Outcomes of bethanechol use after spinal cord injury during inpatient rehabilitation

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Background

Neurogenic lower urinary tract dysfunction is estimated to occur in about 70-84% of spinal cord injury (SCI) patients (1). SCI can affect storage, emptying, and sensation of bladder fullness depending on level of injury. In addition to standard of care SCI bladder programs, pharmacologic intervention can assist in improving bladder function. Bethanechol has been labeled for treatment of neurogenic atonic bladder by binding to postganglionic M3 muscarinic receptors to increase detrusor muscle tone and promote bladder emptying.

Despite biological and pharmacological rationale, bethanechol has little evidence-based clinical support for underactive bladder due to the low quality of current literature (2,3,4). Within the spinal cord injury population, even less is known.

Study Aims

1) Examine efficacy and patient adherence to bethanechol to determine its clinical utility.
2) Elucidate demographic and clinical factors that may be associated with improved treatment outcomes and improved adherence to bethanechol treatment.

Methods

Design	Retrospective, Chart Review, Uncontrolled, Single-site
Population	All SCI patients prescribed Bethanechol
Setting	Acute Academic Inpatient Rehabilitation Facility (IRF) 2018-2021
Time Points	First prescribed, IRF discharge, first follow up, 1-year follow up
Data Sources	SlicerDicer (EPIC), E-Rehab
Variables	Demographics, injury characteristics, hospital course, bladder history, and functional outcomes
Outcome measures	Primary: return to volitional voiding at discharge. Secondary: bethanechol adherence, adverse effect and reason for discontinuation

Results

Table 1. Demographic characteristics

Variable	Count (%) or mean (range)
Age	57 (18-87)
Race	
White	36 (61%)
Black	10 (17%)
Not available	13 (22%)
Gender	
Male	32 (54.2%)
Female	27 (45.8%)
Etiology	
Traumatic	26 (44.1%)
Non-traumatic	33 (55.9%)
Admit LEMS*	32.6 (0-50)

*No lower extremity motor score for 3 patients

Table 2. Hospital course of bethanechol

Outcome	Count (%) or mean (range)
Admit bladder emptying method	
ICP	30 (50.8%)
Indwelling	28 (47.5%)
External	1 (2.7%)
Total days post-injury Bethanechol start **	21.3 (3-69)
Total days on bethanechol at IRF***	110.7 (3-1232)
Median maximum daily dose of bethanechol (mg)	50 (15-150)

** N/A for 2 patients
*** No data for 1 patient; 3 patients still on bethanechol
D/C – discharge; ICP – intermittent catheterization program; SNF – skilled nursing facility

Table 3. Discharge data of patients on bethanechol

Outcome	Count (%)
D/C bladder emptying	
Micturition w/o meds	5 (8.5%)
Micturition w/ meds	27 (45.7%)
ICP	23 (39.0%)
Indwelling foley	3 (5.1%)
ICP/Indwelling foley	1 (1.7%)
D/C location	
SNF	11 (18.6%)
Home	42 (71.2%)
Hospital transfer	1 (1.7%)
Not available	5 (8.5%)
Bethanechol Use: D/C	
Yes	41 (69.5%)
No	18 (30.5%)
Bethanechol Use: 1st appt	
Yes	25 (42.4%)
No	26 (44.1%)
No follow-up	8 (13.5%)
Alpha-blockers use: D/C	
Yes	42 (71.2%)
No	17 (28.8%)

Table 4. Multiple logistic regression model: association between variable and return to normal micturition at discharge

Variable	Adjusted OR	95% Confidence Int.	p-value
Race (Black=1, White=0)	32.879	1.415-3511.281	0.068
Presence of spine surgery	1.685	0.083-28.992	0.705
Traumatic Etiology	1.184	0.171-8.528	0.861
Admit LEMS	1.110	1.018-1.252	**0.040**
Bethanechol Start Days Post Injury	1.030	0.959-1.124	0.441
Age	1.024	0.953-1.120	0.536
Total days of bethanechol	0.998	0.995-1.001	0.238
Maximum daily bethanechol dose	0.956	0.909-0.994	**0.036**
Sex (Male=1)	0.913	0.124-6.939	0.927
Admit Bladder Emptying Method (ICP=1, indwelling cath=0)	0.759	0.117-4.473	0.760

From 2018-2021, 59 spinal cord patients were identified to have received bethanechol during acute hospitalization or inpatient rehab stay. On admission to inpatient rehab, 58/59 patients required some for of catheterization for bladder management. On average, patients started bethanechol 21.3 days post injury. At time of discharge, 32 patients were continent with normal micturition.

Regression analysis found 2 variables of significance: Admission lower extremity motor score and maximum daily bethanechol dose.

Discussion

The primary outcome of this study was return to volitional voiding at discharge. 32/59 (54%) returned to normal micturition at discharge. Meanwhile, 33/59 (56%) failed bethanechol therapy (either discontinuing use before discharge or being discharged without voiding). Adherence to bethanechol at discharge was fairly high at 69.5%, but adherence at follow-up was much lower. Reasons for discontinuation were often not clearly recorded but only 2 cases demonstrated adverse effects outside of urinary symptoms. In addition, admit LEMS was significantly positively associated with return to normal micturition, while maximum daily bethanechol dose was significantly negatively associated with this outcome variable ($p<0.05$). These results may be useful in assessing outcome variables (i.e: dosage, LEMS scores) for prospective controlled study planning.

As an uncontrolled study, these results cannot be used to comment on bethanechol's efficacy and may reflect natural recovery with selection bias. However, there is some suggestion of utility with appropriate patient selection. Options for catheter free micturition after SCI remain limited and despite being an older medication, few studies on bethanechol exist for a SCI specific population. Larger, retrospective studies may be warranted but ultimately a controlled prospective study of efficacy in a specific subset of the SCI population would be a reasonable next step.

References

References:
(1) Manack, A., Motsko, S. P., Haag-Molkenteller, C., Dmochowski, R. R., Goehring, E. L., Jr, Nguyen-Khoa, B. A., & Jones, J. K. (2011). Epidemiology and healthcare utilization of neurogenic bladder patients in a US claims database. *Neurourology and urodynamics*, *30*(3), 395–401. https://doi.org/10.1002/nau.21003
(2) Moro C, Phelps C, Veer V, Clark J, Glasziou P, Tikkinen KAO, Scott AM. The effectiveness of parasympathomimetics for treating underactive bladder: A systematic review and meta-analysis. Neurourol Urodyn. 2022 Jan;41(1):127-139. doi: 10.1002/nau.24839. Epub 2021 Nov 24. PMID: 34816481.
(3) Kaplan PE, Nanninga JB, Lal S. Urinary bladder smooth-muscle electrical activity: response to atropine and bethanechol. Arch Phys Med Rehabil. 1978 Oct;59(10):454-8. PMID: 718409.
(4) Diokno AC, Koppenhoefer R. Bethanechol chloride in neurogenic bladder dysfunction. Urology. 1976 Nov;8(5):455-8. doi: 10.1016/0090-4295(76)90274-0. PMID: 982732.
(5) National Center for Biotechnology Information (2022). PubChem Compound Summary for CID 2370, Bethanechol. Retrieved March 20, 2022 from https://pubchem.ncbi.nlm.nih.gov/compound/Bethanechol.