SUYASH
Uro Times

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NON SURGICAL THERAPY OF BPH

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WATCHFUL WAITING

Indications

- Lower urinary tract symptoms (LUTS) are not bothersome
- Adverse events of treatment are likely to be more than inconvenience of symptoms
- Reluctance to take a daily tablet due to side effects and/or the cost of treatment

Methods

Reassurance

- This is not a cancer
- This is not a life threatening disease
- Delay in treatment will not have irreversible consequences

Life style modification

- Decreasing fluid intake especially before bedtime
- Reducing intake of alcohol and caffeine containing products
- Timed voiding

Medical Therapy

- Prior to the 1980s prostatectomy was the only widely accepted treatment for BPH
- Although **medical therapies do not achieve the same efficacy as prostatectomy,** clinically significant outcomes are obtained with few, less serious and reversible side effects
- Medical therapy is currently considered the preferred treatment alternative for those individuals who lack absolute indications for surgery
- The ideal candidate for medical therapy.
  - Should have bothersome symptoms negatively affecting quality of life
  - Willing to make a lifetime commitment to medical therapy
  - The drug is effective and adverse effects are either nonexistent or minimal

PATIENTS PRESENTING WITH ABSOLUTE INDICATIONS FOR INTERVENTION SHOULD BE DISCOURAGED FROM SELECTING MEDICAL THERAPY.

Drugs available

- α-adrenergic blockers
- 5α-reductase inhibitors
- Aromatase Inhibitors
- Antimuscarinic drugs
- Phosphodiesterase inhibitors (PDEIs)
- Plant extracts
- Combinations

α-Adrenergic Blockers (AB)

Introduction

- AB are widely used as initial pharmacotherapy in the treatment of men with LUTS/BPH
- They offer symptomatic relief and generally are well tolerated

Rationale

- LUTS are partly caused by α1 receptors associated prostatic smooth muscle contraction – dynamic obstruction
- There are two subtypes of α receptor - α1 and α2
- α1 receptors are present in prostate
- α2 receptors are present in vessels
- There are three subtypes of the α1 receptor
- The α1A receptors are predominant in the human prostate stroma
- The α1B receptors are predominant in the prostate epithelium
- In prostate glands from men with BPH a 3 fold increase in alpha-1d receptors are found compared to normal individuals
- The alpha-1d receptors are also present in the detrusor muscle and lumbosacral spinal cord where they facilitate the micturition reflex

Mechanism of action

- α -1 receptor blockage leads to relaxation of prostatic smooth muscle thereby counteracting the dynamic component of BOO caused by BPH
- Non-subtype selective α receptor blockers display similar affinity for all α receptor subtypes and cause vasodilation by blockade of α receptors in large blood vessels.

Safety and efficacy

- All the α receptor blockers have similar efficacy with total symptom score improved by 30-40% and peak flow rates by 16-25%, but differ in terms of safety profile

Advantages

- The clinical response is rapid and dose dependent and durable
- The long-acting α1 blockers are well tolerated
- They are safe in the elderly, diminish BOO, and reduce the risk of retention
- Terazosin and doxazosin significantly lower blood pressure only in hypertensive subjects, allowing treatment of coexisting BPH and hypertension

Adverse effects

- The adverse events particularly problematic in the elderly are dizziness, orthostatic hypotension, syncope, nasal congestion, flu like syndrome and asthenia
- Ejaculatory dysfunction and sometimes (relative) anejaculation is frequently seen with tamsulosin and more with silodosin than with other drugs of this class.

Classification

- α- blockers are classified according to α receptor selectivity and serum half-life
- Non selective, Selective, Sub type selective
- Short acting, Long acting

Non-selective α blockers

Phenoxybenzamine

- The first α blocker shown to produce improvements in symptom and flow rates
- Was highly effective for BPH

- High incidence and severity of adverse effects
- Presently not used for BPH treatment

Selective α blockers

Short acting

Prazosin

- α1 receptor selective
- The efficacy of phenoxybenzamine and prazosin are comparable
- Prazosin is better tolerated except for postural hypotension
- Prazosin and other α1 antagonists like intermediate-release (IR)alfuzosin and indoramin, require twice-daily dosing due to short half-life
- Presently not much used for BPH treatment

Long acting

- Terazosin and doxazosin, and extended-release alfuzosin are long-acting α blockers with once-a-day dosing

Terazosin and Doxazosin

- Both agents have comparable efficacy
- Dose titration required to avoid first dose adverse effects
- Doxazosin has a longer half-life
- Both agents are established for treatment of hypertension. 30% of men treated for BPH have coexisting hypertension. They can be used for treating both BPH & hypertension
- Doxazosin has beneficial impact on sexual function due to vasodilatory action within corpora cavernosa
- Doxazocin has high incidence of congestive heart failure limiting clinical utility
- Dose–Terazocin 5-10 mg once a day, Doxazocin 4-8 mg once a day

Subtype-selective alpha-blockers

Tamsulosin

- Uro selective α1 blocker
- Dose 0.4 mg once a day
- It exhibits selectivity for the α1A versus the α1B receptor
- The advantage is that dose titration is not required
- Less effect on blood pressure in hypertensive men
- Adverse events were generally mild
- A unique problem with this drug is Intra operative floppy iris syndrome interfering with cataract surgery which is very commonly required in this age group

Alfuzosin

- Though not sub type selective, this agent is still called Uro selective because of lack of adverse effects and blood pressure changes
- Dose 10 mg once a day
- It has similar efficacy to other agents with good tolerability
- The advantage is dose titration not required
- It has beneficial effect on the quality of life due to impact on sexual function
- Low penetration through blood brain barrier probably lowers its adverse effects

Silodosin

- Silodosin is a relatively new Uro selective α blocker
- This agent shows 162:1 selectivity for α1A versus α1B adrenoreceptors
- It shows rapid and sustained effect
- Dose 8 mg once a day
- Shows improvement in quality of life scores
- Shows increased urine flow in 2 to 6 hours after the initial dose
- Improvement is seen in 3 to 4 days regardless of age or severity of symptoms.
- It has low incidence of adverse events

Naftopidil

- Another sub-type selective α blocker
- It has a three-fold affinity for the alpha-1d over the alpha-1a receptor subtype
- Clinical usage presently is limited

Androgen Manipulation

Rationale

- The embryonic development of the prostate is dependent on the androgen dihydrotestosterone (DHT)
- Testosterone is converted to DHT by the enzyme 5α-reductase
- The genetic deficiency of 5α-reductase in men results in a rudimentary prostate and in feminized external genitalia
- The development of BPH is also an androgen-dependent process
- Castration and pharmacologic agents suppressing testosterone and DHT synthesis or action reduces prostate volume in men with established BPH

Effects

- Androgen suppression causes regression of the epithelial elements of the prostate
- Reducing prostate volume decreases the static component of BOO resulting from BPH
- Maximal reduction of prostate volume is achieved within 6 months
- Subjects with larger prostates achieve the greatest therapeutic benefit
- Both symptoms and flow rates are improved, espcially in men with larger glands

Adverse events : Impotence and decreased ejaculatory volume

Clinical usages

- Symptomatic BPH in patients with large prostate
- Haematuria associated with BPH
- To reduce risk of developing urinary retention in diagnosed case of BPH

Limitation

- Pathophysiology of clinical BPH and LUTS are not dependent on protate size
- Controlling the static component does not lead to symptom improvement in all cases

Finasteride

- Finasteride is a competitive inhibitor of the enzyme 5α-reductase. Two isozymes (type 1 and 2) of 5α-reductase exist. Finasteride is a selective inhibitor of the type 2 isozyme
- It lowers serum and intraprostatic DHT levels, however not to castrate levels as circulating testosterone is converted to DHT by type 1 isozyme that exist in skin and liver
- The greatest change in symptom scores and PFR occurs within the first 2 months
- The risk reduction of retention of urine is 70%
- It reduces prostate volume approximately 20%
- This drug does not mask the diagnosis of prostate cancer
- Dose 5 mg once a day
- Finasteride reduces serum PSA levels approximately 50% . Hence PSA should be determined before beginning finasteride therapy. A biopsy should be performed if PSA is elevated or rising during treatment

Dutasteride

- Dutasteride is a dual inhibitor of 5α-reductase types 1 and 2 and therefore has a greater impact on suppressing serum DHT levels
- Dose 0.5 mg once a day
- Onset of action is rapid
- Dutasteride reduces prostate cancer risk by 23%

Zanoterone

- Zanoterone is a steroidal competitive androgen receptor antagonist
- Dose – 200 mg once a day
- Clinical response minimal and inconsistent
- High incidence of breast pain and gynaecomastia
- The incidence and severity of adverse effects and the equivocal efficacy precluded further development of this drug for BPH
- Presently not in clinical use for this indication

Flutamide

- Flutamide is an orally administered nonsteroidal antiandrogen that inhibits the binding of androgen to its receptor
- High incidences of breast tenderness and diarrhea
- Clinical response in patients with BPH inconsistent
- Presently not in clinical use for this indication

Cetrorelix

- Cetrorelix is a gonadotropin-releasing hormone antagonist investigated for BPH
- Potential advantage is the ability to titrate the level of androgen suppression
- It reduces prostate volume and improved LUTS without significant adverse events
- Disadvantage is problems with the drug formution, requirement for an injection and the cost

Aromatase Inhibitors

Atamestane

- Rationale is that estrogens may be involved in the pathogenesis of BPH
- The estrogenic effect most likely mediates stromal-epithelial interactions that regulate the proliferative activity of the prostate
- Atamestane is a highly selective aromatase inhibitor that lowers both serum and intraprostatic levels of estradiol and estrone
- Dose 400 mg once a day
- Clinically not found to be effective
- Presently not used clinically for treatment of BPH

Antimuscarinic Therapy

- Anti-muscarinics are used in the overactive bladder syndrome (OAB)
- They improve symptoms by reducing the frequency and strength of non-voluntary detrusor contractions (detrusor overactivity (DO))
- There is an overlap between symptoms due to BPH and those due to OAB
- OAB symptoms may coexist with BPH and may be secondary to obstruction or unrelated
- Antimuscarinic agents can be safely given to carefully selected men with OAB and BPH
- Anti-M are not recommended in men with a raised PVR >200 ml, low peak flow rates or who have larger prostates or a prior history of urinary retention
- Drugs available are Tolterodine, oxybutynin, solifenacin, fesoterodine and darifenacin

Phosphodiesterase Inhibitors

- Erectile dysfunction (ED) is commonly found in the male population who are at risk for LUTS/BPH
- PDE5 inhibitors are an established treatment for ED
- Several hypotheses for common pathway in the pathogenesis of LUTS and ED are suggested
- PDE5 is expressed in the prostatic urethra, prostate and bladder neck, and supplying blood vessels. PDE5 inhibitors cause relaxation of detrusor, prostate and pelvic vasculature muscle strips
- Other possible mechanism is improved pelvic oxygenation, effect on the afferent nerves or reducing prostatic inflammation
- PDE5 inhibitors can be used in BPH to improve LUTS and any coexistent sexual dysfunction, whether pre-existent or consequent upon therapy taken for LUTS/BPH such as 5-alpha reductase inhibitor
- Drugs available are sildenafil, vardenafil and tadalafil
- Adverse events are mild like flushing, gastroesophageal reflux, headache, and dyspepsia
- PDEIs improve urinary symptoms scores however they do not improve flow rates
- Present status - safety and cost-effectiveness, especially for combination therapy is being studied

Phytotherapy

- The pharmacologic use of plants and herbs for treatment of LUTS/BPH is common
- These agents have been marketed to "promote prostatic health".
- Additional factors that contribute to their widespread use include
  - being "natural" products (not "medications")
  - presumed safety
  - ease of accessibility (no prescription necessary)
  - avoidance of prostate surgery (?)
  - prevention of prostate cancer (falsely assumed)
- Phytotherapeutic products are not the actual plant but are extracts derived from either roots, seeds, bark, or fruits of various plants used.
- The composition of plant extracts is very complex. They contain a wide variety of chemical compounds like phytosterols, plant oils, fatty acids and phytoestrogens
- Mechanism of action of phytotherapeutic agents are generally unknown. Postulated mechanisms are anti-inflammatory effects modulated by effects on prostaglandin synthesis, 5α-reductase inhibition, growth factor alteration, antiandrogenic effect, estrogenic effect and placebo effect
- Preparations available are *Serenoa Repens* (Saw Palmetto Berry), *Pygeum africanum* (African Plum), *Hypoxis rooperi* (South African Star Grass), *Urtica dioica, Cucurbita pepo, Secale cereale,* and *Opuntia*

Limitations

- It is not certain which of the many mechanisms is responsible for clinical responses
- Most preparations are plant extracts with different components manufactured by different extraction procedures, this prevents comparison of the preparations
- Which of the chemical compounds is the active component is not known
- Randomized placebo-controlled clinical trials to ascertain and confirm the efficacy of these products are not available

Combination Therapy

α- Blockers and 5α-Reductase Inhibitors

Rationale

- Alpha blockers have rapid onset of action but no effect on prostate size
- 5 alpha reductase inhibitors have slow onset of action but produce regression in size of prostate in due course of time
- Combination usage will have benefits of both

Important considerations

- combination therapy has better outcome than monotherapy in reducing progression of disease
- The combined use was shown to decrease the severity of LUTS
- Need of requiring invasive therapy was significantly reduced by combination therapy
- Risk of developing acute retention of urine was also significantly reduced
- adverse events were similar

Present recommendations

- European Association of Urology guidelines recommends the combination therapy approach of an alpha-1 antagonist and 5-alpha reductase inhibitor in men with bothersome LUTS and a prostatic volume of greater than 30 cm3

Combinations available

- Tamsulosin 0.4 mg & Finasteride 5 mg
- Tamsulosin 0.4 mg & Dutasteride 0.5 mg
- Alfuzocin 10 mg & finasteride 5 mg
- Alfuzocin 10 mg & Dutasteride 0.5 mg
- Silodosin 8 mg & Dutasteride 0.5 mg

α- blockers and Phosphodiesterase Inhibitors

Rationale for use

- ED is commonly found in the male population who are at risk for LUTS/BPH
- Combination of alpha blocker and PDE 5 inhibitors can be used for treating both conditions together

Important considerations

- The combination of α- blockers and PDEIs leads to a synergistic benefit thereby improving LUTS
- This combination may lead to symptomatic hypotension as both drugs are vasodilators
- concomitant treatment with PDEIs should only be initiated once the patient's condition has been stabilized on α-adrenergic blocker therapy

α-Adrenergic Blockers and Anticholinergic

Rationale

- Many patients with BPH have predominant storage symptoms not responding to alpha blockers. These could be due to OAB(Overactive bladder). Adding antimuscarinics will benefit in such cases

Important considerations

- The combination of antimuscarinic agents and α- blockers may improve both storage and voiding symptoms
- Combination is safe with minimal risk of retention in carefully selected men
- It is advisable to avoid this combination in men with high residual urine (more than 200 ml)
- Patients on combination treatment developing increased hesitancy or showing signs of increasing PVR or clinical evidence of retention should be warned to stop the antimuscarinic element of the combination immediately
- Men with significant obstruction and large, persistent residual urine volumes should be considered for surgical therapy rather than the addition of antimuscarinic agents

Managing BPH Part -3

Surgical Treatment In Next Issue

Rajeev Gandhi Jeevandayee Aarogya Yojna

Facility available for Selected Cases

NOCTURNAL ENURESIS (NE)

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Synonyms
Bedwetting/ Sleep wetting
Night time Urinary Incontinence

Definition
Involuntary urination while in deep sleep after age at which bladder control usually occurs

Introduction
NE is most common childhood urological problem and one of the most common pediatric issue. Most of the time NE is due to developmental delay and not an emotional problem or physical illness. Only 5 to 10 % of bed wetting are caused by specific medical conditions. Girls dry by age six and boys by seven. Adult bed wetting rate is 0.2 to 2.3%

Type PRIMARY : Most common
Regular bed wetting Girls ; +6yrs Boys ; +7yrs

SECONDARY : Patient goes through extended period of dryness at night (more than six month) and revert to night wetting. Common due to emotional Stress or urinary infections

American Psychiatric Association allows Psychiatrics to diagnose NE if the wetting causes the patient significant distress even if the case does not meet the definition or standard criteria

Etiology Primary NE

A) Neurological Developmental Delay : Studies suggest that NE may be due to nervous system that is slow to process the feeling of full bladder

B) Genetics : Children whose parents were not enuretics incidence 15%. When one or both parents were having H/O NE incidence 44 % & 77% Genetic research shows that NE is associated with gene on chromosomes 13q and 12q (possibly 5&22 also) There is no test to prove that NE is only a developmental delay. Also genetic testing offer little or no benefit

C) Other causes :

1. Attention deficit hyperactivity disorder
2. Excess caffaine or beverage consumption
3. Constipation
4. Urinary tract infection
5. Insufficient Antidiuretic hormone production
6. Children with Intellectual disorder or disabled
7. Physically abnormally small capacity bladder/severe hypospadias
8. Sleep apnea due to tonsillitis
9. Type 1 diabetes
10. Psycological- sexually abused child

Mechanism
A) Hormonal It reduce urine production at night
(Arginine Vasopressin AVP)
B) Ability to wake up when bladder full
C) Hereditary not known

Impact
Many medical studies shows that psychological impact of NE is more important than the Physical consideration. It is often that Childs and family members reaction to NE that determines it is problem or not

1 Self Esteem It affect children
Being teased by sibling
Being punished by parents
Being afraid that friends will find it out

2 Behavioral Impact
Child become shy and avoid mix up with friends
Avoid night stay at relatives or out side

3 Loss of self confidence and feeling of guilt

4 Parents are stressful

Treatment
Following options apply when NE is not caused by specific identifiable condition

1. Behavioral Modifications
   a) Watchful waiting - wait at least till child is 6 to 7 yrs Earlier treatment can be considered if damaging childs self esteem or family relations
   b) Bedwetting Alarms
   c) Toilet training
   d) Waterproof Mattress
2. DDAVP Desmopressin (Desmotab) Oral form is safe than nasal spray, tab is synthetic replacement of Antidiuretic hormone
   Tab taken at bed time restrict water one hour before & 8 hours after dose Start with 200 microgram & later 120 microgram for 3 months
3. Tricyclic Antidepressant Imipramine 25 mg once a day
4. Unproven Acupuncture
5. What does not Help
   A. Punishment **B.** Humiliation
   C. Teaching child to "Hold it till morning" **D.** Keeping child Thirsty
   E. Diapers Give wrong massage

NE is a comprehensive issue can be delt with good counselling, active involvement of parents by educating them and without hurting childs self esteem.

Presentation at Usicon 2014 Delhi, National conference of Urology society of India on "Laparoscopic dismembered pyeloplasty in solitary pelvic kidney"

FACILITIES AVAILABLE

- Endoscopic Treatment Of Stone In Kindey, Ureter and Bladder
- Endoscopic Treatment Of Prostate (TURP)
- LASER - 50 Watt, German Technology Auriga XL excellent energy source for all Urology applications
- Female Urology
- Paediatric Urology (Endoscopy, LASER)
- Male Infertility
- Kidney Transplant
- Laparoscopy
- Video Endoscopy
- Well equipped Operation Theatre
- Multipara monitor, defibrillator
- C - arm X - Ray machine
- Lithotripsy
- Central oxygen & monitoring system
- Uroflometry
- Ultra sonography Department
- Pathology Laboratory
- Digital X-Ray Machine
- Lift & Generator facility
- Cashless Insurance facility
- 24 hrs Pharmacy

First time in India with OCDS Technology Oral Controlled Delivery System
Newly Introduced ECOPACK
Assuring 30 days of max control Economical Pack
Urimax 0.4 Capsules
Cipla
Once Daily Urimax
Also available in 15's Strips
For Symptomatic BPH Patients with Enlarged Prostate

World's First Combination of Tamsulosin (0.4 mg) & Dutasteride (0.5 mg)
Once Daily UrimaxD
Tamsulosin Hydrochloride 0.4 + Dutasteride 0.5
Relax, it works like a charm.
For Symptomatic BPH Patients with Enlarged Prostate

For Symptomatic BPH Clinically Uroselective Alpha$_{1A}$- Blocker
Once Daily Alfusin
(Alfuzosin Hydrochloride 10 mg Extended Release Tablets)
Be in full flow.
Reduces PVR, Effective in the Mangement of AUR Improve success rate of TWOC in Patient with AUR for Sexually Active BPH Patients

In Patients with Symptomatic BPH
Once Daily SILOFAST
Silodosin Capsules 4 mg / 8 mg
Faster. Safer. Better.
Rapidly relieves symptoms

In Patients with Symptomatic BPH and Enlarged Prostate
Once Daily SILOFAST D
Silodosin + Dutasteride
Halts progression with Rapid Action