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COMPARATIVE EFFECTS OF INTRAVESICAL BOTULINUM-A TOXIN AND RESINIFERATOXIN ON DETRUSOR OVERACTIVITY INDUCED BY CYCLOPHOSPHAMIDE INDUCED CYSTITIS MODEL IN RATS

Hypothesis / aims of study

Resiniferatoxin(RTX) and botulinum toxin(BTX) has recently been used clinically to treat detrusor overactivity(DO) or painful bladder syndrome(PBS). Cyclophosphamide (CYP)-induced chemical cystitis model in rats has been proposed in investigation of DO or PBS because it may also induce similar pain characteristics in humans. The purpose of this study was to compare the effects of RTX and BTX on bladder function and histology in rat CYP-induced cystitis model.

Study design, materials and methods

Female Sprague-Dawley rats were divided into 5 groups, namely group 1 - saline treated intraperitoneally instead of CYP(control group), group 2 - CYP and BTX treated, group 3 - CYP and RTX treated, group 4 and group 5 - CYP treated. 100mg/kg CYP was injected every third day for five weeks intraperitoneally to induce bladder inflammation. At 7th day; group 2 was injected with 4-5U BTX in five separate locations within the bladder; group 3 was injected with 10ng/L RTX intravesically through urethral catheter (RTX treated); group 4 and 5 had sham operations as counterpart of group 2 and 3 respectively with normal saline. Cystometrograms were performed in rats one, two, four weeks after surgery. Rats underwent urethane anesthesia, after which midline incision was performed to the symphysis pubis. Bladder, bladder neck and the entire urethra was visualized, and a specially manufactured triple lumen catheter was introduced through a separate incision in the bladder dome and fixed the tip at the bladder neck to measure intra-urethral pressure, and fixed within the bladder, filled with 4.5ml/h normal saline, through which intravesical pressures were recorded through polygraph. Histologic characteristics of CYP induced cystitis were compared after experiment.

Results

Table 1. Comparative cystometric parameters among different experimental groups

	CYP	Normal control	BTX	RTX
Micturition frequency (time/min)	1.35±0.49*	0.85±0.11	0.79±0.39	0.71±0.37
Pvesmax at CMG (mmHg)	10.46±3.30*	5.86±2.54	5.77±2.25	4.33±2.22
Pvesmax at Pr/flow (mmHg)	76.14±25.74*	43.40±9.43	45.12±9.66	38.86±24.69
Dhfo (sec.)	38.90±14.70	45±11.8	40.75±17.23	43.5±14.88
Involuntary contraction (time/min.)	1.06±0.64*	0	0.125±0.28	0.49±0.84
Functional Bladder capacity (mL.)	0.437±0.02	0.68±0.032*	1.1±0.34*†	0.56±0.01*

Pvesmax at CMG(mmHg): Maximal vesical pressure before the micturition
Pvesmax at pr/flow(mmHg): Maximal vesical pressure during micturition
Dhfo: Duration of high frequency oscillation
*: $p<0.05$ (CYP vs. normal control, BTX, RTX)
†: $p<0.05$ (BTX vs. normal control, RTX)

Interpretation of results

1. Comparative results between normal control and CYP-treated group

Time of micturition frequency was significantly increased in CYP-treated (1.35±0.49 /min) than in control group (0.85±0.11/min) ($p<0.05$). Pvesmax at CMG and Pvesmax at pr/flow were also increased in CYP-treated (10.46±3.30, 76.14±25.74 respectively) than in control group (5.86±2.54 cm H2O, 43.40±9.43 cmH_2O respectively) ($p<0.01$). Functional bladder capacity was decreased and episode of involuntary contractions was significantly increased in the CYP-treated group ($p<0.01$).

2. Comparative results between CYP only and CYP/BTX–treated or CYP/RTX group.
Time of micturition frequency was significantly decreased in CYP/BTX or CYP/RTX treated than in CYP group (0.79±0.39, 0.71±0.37, 1.35±0.49 /min respectively) ($p<0.05$). Pvesmax at CMG and Pvesmax at pr/flow were also decreased in CYP/BTX (5.77±2.25cmH_2O, 45.12±9.66cmH_2O respectively) or CYP/RTX (4.33±2.22cmH_2O, 38.86±24.69cmH_2O respectively) treated than in CYP group (10.46±3.30 cm H2O, 76.14±25.74 cmH_2O respectively) ($p<0.01$). Functional bladder capacity was significantly increased and episode of involuntary contractions were significantly decreased in CYP/BTX or CYP/RTX than in CYP treated group ($p<0.001$). There were no significant differences in the cystometric parameters between control and either CYP/BTX or CYP/RTX groups.

3. Comparative results between CYP/BTX–treated and CYP/RTX–treated group
There was no statistically significant difference between the two groups regarding micturition frequency, Pvesmax at CMG and Pvesmax at pr/flow, Dhfo and episode of involuntary contractions ($p>0.05$). However, functional bladder capacity was increased with significantly more degrees in CYP/BTX-treated (1.1±0.34 ml) than in CYP/RTX-treated (0.56±0.01ml)as well as in normal control (0.68±0.032)group ($p<0.05$).

4. Histological study of the CYP-treated rat group
Chronic edema, petechial hemorrhage, increase in tissue thickness and inflammatory cell infiltration was seen in all groups injected with CYP whereas in none with normal control. However these changes were most pronounced in the rats sampled at the 1st week after CYP treatment and decreased as it approached the 4th week.

Summary and Conclusion
Intravesical administration of BTX or RTX blocked CYP-induced detrusor overactivity as shown by the restoration of the micturition frequency, intravesical pressure and, involuntary contraction episode to a control level. Increases in the bladder capacity are greater in BTX-treated than in normal control as well as in RTX-treated rats, suggesting the possibility of paralytic action of the BTX against the normal detrusor contractility with presumable postvoid residual urine.

References

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