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Fraser M O[1], Lloyd J C[2], Le N B[2], Wiener J S[2], Dolber P C[3]

1. *Duke University and Durham Veterans Affairs Medical Centers, Institute for Medical Research,* ***2.*** *Duke University Medical Center,* ***3.*** *Duke University and Durham Veterans Affairs Medical Centers*

SUPERIOR EFFICACY OF COMBINATION PHARMACOTHERAPY FOR TREATMENT OF NEUROGENIC DETRUSOR OVERACTIVITY

Hypothesis / aims of study

Antimuscarinics are the mainstay of pharmacotherapy for neurogenic detrusor overactivity (NDO); however, bothersome side effects are common, including dry mouth, constipation, and even cognitive impairment. Other compounds that are or have been used to treat detrusor overactivity include alpha1-adrenergic antagonists, beta3-adrenergic agonists and gabapentinoids. Previous studies have demonstrated pharmacological synergy between antimuscarinics and gabapentinoids in bladder irritation models [1]. The use of pharmacological combination approaches to treat symptoms of NDO may afford the opportunity to utilize lower doses of each individual drug, allowing achievement of the same or better clinical benefit with fewer side effects. We sought to determine whether combination therapy would improve indices of detrusor overactivity in a rat model of chronic spinal cord injury (SCI).

Study design, materials and methods

Female Sprague-Dawley rats (n=84; 250-275 g BW) were anesthetized with isoflurane and underwent spinal cord transection at the T9-T10 level and a piece of Gelfoam was placed between the cut ends of the cord to promote healing of the dura. The muscle was closed with suture and the skin closed with wound clips. Bladders were emptied twice daily by manual crede until terminal experimentation (minimum of 28 days). Rats were acclimated to 1 hour/day of restraint in Ballman restraint cages on 3 separate occasions the week prior to experimentation.

At ≥28 days post-SCI, rats were anesthetized with isoflurane and saline filled jugular and heparinzed saline-filled carotid catheters were implanted and exited via subcutaneous tunnels through a small incision in the back of the neck. Following a midline lower abdominal incision, the distal colon was loosely ligated at the splenic flexure and cleared of feces by gentle massage. The proximal ureters were cannulated with PE-10 tubing to divert urinary output externally. A flared-tipped PE-50 catheter was inserted into the bladder dome for bladder filling and pressure recording and secured by ligation. The abdominal cavity was closed in layers with the bladder catheter exiting via the rostral end of the wound. While still anesthetized, the animals were mounted in Ballman restraint cages. Food and water were provided and the bladder catheters were connected to the recording system.

Normal saline was continuously infused at an initial rate of 0.1-0.2 ml/min via the bladder-filling catheter for a minimum of 60 minutes to obtain a baseline of lower urinary tract activity, during which time flow rates may have been adjusted up or down to allow for a minimum of three micturition cycles per control test period. Subsequent to the control period, 3 vehicle injections were made at 30 minute intervals to determine vehicle effects, if any, and to further stabilize the preparation. Finally, 3 increasing doses of a selected active agent (Doxazosin, D, an alpha1-adrenergic antagonist; Fesoterodine, F, an antimuscarinic; CL-316,243, CL, a selective beta3-adrenergic agonist; and Pregabalin, P, a gabapentinoid) at half log increments, or combinations of agents using the same doses as utilized in the individual agent experiments as a Low, Middle (Mid) and High dose combination series, were administered intravenously at ~30 minute intervals in order to construct cumulative dose-response relationships. At the end of the control saline cystometry period, the third vehicle, and 20 minutes following each subsequent treatment, the infusion pump was stopped, the bladder was emptied and a single filling cystometrogram was performed at the same flow rate for True Bladder Capacity (TBC).

Results

All but one treatment (F+D) resulted in a statistically significant increase in TBC. When comparing across individual compounds, no differences were seen between the four individual treatments. When comparing across the combination treatments only, P+CL and F+CL were both found to be superior in efficacy to both D+CL, and F+D (range $P<0.01$-0.001). When comparing across all treatments, the effects of P+CL were greater than those of D, Cl, P, D+CL, and F+D (range $P<0.05$-0.01), and the effects of F+CL were greater than those of D, Cl, P, D+CL, and F+D (range $P<0.01$-0.001). Only two treatments (D and CL) resulted in a statistically significant decrease in NVC Count. Two other treatments approached significance for this measure (P at $p=0.0814$ and D+CL at $p<0.0620$). Only four treatments (D, P, P+D and P+F) did *not* result in a statistically significant decreases in NVC Maximum Amplitude (although P+F approached at $p<0.07$). When comparing across all treatments F+CL reduced NVC Maximum Amplitude better than both D and P ($P<0.05$).

Interpretation of results

It is of interest to note that the combinations P+CL and F+CL provided statically superior efficacy when compared to P, CL and D for TBC. These results suggest that the combined effect of depressing the parasympathetic reflex arc (by P via afferents and F by efferents) with decreased spontaneous myogenic activity (by CL) is superior to either approach alone. Moreover, the effects of both P+D and P+CL combinations were significantly greater than additive when compared to their individual responses (data not shown), suggesting possible pharmacologic synergy. While no significant effect was seen on NVC count by any of these combinations, there was also a significant decrease in NVC Max Amplitude with P+CL. These findings, together with the potential for pharmacological synergy of this particular combination, make the combined treatment of P+CL the overall best performer of the treatment groups in this study, with F+CL as a close second.

Concluding message

These data strongly support the concept that combination pharmacological approaches may allow for the same or greater efficacy at lower doses than individual compounds alone. Such additive/synergistic effects on efficacy can be achieved while simultaneously reducing mechanism of action or molecule-specific side effect burdens.

References
1. Fraser MO et al., 2011, Methods for treating lower urinary tract disorders using alpha2delta subunit calcium channel modulators with smooth muscle modulators. USPTO - A1-20110294881

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