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Intravesical Oxybutynin for Neurogenic Bladder in Children

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Abstract

Neuropathic bladder dysfunction caused by spinal cord disease may lead to irreversible renal damage and urinary incontinence. The majority of affected children can be successfully managed with standard medical treatment such as oral anti-cholinergic medication (typically oxybutynin or tolterodine) with or without Clean Intermittent Catheterization (CIC). The efficacy of this treatment, however, may be hampered as some of these patients experience severe Adverse Events (AEs) or insufficient suppression of detrusor over activity following oral anti-muscarinic pharmacotherapy. Intravesical oxybutynin chloride is an effective therapy for neurogenic bladder dysfunction; this review considers the indications, administration, safety, and efficacy of intravesical oxybutynin chloride instillation. In addition, some cases of children treated with intravesical oxybutynin chloride solution supplemented with hydroxypropylcellulose (modified intravesical oxybutynin) are described.

Keywords: Neurogenic bladder; Intravesical oxybutynin; Pharmacotherapy

Introduction

Children with spinal cord disease (e.g. myelomeningocele, myelodysplasia, spina bifida, and spinal tumors) can present with neurogenic bladder, a condition in which the bladder partly or completely loses its ability to store urine and to void at low pressure. A bladder with low compliance may cause urinary incontinence, which impacts negatively on Quality of Life (QOL) [1] and also on renal function [2]. Long term high pressure neurogenic bladder increases the risk of deteriorations in the functional status of the kidneys. Therefore, early identification and treatment of children at high risk of urinary dysfunctions is needed in order to protect renal function and avoid urinary incontinence [3]. Recently, anti-muscarinic pharmacotherapy (typically oxybutynin or tolterodine) has been generally considered to be one of the most effective treatments with CIC in these patients. However, some patients do not respond to oral medication or have unacceptable AEs, e.g. dry mouth, constipation, drowsiness, and cognitive dysfunctions, which may result in medical withdrawal for these patients [4]. In order to decrease AEs, some approaches have been suggested, for example, slow-release formulas, transdermal administrations, and intravesical instillation of oxybutynin. Intravesical instillation of oxybutynin was firstly reported by Brendler et al. in 1989, and had less AEs and better effects than its oral administration [5]. There is increasing evidence that intravesical oxybutynin chloride is an effective therapy against overactive bladder [6-10]. This review considers the indications, administration, safety, and efficacy of intravesical oxybutynin chloride instillation. Furthermore, the safety and efficacy of intravesical oxybutynin chloride solution supplemented with Hydroxypropylcellulose (HPC) (modified intravesical oxybutynin), a mucosal adhesion substance, are also presented in this article.

Pharmacokinetics and Mechanisms of Oral Oxybutynin Therapy

In physiologic bladder, the neurotransmitter acetylcholine is released from nerves of the parasympathetic system with subsequent activation of muscarinic receptors in the bladder. This leads to detrusor contraction and resultant micturition. On the other hand, disordered innervations have been identified in neurogenic bladder, typically resulting in dyssynergia between the detrusor and external sphincter, with adverse effects on bladder function. So far, the expressions of five different subtypes of muscarinic receptors have been described in the bladder. M2 receptors are the most abundant, but M3 receptors appear to be more functionally active [11]. These receptors can be effectively blocked with oral anti-cholinergics, such as oxybutynin and tolterodine, with subsequent inhibition of the contraction of bladder smooth muscle, and, therefore, are well established as first-line pharmacotherapy for neuropathic bladder in adults in Japan. Oxybutynin chloride is a tertiary amine that possesses nonspecific anti-muscarinic, spasmolytic, and local anesthetic properties. In experimental studies, oxybutynin demonstrated a protective effect on the bladder by normalizing ultrastructural changes that were associated with neurogenic bladder, such as collagen infiltration into the detrusor muscle [12,13]. These alterations are subsequent to the decreased smooth muscle hypertrophy of neurogenic bladder. Oxybutynin is absorbed from the gastrointestinal tract, with the highest concentrations occurring 60-120 minutes after oral intake, followed by a rapid decrease. Oral oxybutynin passes into the liver via the portal vein immediately after being absorbed, with rapid hepatic metabolism by liver microsomes to oxidation products, mainly N-Desethyl-Oxybutynin (DEOB) and oxybutynin N-oxide [14-16]. Autret et al. showed in children that after ingesting a 5 mg tablet, the peak plasma concentration occurred at a mean of 60 minutes later; subsequent excretion was rapid and, after 12 hours, oxybutynin was not detectable in plasma from any patients [17]. In adults, Douchamps et al. reported that the peak plasma concentration of oral oxybutynin occurred after 48 minutes, with an excretion half-life of 2 hours; the plasma concentration after 5 hours was almost zero [18].

Mechanisms and Efficacies of Intravesical Instillation of Oxybutynin

The aim of treatment for patients who have neurogenic bladder

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due to spinal cord disease is to protect renal function, reduce urinary infections, ameliorate urinary incontinence, and increase QOL. The primary goals of pediatric neurogenic bladder management are to normalize vesical pressure and achieve social continence [19]. While it is true that oral oxybutynin chloride is the first-line therapy, the high incidence of systemic AEs has compromised compliance, resulting in dose reductions or even discontinuation of treatment. In 1989, Brendler et al. first reported the treatment of intravesical oxybutynin chloride for neurogenic bladder [5]. Since then, evidence of the efficacy of intravesical oxybutynin has been reported [8,9,20]. Generally, the majority of children with neurogenic bladder (70-90%) respond well to oral anticholinergic agents with or without CIC [21]. This therapeutic approach allows a high concentration of the drug to be delivered to the target tissue with the maximum pharmacological response and, theoretically, minimum AEs. However, the pharmacokinetic mechanisms of oxybutynin are not well known [22]. It has been suggested that intravesical oxybutynin chloride results in a longer half-life, even considering the higher peak levels. Actually, Madersbacher and Knoll reported that the reabsorption of intravesical oxybutynin is slower than after an oral dose; peak levels are reached later and are maintained at a higher level after 6 hours [20]. An increasing amount of evidence suggests that high plasma levels of DEOB, an active oxybutynin metabolite, cause systemic AEs [7,14]. Indeed, Buyse et al. reported that a significantly lower ratio of AUC (area under the plasma concentration time curve) of DEOB over oxybutynin may reduce systemic AEs [7]. Therefore, intravesical oxybutynin chloride, which reduces plasma levels of DEOB to lower than that with oral administration of oxybutynin chloride, is an effective therapy against overactive bladder, which is intolerable or severe AEs have occurred after oral oxybutynin medication. The mechanism of action of intravesical oxybutynin may involve a direct effect on the bladder muscle, a topical anesthetic effect, or an indirect effect of absorbed oxybutynin and its metabolites [23]. Stasi et al. also reported that this therapeutic effect is a direct localized action within the bladder wall, probably through local anesthesia of the afferent arm of a reflex arc and possibly via a small degree of diffusion down to the M3 receptors in the detrusor [24]. Immunohistochemistry and RT-PCR techniques have revealed that both M2 and M3 muscarinic receptor subtypes are expressed in the rat urothelium, and that M2 receptors are expressed on the human urothelium and are closely associated with sensory nerves [25,26]. Recently, Kim et al. reported that intravesical administration of oxybutynin not only suppresses muscarinic receptor-mediated detrusor muscle contraction, but also blocks muscarinic receptors in bladder-afferent pathways in rats [27]. Actually, Haga et al. reported that oral administration of low-dose oxybutynin decreased c-Fos expression in the spinal cord, which was induced by continuous infusion of saline into the rat bladder [28]. Further studies are needed to resolve the pharmacokinetics of intravesical oxybutynin chloride. Guerra et al., based on their 8 reviews, revealed a significant reduction in pressure at maximum bladder capacity relative to conventional oral drug administration [29]. They reviewed the effectiveness of intravesical oxybutynin precisely and investigated changes in the following scores; Maximum Bladder Capacity (MBC), pressure at MBC, bladder compliance, and the number of urinary incontinence. Surprisingly, almost all of those scores recovered in all reports. In addition, our previous report involving four children also showed ameliorations in MBC, bladder compliance, number of UICs, and urinary incontinence except for one patient who dropped out because of an upper UTI [30].

Therefore, intravesical oxybutynin is an effective treatment in patients who exhibit severe AEs or insufficient suppression of detrusor overactivity following oral anti-muscarinic pharmacotherapy. Further experiments with more patients are needed. Tables 1-4 show the effectiveness of intravesical oxybutynin on each score [6,8,30-34].

Indications of Intravesical Instillation of Oxybutynin

Previously, oxybutynin was mostly administered orally; however, the high incidence of systemic AEs has resulted in dose reductions or the withdrawal of medication. If oral anti-cholinergics are not suitable for children who cannot tolerate systemic AEs or treatment if insufficiently effective, then intravesical oxybutynin chloride is indicated. In Japan, intravesical oxybutynin is not an established treatment for neurogenic bladder due to spinal cord disease in children; however, in "clinical practice guidelines for lower urinary tract dysfunction in patients with spinal cord injury", the lower incidence of AEs and higher effectiveness of intravesical oxybutynin has been introduced [31]. Therefore, after

Author	Before treatment	After treatment	Mean change	% Mean change
Greenfield and Ferra [8]	NR	NR	10-140	11-335
Conor et al. [32]	NR	NR	NR	41
Kasabian et al. [6]	159.3 ± 113.4	246.0 ± 128.7	86.7 ± 19.7	54.4
Kaplinsky et al. [10]	99.7 ± 85.5	199.6 ± 97.3	99.9 ± 25.7	100.0
Painter et al. [45]	209.0 ± 103.0	282.0 ± 148.0	73.0 ± 28.5	34.9
Buyse et al. [10]	114.0 ± 54.7	214.0 ± 78.1	100.0 ± 25.7	87.7
Ferrara et al. [34]	132.0 ± 103.0	226.0 ± 118.0	94.0 ± 12.7	71.2
Guerra et al. [45]	200.5 ± 100.5	243.6 ± 118.9	43.1 ± 10.7	21.5
Hayashi et al.* [30]	23.9 ± 22.9	118.5 ± 76.2	94.6 ± 53.7	395.8

* Volume at an intravesical pressure of 30 cm H_2O.

Table 1: Change in Max Bladder Capacity (MBC) (mean ml ± SD) after treatment with intravesical oxybutynin.

Author	Before treatment	After treatment	Mean change	% Mean change
Greenfield and Ferra [8]	NR	NR	−15-−140−33-	−66
Connor et al. [32]	NR	NR	NR	−47
Kasabian et al. [6]	47.3 ± 22.5	36.6 ± 21.4	−10.7 ± 6.25	−22.6
Kaplinsky et al. [10]	60.1 ± 31.8	35.6 ± 20.0	−24.4 ± 6.31	−31
Painter et al. [43]	63.0 ± 24.0	56.0 ± 31.0	−7.0 ± 2.84	−11.1
Buyse et al. [44]	57.0 ± 25.6	30.8 ± 15.8	−26.2 ± 6.75	−46.0
Ferrara et al. [34]	53.0 ± 30.0	34.0 ± 11.0	−19.0 ± 2.4	−35.8
Guerra et al. [45]	47.7 ± 25.6	34.4 ± 22.9	−13.3 ± 3.5	−29.1
Hayashi et al. [30]	NR	NR	NR	NR

Table 2: Change in pressure at MBC (mean cm H_2O ± SD) after treatment with intravesical oxybutynin.

Author	Before treatment	After treatment	Mean change	% Mean change
Greenfield and Ferra [8]	NR	NR	NR	NR
Connor et al. [32]	NR	NR	NR	NR
Kasabian et al. [6]	NR	NR	NR	NR
Kaplinsky et al. [10]	2.0	9.4	7.4	370
Painter et al. [43]	NR	NR	NR	NR
Buyse et al. [44]	NR	NR	NR	NR
Ferrara et al. [34]	8.5 ± 6.1	16.0 ± 11.0	7.5	88
Guerra et al. [45]	5.3 ± 3.7	19.3 ± 45.1	13.8 ± 44.65	260
Hayashi et al.* [30]	0.67 ± 0.90	6.73 ± 3.25	6.07 ± 3.43	905

*Calculated as the total volume divided by the end-fill pressure

Table 3: Bladder compliance (mean ml /cm H_2O ± SD) change after treatment with intravesical oxybutynin.

Author	% Dry or Improved (No. pts/total No.)	Comment
Greenfield and Ferra [8]	80 (8/10)	5 Pts (50%) became completely dry, 3 (30%) became dry during day
Connor et al. [32]	61.5 (8/13)	5 Pts (38.5%) became dry, 3 (23%) reported reduction in pads
Kasabian et al. [6]	83 (5/6)	5 Pts became continent, 1 (17%) still had minimal incontinence
Kaplinsky et al. [10]	81 (17/21)	12 Pts (57%) became dry, 5 (24%) were dry only during day
Painter et al. [43]	76 (22/29)	3 Pts (10%) became dry, 19 (66%) decreased pad use
Buyse et al. [44]	61.5 (8/13)	8 Pts achieved "social incontinence"
Ferrara et al. [34]	NR	Continence was not addressed
Guerra et al. [45]	36 (17/47)	17 Pts became dry between bladder catheterization
Hayashi et al. [30]	75 (3/4)	2 Pts (50%) became completely dry, 1(25%) decreased the number of incontinence

Table 4: Urinary incontinence change after treatment with intravesical oxybutynin.

Author	Number of patients	Anticholinergic side effects	Urinary tract	Others
Greenfield and Ferra [8]	10	0 (0%)	0 (0infections%)	0 (0%)
Connor et al. [32]	13	2 (15.4%)	1 (7.7%)	1 (7.7%)
Kasabian et al. [6]	11	2 (18.2%)	1 (9.1%)	2 (18.2%)
Kaplinsky et al. [10]	21	7 (33.3%)	0 (0%)	0 (0%)
Painter et al. [43]	29	0 (0%)	0 (0%)	0 (0%)
Buyse et al. [44]	15	4 (26.7%)	0 (0%)	1 (6.7%)
Ferrara et al. [34]	34	6 (17.6%)	0 (0%)	0 (0%)
Guerra et al. [45]	-	26	0 (0%)	3
Hayashi et al. [30]	4	0 (0%)	0 (0%)	0 (0%)

Table 5: Incidence of adverse events related to intravesical oxybutynin therapy.

informed consent from patients, it is an alternative treatment for children under CICs. In fact, Connor et al. and Kasabian et al. considered intravesical oxybutynin treatment as a safe and effective procedure [6,32]. On the other hand, augmentation is a suitable procedure for children who cannot continue oral oxybutynin due to AEs; however, as the invasiveness of the operation has been highlighted, it should be carefully selected for children with neurogenic bladder.

Adverse Events of Intravesical Instillation of Oxybutynin

Intravesical oxybutynin chloride is a useful therapy for patients with neurogenic bladder; however, there are some untoward effects and AEs. Kasabian et al. reported that among 19 patients, there was 1 patient with facial flushing, 3 patients with dry mouth, 1 with a Urinary Tract Infection (UTI), and 2 patients who had difficulty retaining the solution in the bladder [6]. Based on these and other previous reports, anti-cholinergic AEs and difficulty retaining the solution in the bladder are common drawbacks, although Palmer et al. reported that facial flushing, dizziness, agoraphobia, and hyperactivity were the main AEs in their cohort [33]. A previous report compared differences between an orally medicated group and intravesical medicated group in children with spina bifida. In this report, intravesical oxybutynin chloride caused a higher prevalence of central disorders such as hallucination, drowsiness, and cognitive impairment than after oral administration [34]. Oxybutynin can cause AEs in the Central Nervous System (CNS) because it is a lipid-soluble agent that can cross the blood-brain barrier [35]. When oxybutynin is administered via oral intake, it metabolizes quickly to DEOB. However, when taken via bladder instillation, the plasma concentration of oxybutynin chloride stays higher than that of oral intake. Higher plasma oxybutynin severely affects the CNS because it binds to muscarinic receptors, which are well represented in the CNS [35]. Few reports compare the incidence rates of AEs with oral oxybutynin therapy and intravesical oxybutynin medication. Ferrara et al. reported incident rates of 16.4% (11/67) and 17.6% (6/34), respectively [34]. Therefore, more studies should be conducted to compare AEs in these two groups. Other problems have been reported where the inconvenience of the preparation is often cited as a reason for drug withdrawal, accounting for 25% of study dropouts [36]. Guerra et al. reported AEs with intravesical oxybutynin treatment [29]. We added our experience to this report and results can be seen in table 5.

Modified Intravesical Oxybutynin Chloride

Intravesical oxybutynin chloride is an effective method with less AEs than that with oral medication. However, the duration of this method often does not last long enough. Weese et al. reported that among 42 patients administered intravesical oxybutynin medication, 9 patients had difficulty retaining the solution in the urinary bladder [37]. Based on these and other previous reports, difficulty retaining the solution in the bladder is an important problem. To reduce the above mentioned transient effects of intravesical oxybutynin chloride, some clinical techniques have been reported. Hydroxypropylcellulose (HPC), an agent whose effect is adhering to bladder mucosa and retaining drugs in the bladder longer, has been used in some cases. Some reports have investigated HPC mediated intravesical medication with adriamycin and pepleomycin [38]. Yasumoto et al. reported that the half-life of pepleomycin intravesical treatment with HPC was 10 times longer than that without HPC, and suggested that HPC was effective in adhering chemicals to the bladder mucosa [39]. Mizunaga et al. reported that they developed a new oxybutynin solution containing HPC, a mucosal adhesive substance. They reported that plasma concentrations of oxybutynin after intravesical HPC-modified oxybutynin were significantly lower than that after instillation of oxybutynin alone, and the effect of HPC-modified oxybutynin lasted longer than oxybutynin alone. Moreover, favorable clinical effects were achieved, and no AEs were observed for more than six months during medication periods [40]. In our first report on modified intravesical oxybutynin chloride in adult patients [41], six patients were treated with modified intravesical oxybutynin chloride. Although patient numbers were small, a significant increase in bladder capacity was observed. Moreover, in this report, serum oxybutynin and serum DEOB, the active metabolites of oral oxybutynin chloride that are responsible for systemic AEs, were measured before, 1, 2, and 4 hours after the initial treatment with intravesical oxybutynin. Concentration levels of serum oxybutynin chloride were lower than those in the studies of Massad et al. with intravesical oxybutynin chloride without HPC [14]. Plasma levels of DEOB in our study were shown to have no significant differences at all timings after the initial administration. Buyse et al. observed that a significantly lower ratio of AUC of DEOB over oxybutynin may reduce systemic AEs [7]. Thus, our previous data suggested that modified intravesical oxybutynin may possibly reduce absorption of oxybutynin from bladder mucosa and suspend oxybutynin in the bladder longer, and that modified intravesical oxybutynin may reduce systemic AEs relative to those of intravesical oxybutynin without HPC. On the other hand, in our 3-year period study [42], a significant increase in bladder capacity was observed even though there were only 6 patients, and this effect was maintained over the 3-year follow-up period. Ileus, dry mouth, and acute cystitis were observed in one, two, and two patients,

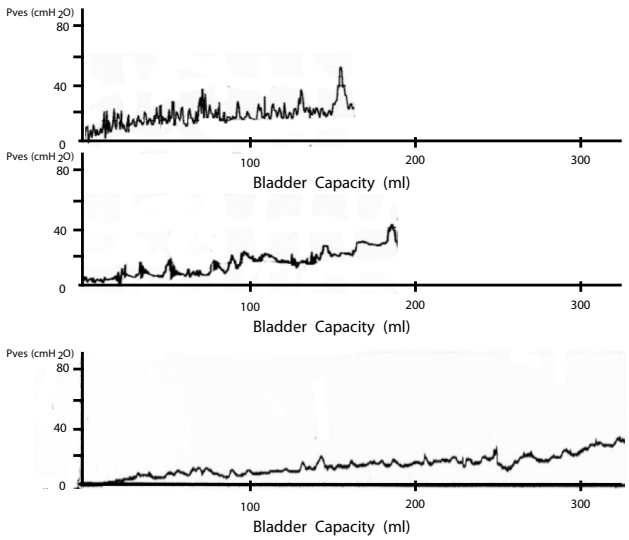
respectively. However, ileus and dry mouth were more likely to have been caused by patient complications. Acute cystitis was observed in two females, and the ratio of this AE may be higher than that of CIC patients without intravesical oxybutynin chloride. No other AEs (e.g. facial flushing or dizziness) were observed. Based on data from the above study [42], although patient numbers were limited, modified intravesical oxybutynin therapy is highly valued by patients who do not respond to oral anti-cholinergics.

Modified Intravesical Oxybutynin; Our Experience

In this section, our experience on modified intravesical oxybutynin chloride in children with neurogenic bladder is introduced according to a previous study generated by this department [31]. In the latter half of this report, we add a new patient to our previously reported 4 patients aged between 1 year and 6 months and 3 years and 7 months. In our previous report, three children had myelomeningocele and one had neurogenic bladder due to resection of a pelvic teratoma. Two patients were treated with oral oxybutynin; the others did not receive anti-cholinergics due to severe constipation. Three patients were using CIC, and one patient was managed with an indwelling urethral catheter because of extremely low bladder compliance. Although the optimal dose for intravesical instillation has not been determined, published studies suggest that an oral dose of 0.2 mg/kg daily can be safely used intravesically [20,23]. Hayashi et al. [30] reported that many authors used 0.2 mg/kg daily (average 10 mg daily), and recommended leaving the drug in the bladder until the "next catheterization" or "3 to 4 hours". Thus, in our previous study, the following component of modified oxybutynin was used; oxybutynin chloride 2.5 mg, sodium chloride 58 mg, hydroxypropylcellulose (HPC) 100 mg, sodium dihydrogenphosphate (anhydrous) 52.6 mg, disodium hydrogenphosphate (anhydrous) 8.7 mg, and water 5 ml (pH 5.85) per one instillation.

Solutions were inserted via the CIC catheter twice a day. We investigated bladder capacity compliance and Uninhibited Contraction (UICs) before treatment, one week after treatment, and one year after treatment. Moreover, during the medication period, we investigated the incidence of UTIs and urinary incontinence. The result was that bladder capacity and compliance were increased 1 week after in all patients. However, 1 year after the treatment, one child, who had left Vesico-Ureteral Reflux (VUR), discontinued the medication because of recurrent upper UTIs. UICs completely disappeared from half of the patients. Severe UTI that caused drug withdrawal appeared only in one patient who had left VUR. UICs at the 1-year period continued only in one patient. However, his frequency of UIC decreased from 4.6 times/day to 3 times/day. Moreover, there were no systematic AEs during the medication period in all children.

The patient with left VUR underwent an operation for VUR at 7 years old. Before his operation, he continued CIC 5-6 times per day, his volume of CIC was 50 ml at one time, and urinary incontinence and recurrences of UTI had continued. His first trial with modified-intravesical oxybutynin chloride failed because of recurrent upper UTIs; however, he retried the treatment after the operation. As his symptoms improved, administration of intravesical oxybutynin chloride was restarted twice per day. Figure 1, upper panel, shows Cystometrograms (CMG) of the patient before modified intravesical oxybutynin. Our data showed that maximum bladder volume was 140 ml, Detrusor Leak Point Pressure (DLPP) was 54 cm H_2O, and many UICs were observed. Figure 1, middle panel, shows CMG one-week after modified intravesical oxybutynin medication. An increase in bladder capacity



Upper panel: Before modified intravesical oxybutynin chloride treatment.

Middle panel: One week after the initial treatment with modified intravesical oxybutynin chloride.

Lower panel: Two months after the initial treatment with modified intravesical oxybutynin chloride.

Figure 1: Cystometrograms of the patient before and after modified intravesical oxybutynin chloride treatment.

(210 ml) and decreases in UICs were observed. Gradually, his bladder capacity increased and urinary incontinence disappeared. Two months after intravesical oxybutynin chloride, there were no UICs and bladder capacity was 325 ml (Figure 1, lower panel). His urinalysis was slightly turbid; however, there was no recurrence of nephritis, and no AEs due to intravesical oxybutynin. Fortunately, in our previous and present studies, modified intravesical oxybutynin chloride is an almost safe and effective method of treatment for neurogenic bladder in children.

In our previous report [31], we demonstrated the excellent efficacy of intravesical oxybutynin treatment. The patient was 1 year and 6 months old, had myelomeningocele, and had taken anti-cholinergic drugs. However, the effectiveness of the treatment was not enough, so his parents decided to try intravesical oxybutynin treatment. One week after he started intravesical oxybutynin, bladder capacity and bladder compliance recovered. During the treatment period, he did not have AEs, for example, UTI or constipation. Therefore, this treatment is suitable for children who have a poor response to oral anti-cholinergic drugs.

Conclusion

Intravesical oxybutynin chloride is relatively safe and has excellent efficacy for neurogenic bladder due to spinal cord disease. As only limited numbers of patients have been studied and drawbacks in the CNS and the frequent occurrence of UTIs were reported in some cases in the literature, further studies and careful observations on this therapy are required.

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