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INTRAVESICAL GEMCITABINE TREATMENT INDUCES BLADDER OVERACTIVITY IN MICE THAT IS ASSOCIATED WITH AN ENHANCED UROTHELIAL RELEASE OF ATP AND PGE2

Hypothesis / aims of study

Gemcitabine is a relatively new chemotherapeutic drug that is used intravesically for the treatment of superficial bladder cancer. While intravesical administration limits systemic absorption of this drug, patients undergoing this localised treatment frequently report significant urological adverse effects, including increased frequency and urgency of urination, haematuria and dysuria. During bladder filling the urothelium releases mediators (ATP, acetylcholine, PGE_2) which influence sensory nerve activity, while efferent nerve stimulation controls the micturition process. However intravesical treatment with cytotoxic drugs may disrupt this process. This study investigated the hypothesis that intravesical gemcitabine treatment in mice causes bladder dysfunction and an overactive bladder phenotype by a mechanism involving altered urothelial mediator release and/or possibly altered neurogenic detrusor contractions.

Study design, materials and methods

Female C57BL/6 ARC mice were treated intravesically with repeated (2) doses of 0.9% saline or 40mg/mL gemcitabine weekly. Voiding pattern analysis was performed before and after treatment using Whatmann filter paper 1. After euthanasia, mouse bladders were isolated and infused with saline. Luminal samples from distended bladders were collected for analysis of urothelially-derived ATP, acetylcholine and prostaglandin E_2 (PGE_2). To examine efferent nerve function bladders were electrically field stimulated (50V, 0.1ms delay, 0.2ms pulse duration) at frequencies of 1, 5, 10 and 20Hz. These were repeated in the absence and presence of L-NNA (100µM) and atropine (1µM) to assess the involvement of nitric oxide and acetylcholine respectively.

Results

Intravesical gemcitabine treatment induced an overactive-bladder phenotype in mice with an increase in the frequency of micturition. The total number of voided events (in 4hours) increased (Fig 1A) and particularly the number of small voids was increased (Fig 1B) after gemcitabine treatment, without any change in the total voided volume.

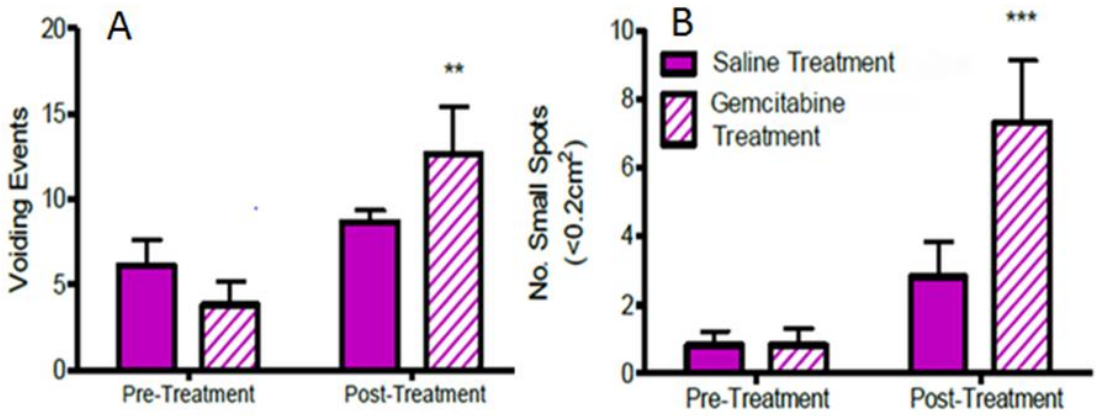

Figure 1: Number of total voids and small voids (<0.2cm^3 on filter paper) during a 4 hours period before and after intravesical gemcitabine treatment. **P<0.01, ***P<0.001

The release of ATP and PGE_2 into the lumen of the bladder was significantly ($p<0.05$) enhanced 2.8- and 4.6-fold respectively following repeated instillations of intravesical gemcitabine compared to saline controls. Neurogenic detrusor contractions were depressed by >50% in gemcitabine treated bladders at all frequencies of stimulation. However in the presence of the nitric oxide synthase inhibitor L-NNA, responses were reduced less and responses to high-frequency stimulation (>5Hz) in gemcitabine treated bladders were actually increased by 1.5-fold. Atropine reduced neurogenic contractions similarly in gemcitabine and saline treated bladders.

Interpretation of results

Repeated instillations of intravesical gemcitabine treatments in the mouse bladder results in altered voiding behaviours and enhanced ATP and PGE_2 release from the urothelium. Furthermore, efferent nerve mediated contractions were significantly depressed in gemcitabine treated bladders, and this appeared to be due to enhanced release of neuronal nitric oxide.

Concluding message

Intravesical gemcitabine in mice causes an overactive bladder phenotype. The mechanisms involved appears to be an enhanced urothelial release of ATP and prostaglandin E_2, both of which have previously been shown to stimulate afferent nerves and stimulate micturition. Neurogenic responses of the detrusor are also depressed illustrating the variety of bladder tissues this treatment affects. The results suggest that the local urological adverse effects observed in patients following intravesical gemcitabine therapy may be due to changes in urothelial function with enhanced release of stimulants of afferent nerve activity.

Disclosures
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