducible isoform of COX-2. Meloxicam caused significant inhibition of oedema and exhibited systemic anticipative action (Santos *et al.* 1998). Meloxicam tablet, given sublingually, was used to treat acute renal colic in three patients. The patients showed pain relief without side effects.

Meloxicam might show its effect through prostaglandin synthesis inhibition. This is the first study to report the efficacy of sublingual COX-2 inhibitor meloxicam in relieving acute renal colic pain due to ureteric calculus. Meloxicam is long acting NSAID and its half-life is 13-20 hrs. This property of the drug prevented pain relapse after 24 hr of drug administration. In addition, the drug was quickly absorbed by sublingual mucosa, which provided rapid onset of analgesia. Using COX-2 inhibitor to treat acute renal colic is a step forward to treat safely this challenged problem. We believe that investigating the effects of COX-2 inhibitors in other renal problems might be useful.

14.6.NSAIDs and Possible Side Effects on the Kidney

In our studies we used NSAIDs to treat many urological diseases including acute renal colic, urinary calculus, primary enuresis, and nocturnal frequency of micturition. The drugs were found to be safe with minimal side effects. However, NSAIDs are capable of inducing a variety of renal function abnormalities, particularly in high-risk patients with decreased renal blood perfusion. Fluid retention is most common complication, which is reversible on discontinuation of the NSAIDs (Whelton & Hamilton 1991).

The next most common complication is acute deterioration of renal functions, which is also reversible. Nephrotic syndrome and interstitial nephritis are rare and reversible complications. Papillary necrosis is the only permanent complication of NSAIDs and is very rare (Whelton & Hamilton 1991). Nevertheless, normotensive patients with biopsy verified chronic glomerulonephritis but with preserved renal functions and without nephritic syndrome have no increase risk of acute deterioration of renal function during administration of NSAIDs compared with healthy subjects (Nielsen *et al.* 1994). Our patients had preserved renal functions and no deterioration was encountered during or after treatment with NSAIDs.

It is well known that prostaglandins and NO are mediators of inflammations. NSAIDs inhibit prostaglandin, NO and calcium influx. Prostaglandins increased in glomerulonephritis and thromboxan A2 plays an important role as an exaggerating factor in the development of chronic glomerulonephritis that accompanying nephrotic syndrome (Niwa *et al.* 1987). In addition, patients with chronic glomerulonephritis, purpura nephritis and lupus nephritis have increased thromboxan A2 generation-capacity of platelet which may cause abnormal enhancement of platelet functions and conceivably constitute an aggravating factor of glomerular microvascular drugs (Nakano *et al.* 1988). Therefore, inhibition of prostaglandins in some circumstance might be useful. Purkerson *et al.* (1985) showed that inhibition of thromboxane synthesis could ameliorate renal diseases. More works must be conducted on COX-2 inhibitors to minimize possible complications.

15. Conclusion and further works

15.1. Main findings of the Linked studies

All the steps of the studies have been carried out with original and linked results. Inhibition of prostaglandins with NSAIDs or carbamazepine caused significant improvement in patients with frequency of micturition, primary nocturnal enuresis or resistant enuresis. In addition these drugs inhibited NO, which as we hypothesized that, might be implicated in the pathogenesis of these diseases. Other effects of the drugs on antidiuretic hormones and water metabolism might be part of their action. In renal colic, the results showed that prostaglandin inhibition by long and short acting NSAIDs or calcium antagonist, nifedipine, provided significant analgesic effects on acute renal pain.

Short acting NSAIDs, indomethacin suppository, was found effective to treat resistant urinary colic. Long acting NSAIDs are better than short acting NSAIDs particularly in prevention of pain relapse. In addition, long acting NSAIDs are better than buscopan compositum regarding efficacy, pain relapse, onset of action and cost of the treatment. These make long acting NSAIDs more acceptable and appropriate for treatment of acute renal colic. On the other hand, the results showed for the first time that COX-2 inhibitor, meloxicam, has quick analgesic affect on acute renal colic and prevent pain relapse. In addition, indomethacin and nifedipine have prophylactic effects against pain due to urinary calculus. Both drugs were found for first time to facilitate passage of urinary calculus. All these results have been confirmed by others.

The effects of NSAIDs or nifedipine might be attributed to inhibition of prostaglandin synthesis. However, other inhibitory actions of the drugs on calcium influx, smooth muscle contractions, and neuropeptide Y or NO production during urinary obstructions, or their central effects or anti-inflammatory properties might involved in their therapeutic effects.

15.2.Conclusion

All the issues mentioned in the purposes of studies included in the thesis are answered and achieved with the conduction of the eleven studies and 17 steps. According to our hypothesises and research findings and to the subsequent publications by others that substantiated our works, we could conclude that

1- Prostaglandins may have an important role in the aetiology and pathogenesis of primary nocturnal enuresis and nocturnal frequency of micturition, and the inhibition of prostaglandin with indomethacin, diclofenac sodium, and to lesser extent carbamazepine, are effective in the treatment of primary enuresis and nocturnal frequency of micturition. The responses are apparently dose-related.
2- The mechanism of action of indomethacin in primary enuresis is mainly related to the reduction of urine volume, urinary solutes excretion, free water clearance, filtered sodium and fractional sodium excretion brought about by indomethacin treatment. In addition, it might have effects on bladder capacity, urethral and bladder neck pressure and CNS.
3- Indomethacin reduced bedwetting in normal and small predicted functional bladder capacity.
4- Indomethacin could reduce bedwetting in resistant enuresis, not responding to imipramine, spasmolytics or fluid restriction.
5- Urinary concentration of nitrite, the end product of NO, is increased in primary enuresis, which was decreased significantly with indomethacin treatment. NO might be implicated in the pathogenesis of enuresis.
6- The effects of NSAIDs or carbamazepine on primary enuresis might be contributed to their inhibitory effects of prostaglandin and/or NO production.
7- Inhibition of prostaglandin by indomethacin, tenoxicam, piroxicam, and diclofenac sodium are effective in the treatment of acute renal colic.
8- Long acting NSAIDs piroxicam or tenoxicam, and short acting NSAIDs, indomethacin or diclofenac sodium, provided similar therapeutic effects on pain of acute renal colic.
9- Long acting NSAIDs are better than spasmolytics regarding efficacy, onset of action, cost of the treatment and the rate of pain relapse.
10- Long acting NSAIDs caused lower rate of the pain relapse than short acting NSAIDs.

11- Inducible-COX-2 may be involved in the pathogenesis of urinary diseases. Meloxicam could possess a potential therapeutic effect in the treatment of acute renal colic and prevention of pain relapse.

12- Indomethacin suppositories are effective in the treatment of acute resistant renal colic, facilitate passage of urinary calculus and have prophylactic effects against pain recurrence due to calculus.

13- Nifedipine is effective to treat acute renal colic, facilitates passage of urinary calculus and could prevent pain recurrence.

14- Administration of the drugs tested through rectal, sublingual, i.m. or i.v. routes showed rapid onset of action, which is badly needed in cases of acute crisis and in patients with nausea and vomiting. Rectal and sublingual methods are easy and self-administered. This is important when there are limited health services and a lack of sophisticated measures available to patients.

15- Mild side effects were recorded with use of the tested drugs during short course or long course treatment.

16- NSAIDs, nifedipine or carbamazepine did not deteriorate renal functions in all our patients who had normal renal function tests before the treatment.

In summary of conclusion, the results of our studies showed that prostaglandin synthesis inhibition with NSAIDs, calcium antagonist, nifedipine, or carbamazepine, as part of their mechanism of actions, has a potent clinical application to treat many common challenging problems including frequency of micturition, primary nocturnal enuresis, acute and chronic obstructive renal colic, and urinary calculus. The drugs investigated were indomethacin (capsule and suppository), diclofenac sodium (tablet and i.m.), tenoxicam (i.m., i.v.), piroxicam (i.m.), meloxicam (sublingual), nifedipine (sublingual), and carbamazepine (tablet). These drugs were tolerated well by all the patients and only a few side effects were reported. Different routes of administration were used and our goals were to achieve rapid absorption, safe method of administration and easy or self-administration of drugs. In acute status, such as acute renal colic, i.v, i.m, rectal suppository or sublingual routes were used to achieve rapid onset of analgesia and to avoid oral route, which might be not suitable for patients with nausea and vomiting.

15.3. Suggestions for Future Work

Our works raise a lot of questions and scientific matters that will be excellent fields for further researches. The effects of COX-2 inhibitors on the urinary diseases will be fruitful topic of research since these inhibitors have fewer side effects. Further studies investigating methods to facilitate passage of urinary calculus, as well as prevention of stone formation or recurrent urinary colic due to urinary calculus with use of NSAIDs and calcium antagonists are warranted. Using a combination of desmopressin and prostaglandin inhibitors might have better effects, which need further studies. Studies to investigate the effect of selective NO inhibitor in patients with primary enuresis or renal colic are warranted.

Our previous hypothesis and findings suggested that prostaglandin inhibition might be useful for treatment of carcinoma, and immunodeficiency and anemia associated with malignancies and chronic inflammatory conditions (Al-Waili *et al.* 1980; Al-Waili *et al.* 1983, Al-Wail & Al-Azzawi. 1985; Al-Waili 1988). Therefore, further studies to investigate the possible effects of NSAIDs, particularly COX-2 inhibitors, on the malignant and chronic inflammatory diseases of urological system will be of great value. In addition, further studies investigating their effects on renal functions during and after treatment of urinary diseases are extremely important.

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Appendix 1

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