Does reduction of number injection sites of abobotulinum toxin A impact efficacy in Neurogenic Detrusor Overactivity (NDO) in the spinal cord-injured (SCI) rat model?

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OBJECTIVES

Spinal cord injury (SCI) induces plasticity within neural pathways innervating the lower urinary tract (LUT), with the recruitment of nociceptive "silent" C-fibers leading to the development of an abnormal autonomic micturition reflex and emergence of neurogenic detrusor overactivity (NDO), thereby greatly compromising bladder filling during the micturition cycle.

In SCI patients, botulinum toxin A has been evaluated for the treatment of refractory NDO and have been reported to decrease urinary incontinence frequency and maximum intravesical pressure while increasing bladder capacity and compliance

Onabotulinum (Ona) toxin A intradetrusor injections is registered as a second-line treatment to treat NDO in humans. Injection protocol remains variable among clinical studies. However approved Ona label recommends 30 injection points in the bladder wall.

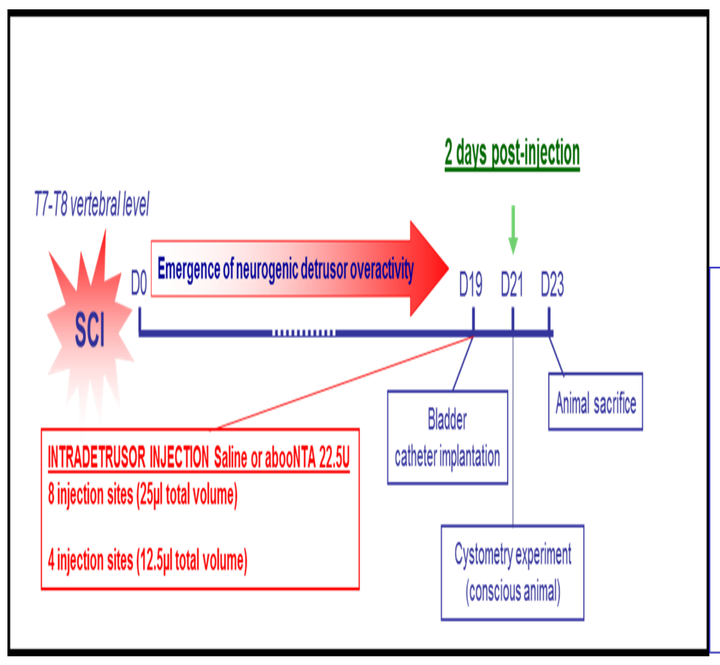
The main objective of this study was to determine the effect of reducing the number of injection sites by comparing

the effect of 4 versus 8 injection sites with abobotulinum toxin A (aboBoNTA) in the SCI rat, a relevant model of NDO

METHODS

Experimental design

Nineteen days post-SCI, rats received intradetrusor injections in 4 or 8 sites of saline or aboBoNTA 22.5U. Two days after injections, effect of aboBoNTA on urodynamic clinically relevant parameters was determined by analysis of variance test versus aggregated saline groups (ASG). Four experimental groups were considered: saline (NaCl 0.9%) 4 sites (12.5µl total volume, n=12; S-4sites), saline 8 sites (25µl total volume, n=11; S-8sites), aboBoNTA 4 sites (12.5µl total volume, 5.6U per site, n=20; aboBoNTA-4sites) and aboBoNTA 8 sites (25µl total volume, 2.8U per site, n=20; aboBoNTA-8sites).



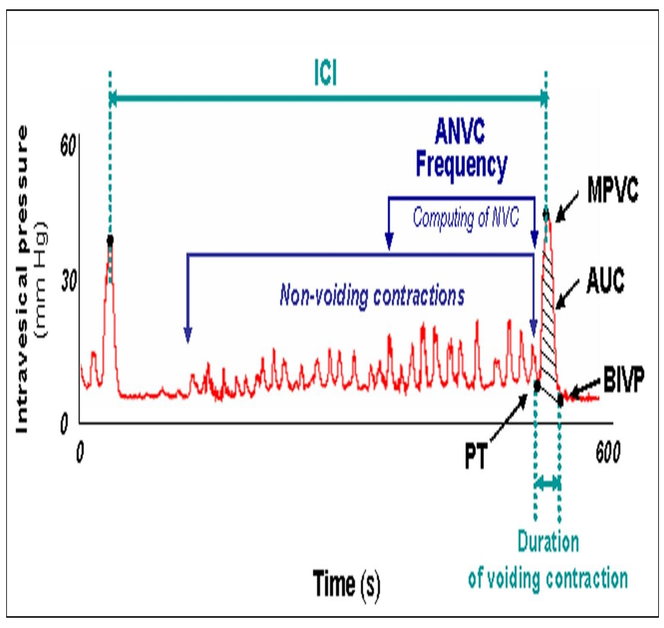
Animal preparation

Spinalization female Sprague-Dawley rats (n=63; 250-275g; Janvier, France) underwent a T8-T9 spinal cord transection. Urodynamic investigation was performed at 2 days post-intradetrusor injections and rats were euthanized at D4.

Cystometry experiments. Forty-eight hours after intradetrusor injections, Cystometry was performed in conscious rats 48 hours after intradetrusor injections as previously described [1]. Bladder pressure was recorded using a pressure transducer . A weighing device was used to make direct measurements of micturition volumes. After a 30-min acclimation, the bladder was continuously perfused (50 µl/min) with saline until two to three reproducible micturition cycles were obtained. A 60-min evaluation period was recorded to determine the effect of aboBoNTA or saline on the micturition reflex.

Data and statistical analysis.

All data were expressed as mean plus or minus the standard error of the mean and averaged per treatment group. A Grubbs test was used for exclusion of outliers. An unpaired Student's t-test was used for the comparison of body weight. The area under curve of body weight loss was also compared between aboBoNTA-4sites or aboBoNTA-8sites groups for homogeneity with Fisher's test and for significance with Student's t-test . For each cystometry parameter, an analysis of variance was performed to compare the S-4sites and S-8sites saline groups to allow their aggregation and the aboBoNTA-4sites or aboBoNTA-8sites groups versus the aggregated saline groups .



Drugs and chemicals. AboBoNTA was provided by Ipsen Biopharm Ltd, Wrexham, UK. Antibiotics (except gentamicin) and anaesthetics were purchased from Centravet (Dinan, France) and Roche Pharma (Neuilly-sur-Seine, France).

References

1-Behr-Roussel D, Oger S, Pignol B, Pham E, Le MA, Chabrier PE, et al. Minimal effective dose of dysport and botox in a rat model of neurogenic detrusor overactivity. Eur Urol 2012 May;61(5):

RESULTS

I- Effect of intradetrusor injections of aboBoNT-A 22.5U in 4 or 8 sites in rats 19 days after SCI-induced NDO

A-Effect on saline groups

To perform statistical analysis versus aboBoNTA treated groups, S-4sites and S-8sites groups were aggregated as they were not significantly different for all urodynamic parameters (ns, P>0.05; Table 1)

Table 1:
Rats received inj. in 4 or 8 sites of saline

Fig.	Corresponding clinically relevant parameters	Treatment	Saline (4 vs 8) , mean ± sem Stat , ns → aggregated	
		Nber of inj. sites	4	8
1	Maximal pressure at contraction (P Max)	Maximal amplitude, mmHg	30.3±1.4	30.0±1.9
	Post-void residual volume in bladder	Voiding efficiency, %	87.2±4.9	87.3±3.9
2	bladder storage capacity	Infused volume, µl (Bladder capacity)	801.1±45.6	898.9±69.6
3	Compliance (index, ml or cm H_2O)	Compliance, ml/mmHg	0.13±0.02	0.19±0.03
4	Pressure at first involuntary contraction	NVC amplitude, mmHg	5.9±0.8	5.1±0.4

B-Effect on physiological parameters

- Before intradetrusor injections, body weight of SCI rats was similar between all experimental groups of rats.
- Four days post-intradetrusor injections, body weight was significantly lower for aboBoNTA-4sites compared to S-4sites (237.2±3.8 versus 279.8±4.1g respectively, P<0.001) and aboBoNTA-8sites compared to S-8sites (253.3±5.5 versus 279.9±6.0g respectively, P<0.01).

However, there was no difference in the AUC of body weight loss between aboBoNTA-4sites and aboBoNTA-8sites groups

II-Does reduction of number injection sites of abobotulinum toxin A impact efficacy in NDO in the SCI rat model?

Fig 1: Effect on Maximal pressure

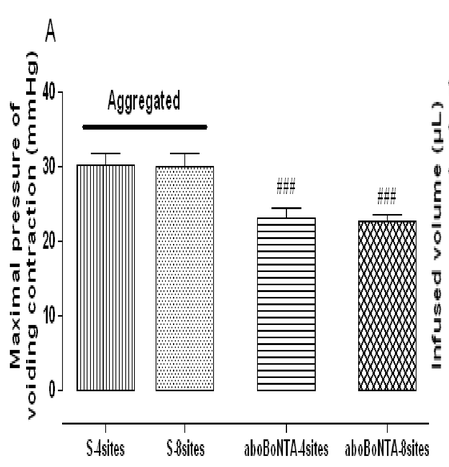


Fig 2: Effect on Bladder capacity

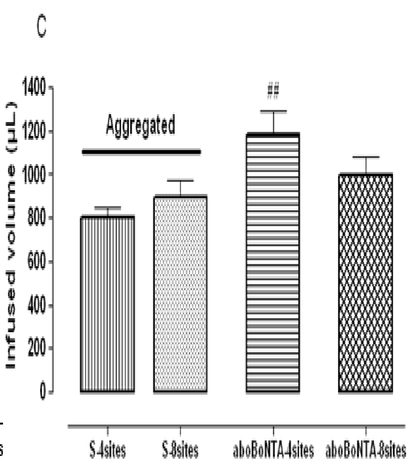


Fig 3: Effect on Compliance

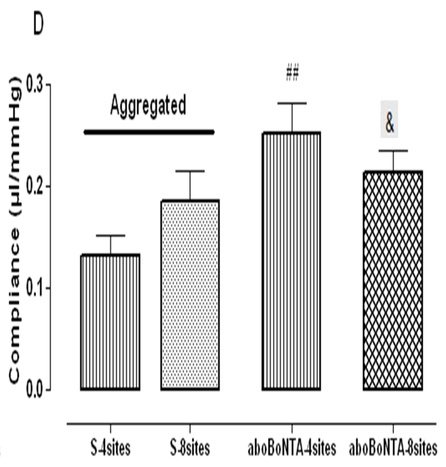


Fig 4: Effect on non-voiding contraction

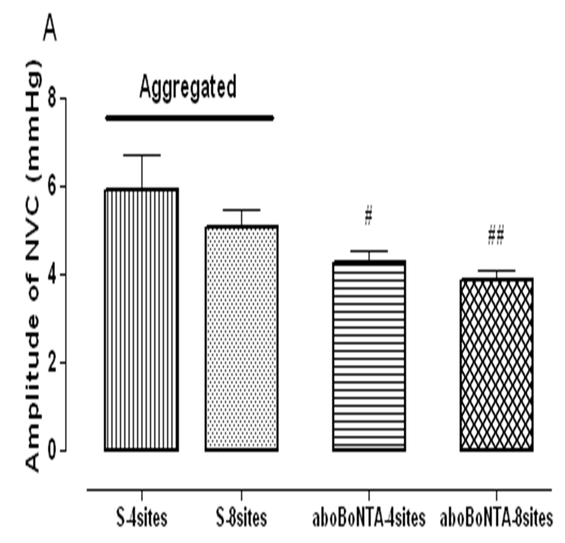


Fig 1- AboBoNTA 22.5U administered either in 4 or 8 sites significantly and similarly decreased maximal pressure of voiding contraction compared to aggregated saline groups , without affecting voiding efficiency.

Fig 2-AboBoNTA 22.5U increased, significantly (-4Sites) and non significantly (-8Sites), the infused volume , index of bladder capacity.

Fig 3-AboBoNTA 22.5U improved compliance of the bladder albeit at the limit of significance when injected in 8 sites

Fig 4- Whatever the number of sites, the amplitude of NVC (Pressure at first involuntary contraction) was significantly decreased.

CONCLUSION

- **This study is the first preclinical investigation comparing the effect of aboBoNTA intradetrusor injections when reducing the number of injection sites in the SCI rat model and showing similar efficacy of aboBoNTA in NDO regardless of the number of injections.**
- **This may provide insights for improvement and flexibility of clinical injection procedures of BoNTA to treat NDO and further in idiopathic overactive bladder (iOAB).**
- **Larger preclinical studies are warranted to better understand BoNTA effects according to injection procedure variations, thereby setting the grounds for optimized dosing schemes to improve the risk-benefit ratio of BoNTA -based treatment modalities for NDO and iOAB**

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This study was sponsored by Ipsen Pharma. Presented at TOXINS 2015, Lisbon, Portugal, 14–17 January 2015