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Farr S[1], Chess-Williams R[1], McDermott C[1]
1. *Bond University*

DEPRESSED CONTRACTILE RESPONSES OF THE BLADDER DETRUSOR AND UROTHELIUM/LAMINA PROPRIA FOLLOWING LUMINAL ADMINISTRATION OF THE CYTOTOXIC AGENT GEMCITABINE

Hypothesis / aims of study

Intravesical administration of cytotoxic therapies for the treatment of non-muscle invasive bladder cancer often cause adverse urological side effects including increased urgency and frequency of urination, coupled with dysuria and haematuria (1). In our previous work with doxorubicin (2), these adverse effects were found to be associated with enhanced urothelial contractions and neurogenic detrusor contractions . Intravesical treatment with gemcitabine (GEM) has reported to have similar efficacy to other chemotherapeutics used in intravesical treatment, but is associated with fewer side effects (3).

Study design, materials and methods

Isolated full thickness sheets of bladder wall from the dome of the porcine bladder were set up in gassed (5%CO_2/95%O_2) Krebs-bicarbonate solution and incubated for 60min at 37°C with or without gemcitabine at the clinical dose of 40mg/mL applied to the luminal surface. Following this treatment, strips of intact bladder wall, detrusor strips denuded of the urothelium and lamina propria and strips of isolated urothelium and lamina propria were set up in organ baths and responses were obtained to the muscarinic agonist carbachol and the β-adrenoceptor agonist isoprenaline. Neurogenic contractions of detrusor strips to electrical field stimulation (20V, 0.5ms pulse width, applied for 5s every 100s) with and without the presence of the muscarinic antagonist atropine were also examined. ATP release from isolated urothelium/lamina propria was determined at basal and at approximately 50% stretch.

Results

Carbachol induced a contraction in both the detrusor and urothelium. The responses of the detrusor pre-incubated with gemcitabine at 37°C were significantly depressed (**P<0.01, n=8) compared to the untreated control (n=8) (Figure 1). The contraction of the urothelium/lamina propria pre-incubated with gemcitabine at 37°C (n=12) was significantly depressed compared to the control (*P<0.05, n=12). The potency of carbachol was not different between tissues pre-incubated with gemcitabine compared to the control (detrusor pEC50 values of -5.93±0.36 for control, -5.72±0.17 for 37°C gemcitabine; urothelium pEC50 values of -5.92±0.24 for control, -5.53±0.23 for 37°C gemcitabine).

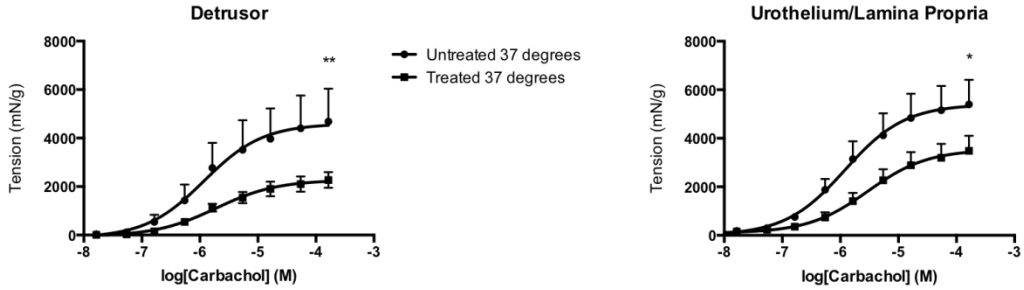

Figure 1: Effect of gemcitabine treated porcine detrusor smooth muscle and urothelium/lamina propria at 37°C on responses to carbachol

Isoprenaline caused relaxation of pre-contracted detrusor and urothelium/lamina propria strips (Figure 2). The responses of the detrusor pre-incubated with gemcitabine at 37°C were significantly depressed (**P<0.01, n=9) compared to the untreated control (n=10) (Figure 2). The relaxation of the urothelium/lamina propria pre-incubated with gemcitabine at 37°C was significantly reduced (*P<0.05, n=12) compared to the control (n=12). The potency of isoprenaline was not different between tissues pre-incubated with gemcitabine compared to the control (detrusor pEC50 values of -6.95±0.70 for control, -6.82±0.22 for 37°C gemcitabine; urothelium pEC50 values of -6.34±0.44 for control, -6.14±0.26 for 37°C gemcitabine).

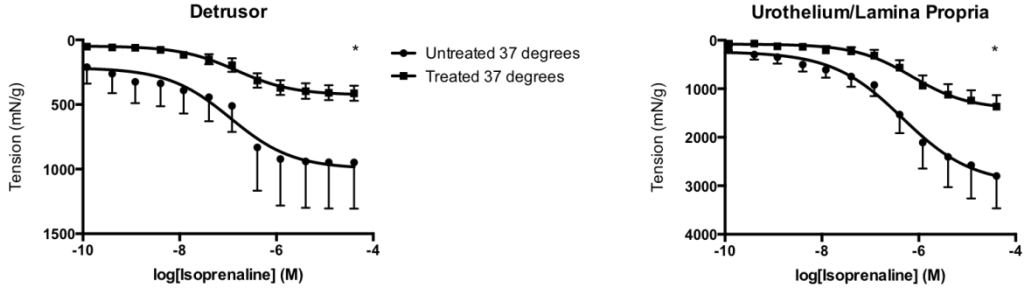

Figure 2: Effect of gemcitabine treated porcine detrusor smooth muscle and urothelium/lamina propria at 37℃ on relaxant responses to isoprenaline

Contraction due to neurogenic stimulation was depressed in the gemcitabine pre-treated detrusor muscle compared to the control, but these were not statistically significant. In the presence of atropine, the response to EFS in gemcitabine pre-treated tissue at 37°C (*P<0.05, n=10) was significantly depressed at 1Hz and 10Hz.

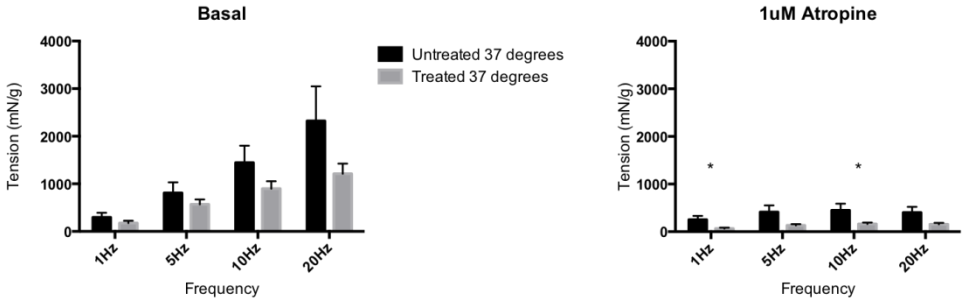

Figure 3: Effect of gemcitabine treated porcine detrusor smooth muscle at 37℃ on responses to neurogenic stimulation in the absence and in the presence of atropine.

There was no change between the basal or stimulated release of ATP from control and gemcitabine pre-treated isolated strips of urothelium/lamina propria.

Interpretation of results

Gemcitabine treated tissues depressed the contractile and relaxant responses in the detrusor muscle and urothelium/lamina propria due to direct stimulation of muscarinic and β-receptors with carbachol and isoprenaline. Neurogenic stimulation with EFS produced a significant depressed response in the gemcitabine treated tissue compared to the control with the addition of atropine. ATP release from the urothelium/lamina propria was not altered with pre-treatment of gemcitabine.

Concluding message

The results suggest that gemcitabine pre-treated tissues at therapeutic concentrations and duration directly alter the responsiveness of the bladder muscle and urothelium/lamina propria, with little effect on neurotransmitter release. These results are in direct contrast to our previous work with the chemotherapeutic doxorubicin, which found enhanced contractile responses to neurogenic stimulation in treated tissues compared to the control. The results seen from this study correlate with the fewer reported side effects from intravesical gemcitabine treatment.

References

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Disclosures

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