Review Article

Pharmacotherapy for Urinary Bladder Dysfunction in Spinal Cord Injury Patients

Knowledge of the neurophysiology of the lower urinary tract has greatly increased in the last 10 years. The activity of the sympathetic, parasympathetic and somatic nerves on the detrusor muscle, the bladder outlet and the striated urethral sphincter has been studied in detail (El Badawi, 1968, 1974). Modifications of the classical autonomic nervous system schemes have been summarised recently (Wein-Barrett, 1988). The changed sensitivity of smooth muscle to neurohumoral transmitters after denervation decentralisation has been described (Westfall, 1981).

From a growing understanding of neurophysiology to the actual use of the pharmacological data in treatment has been but a step. Many more therapeutic possibilities are available nowadays in this aspect. But still many questions remain and much uncertainty still exists. In this article we will provide an overview of pharmacotherapy for urinary bladder dysfunction following spinal cord injury.

Pharmacotherapy as part of the total urological treatment tries to achieve the following goals: preservation of the upper urinary tract; avoidance of urinary tract infection; adequate bladder emptying at low intravesical pressure; and prevention of incontinence; and all these in a socially and vocationally acceptable way.

Pharmacological manipulation of lower urinary tract dysfunction should be based on a clear urodynamic diagnosis whenever possible.

Pharmacological agents can easily be categorised according to their effect on the bladder and/or the lower urinary tract outlet. During spinal shock, parasympathomimetic and alpha-adrenergic blocking agents proved inefficient. No clinical effect on bladder areflexia has been shown (Tulloch-Rossier, 1977).

Therapy to facilitate bladder emptying

Bladder stimulation

A major portion of the mechanism of a physiological bladder contraction is acetylcholine-induced stimulation of the muscarinic-cholinergic receptor sites at the post-ganglionic parasympathetic neuromuscular junctions. Theoretically parasympathomimetic agents might be useful in the management of spinal cord patients who show inadequate bladder contractility. Bethanechol chloride exhibits a relatively selective action on the bladder with little or no action on ganglia or on the cardiovascular system (Taylor, 1980). It is used in the classical denervation supersensitivity test (Lapides, 1962).

Bethanechol chloride may be beneficial in patients with incomplete cord lesions and no detrusor striated sphincter dyssynergia (Awad, 1984). It may also be useful in patients with poor detrusor contractility following surgical relief of neurogenically

mediated outflow obstruction (Yalla, 1977). However, there continues to be a great controversy about the clinical efficacy of this drug. A urodynamic assessment before and after a short trial would demonstrate a possible effect and the rationale for long term treatment.

Bladder outlet obstruction is an absolute contraindication for its use. Some authors have suggested that bethanechol chloride can produce an increase in urethral resistance in patients with a hyperreflexic neuropathic bladder (Sporer, 1978). If a combination with agents which decrease outlet resistance is useful, this is not generally accepted (Khanna, 1976; Wein, 1988).

The effect of other drugs with possible cholinergic effects such as neostigmine, ambenonium, and pyridostigmine is not well documented. Prostaglandins E 2 and F 2 have been used as an intravesical instillation in a limited number of patients with incomplete suprasacral spinal cord injury with some success (Vaiadyanathan, 1981). But the exact role of prostaglandins in the lower urinary tract is still under investigation.

The recent knowledge in the field of neuropeptide physiology with the possible activity of endogenous enkephalins on the micturition reflex might offer new possibilities for stimulation for reflex bladder activity through agents such as narcotic antagonists (Thor, 1983).

In patients with a cervical or high thoracic spinal lesion and perineal spasticity, the successful use of phenoxybenzamine (alpha-blocking drug) to treat detrusor inactivity was described by Mathe *et al.* (1985). This finding was said to support the theoretical inhibitory influence of the sympathetic nervous system on the sacral parasympathetic centre in these patients.

Decreasing outlet resistance

Inhibition of striated sphincter. There is no pharmacological agent which selectively relaxes the striated muscles of the pelvic floor. Diazepam, a centrally acting muscle relaxant, has been reported to relieve external sphincter spasticity (Bogash, 1974). No oral dosage however seems to equal the parenteral effect.

Dantrolene sodium, a peripherally acting muscle relaxant, has been reported to have some effect at a very high dose (Murdoch, 1976). Severe hepatotoxicity is the most worrisome side-effect described.

Baclofen, a gamma amino butyric acid, was found to be clinically useful in the treatment of skeletal spasticity. It decreases detrusor hyperreflexia. As with large doses of diazepam, baclofen can cause an increase in residual urine and even complete detrusor areflexia in individual tetraplegic patients.

Inhibition of smooth sphincter—bladder neck. There is a rationale for alpha adrenergic therapy in the patient with inadequate bladder emptying secondary to neuropathic voiding dysfunction. Parasympathetic decentralisation leads to a marked increase in adrenergic innervation of the bladder and the urethra (Sundin, 1977; Koyanagi, 1979).

Phenoxybenzamine has been used for many years (Hachen, 1980). A recent problem with regard to a potential mutagenicity of this drug needs further investigation. The drug also has a bladder relaxing effect.

Prazosin hydrochloride has an affinity for post-synaptic alpha 1 receptors and some success with this drug has been published concerning the treatment of lower

urinary tract dysfunction (Anderson *et al.*, 1981). Potential side-effects on blood pressure must be considered, and the drug dosage must be determined with great care.

The ergoline derivative nicergoline was used with success by Gallego (1984).

A trial of these or other agents with alpha adrenergic blocking effect may be worthwhile in many spinal cord injury patients. The benefits will become obvious in a few days, and the possible side-effects are reversible.

The phentolamine stimulation test (Olsson, 1977) can usually predict the effectiveness of alpha-adrenolytic therapy.

Therapy to facilitate urine storage

Inhibition of bladder contractility

Atropine and agents which imitate its action can depress detrusor hyperreflexia but only partially, because of what is called 'atropine resistance' (in bladder contractility a non-cholinergic, non-adrenergic transmitter is thought to exist).

Propantheline bromide with its atropine-like effect has been a most commonly used agent for many years (Blaivas, 1980). Other pharmacological agents have both anticholinergic and musculotropic relaxing or antispasmodic effects. Oxybutinin chloride, dicyclomine hydrochloride and flavoxate hydrochloride have been used successfully to increase the bladder capacity and lower detrusor hyperreflexia (Fischer, 1978; Brooks, 1980; Anderson, 1987).

Imipramine hydrochloride is a useful agent to facilitate urinary storage by decreasing bladder contractility and increasing outlet resistance (Castleden, 1981). Personally, we are cautious to use it in patients with possible or known autonomic dysreflexia and long-standing bladder dysfunction. We have encountered several severe dysreflexia attacks caused by increasing the bladder capacity above the patient's usual level. Imipramine can be used in combination with an anticholinergic drug, especially if one intends to convert a storage failure to an emptying failure managed by intermittent catheterisation.

The usefulness of calcium antagonists, like nifedipine and terodiline, of Beta-adrenergic agonists like terbutalin, and of prostaglandin inhibitors like many non-steroidal anti-inflammatory drugs need further examination.

Increase of outlet resistance

The bladder neck and proximal urethral smooth musculature contain alpha-adrenergic receptor sites which, on stimulation, produce contraction. Alpha-adrenergic agonists can be used to improve mild to moderate incontinence due to decreased outlet resistance. Good results could be seen in patients with an incomplete spinal cord lesion and severe urethral dilatation by an indwelling catheter balloon (Wyndaele, 1984).

Ephedrine, norephedrine chloride, pseudoephedrine and phenylpropanolamine hydrochloride either alone or in combination products have been used for this purpose (Weiner, 1980). Alpha-adrenergic agents should be used with caution in patients with hypertension and/or autonomic dysreflexia.

The results with B-adrenergic antagonists, such as propanolol in this situation are not well documented and need further study.

Oestrogen has been used with some success in women with low urethral resistance and hormone deficiency. For long term treatment, the lowest maintenance dose should be used, in the light of a possible predisposition to the development of endometrial carcinoma.

Doses and side-effects

Concerning the therapeutic dosage and the most common side-effects of all of the above mentioned drugs, the reader can find ample information in the urological and pharmacological literature.

Non-urological medication with effects on lower urinary tract function

Many drugs used in non-urological situations have a more or less important action on the lower urinary tract. Their use may influence urological re-education and can change bladder function during follow-up studies.

Many drugs are known for their bladder relaxing effect: anticholinergic anti-Parkinson agents, smooth muscle relaxants used either alone or in combination with other drugs in gastrointestinal therapy; Betha 1 and to a lesser extent Betha 2 adrenergic stimulants; tricyclic antidepressants, prostaglandin inhibitors; calcium blockers; strong psychotropic drugs. A list of all such drugs was published by Jurascheck *et al.* (1985).

Conclusion

Though many questions remain and many controversies still exist, pharmacotherapy has become an important part of urological treatment in spinal cord injury patients. Several drugs can be used to treat detrusor, bladder outlet and striated urethral sphincter dysfunction alone or in combination. Improvement can be obtained at least partially where appropriate drugs are used. Well conducted clinical trials, further pharmacological investigations, together with an increasing personal experience of those in charge of spinal cord injury patients, will probably improve the value of pharmacotherapy in the years to come.

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