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Son H[1], Yang S K[1], Klausner A P[1], Sharma S[1], Brown M L[1], Patel M K[1], Tuttle J B[1], Steers W D[1]

1. University of Virginia

THE NOVEL NA CHANNEL BLOCKER ICM-I-136 REDUCES DETRUSOR OVERACTIVITY IN THE SPONTANEOUS HYPERTENSIVE RAT

Hypothesis / aims of study

Recent studies demonstrate that Na channels may be important in the pathogenesis of detrusor overactivity(1). Knockdown of specific Na channel isoforms using intrathecal administration of antisense deoxyoligonucleotides reversed detrusor overactivity in the spontaneous hypertensive rat (SHR) model(2). However, systemically administered Na channel blockers have not been thoroughly investigated for the treatment of this condition. ICM-I-136, an alpha-hydroxyamide, is a recently identified new class of potent Na channel blockers with high affinity for the inactivated state as compared to phenytoin(3). The purpose of this study was to investigate the effect of ICM-I-136 on voiding function in the SHR and Wister-Kyoto rat (WKY) which are used as genetic controls, using blinded awake cystometries.

Study design, materials and methods

All experiments were approved by the institutional animal care and use committee. Animals of the SHR and WKY strains were prepared for voiding function studies by placing intravesical catheters for cystometry and intraperitoneal catheters for drug administration. Three days following surgery, studies were performed in awake, unrestrained animals with normal saline infusion (10ml/hr). Animals were randomised to receive either vehicle, 30, 100 or 300mg/kg of ICM-I-136. The investigators were blinded to the randomisation scheme. Basal pressure (BP), premicturition pressure (PreMP), Maximum pressure (MP), intercontraction interval (ICI), voided volume (VV), and postvoid residual volume(RU) were recorded. In each animal, results after treatment were compared to results obtained after a stable baseline voiding pattern was achieved.

Results

In SHR, intraperitoneal treatment with 300mg/Kg ICM-I-136 (N=5) resulted in a 22.5% reduction in maximum pressure, a 63.2% increase in intercontraction interval, and a 58.8% increase in voided volume.($p<0.05$) (Fig.1, Table 1) Similar effects on voiding function were observed after treatment with 100mg/Kg ICM-I-136 (N=6); however, results did not reach statistical significance. No effects on voiding function were observed after treatment with vehicle (N=5) and 30mg/Kg ICM-I-136 (N=6) (Fig.1). In WKY, modest reductions in maximum pressure were observed with minimal effects noted on intercontraction interval and voided volume. Effects were most pronounced after treatment with 300mg/Kg ICM-I-136 (N=6) where micturition pressure was reduced by 27.9%.($P<0.05$) (Fig.2, Table 1) After cystometry, all rats had minimal post void residual volumes regardless of treatment type.

Interpretation of results

In SHR, intraperitoneal administration of high-dose (300mg/Kg) ICM-I-136 dose-dependently decreased maximum pressure and increased intercontraction interval and voided volume. In WKY, administrations of ICM-I-136 dose-dependently decrease the maximum pressure, however, no significant effects on intercontraction interval and voided volume were observed. These results suggest that systemic treatment with Na channel blockers such as ICM-I-136 may be effective in the treatment of overactive bladder.

Concluding message

Intraperitoneal administration of the novel Na channel blocker ICM-I-136 reduced detrusor overactivity in the SHR model. These results support the hypothesis that Na channels may play a role in the pathogenesis of detrusor overactivity. Further studies are necessary to determine optimal dosing, route of administration, side effects and effects of chronic treatment. To our knowledge, this is the first report that describes systemic administration of a Na channel blocker for treatment of detrusor overactivity. Potent sodium channel blockers,

like ICM-I-136, should be investigated as potential therapies in the treatment of clinical overactive bladder.

References

1. Tetrodotoxin-resistant sodium channels Na(v)1.8/SNS and Na(v)1.9/NaN in afferent neurons innervating urinary bladder in control and spinal cord injured rats. Brain Res 2003
2. Intrathecal antisense oligonucleotide against the tetrodotoxin-resistant sodium channel (Nav1.8) reduces bladder hyperactivity in the spontaneous hypertensive rat. J Urol 2002
3. Block of human NaV1.5 sodium channels by novel alpha-hydroxyphenylamide analogues of phenytoin. Eur J Pharm Sci 2004

Figure 1. The effect of ICM-I-136 on voiding of SHR

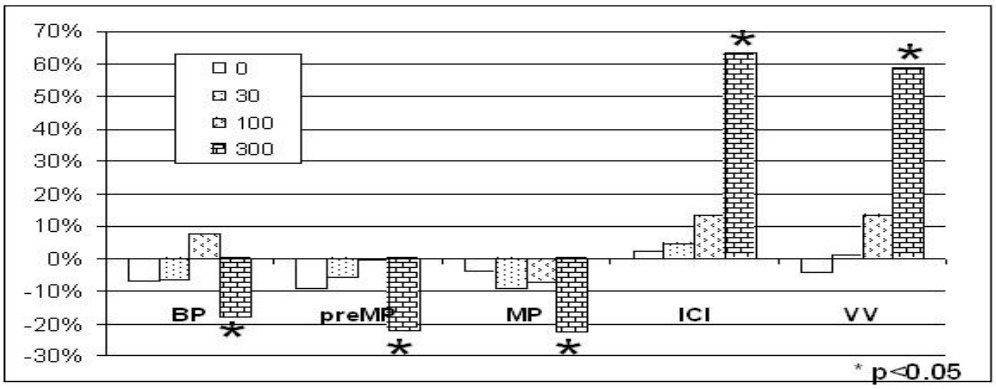

Figure 2. The effect of ICM-I-136 on voiding of WKY

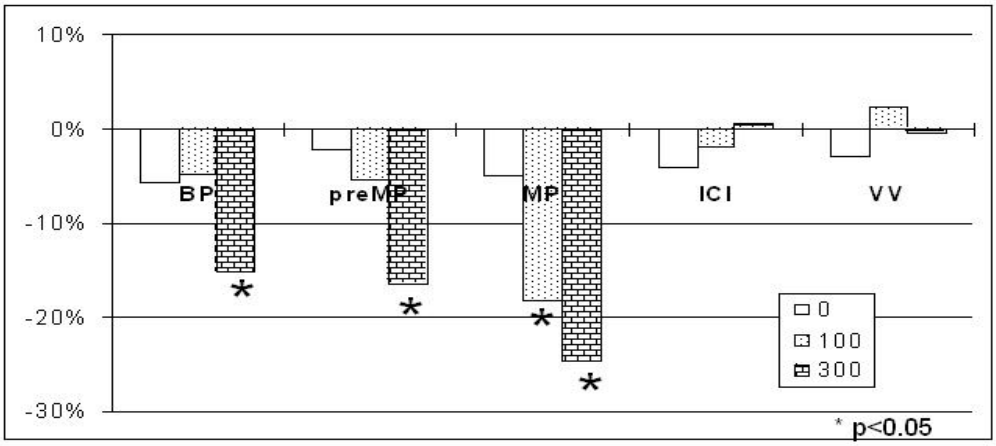

Table 1. Effects of intraperitoneal administration of ICM-I-136 (300mg/kg) on voiding of SHR and WKY

	SHR (n=5)			WKY (n=6)		
	Baseline	Treatment	Mean % changes	Baseline	Treatment	Mean % changes
Basal Pr. (cmH2O)	24.8±12.2	19.7±8.7 *	-20.5%	13.7±4.2	11.3±2.6 *	-17.5%
Maximum Pr. (cmH2O)	70.6±6.1	54.2±15.1*	-23.2%	45.1±14.8	32.5±11.3 *	-27.9%
Intercontraction interval (sec.)	72.4±19.4	106.2±12.7*	46.8%	236.1±43.1	235.1±33.5	-0.4%
Voided volume (ml)	0.19±0.07	0.26±0.04*	34.6%	0.69±0.12	0.68±0.09	-1.6%

* P< 0.05 on Wilcoxon Signed Ranks Test