Adaptation and repair of the urothelium: Responding to both acute and chronic intravesical acrolein administration in the rat

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Acrolein (ACR), a metabolite of cyclophosphamide and ifosfamide, has been reported previously in patients to be urotoxic, causing erosion of the urothelial layer resulting in haemorrhagic cystitis (1). It has been previously demonstrated that acute and repeated administration of ACR directly into the bladder of rats induces an inflammatory cascade resulting in sensitisation of the urinary system, with bladder hyperactivity and an increase in voiding frequency observed (2). The present study was designed to determine the effects on micturition parameters in conscious rats (voiding frequency, total voided volume and average volume per void), urine cytokine levels, histopathology and the time course of recovery following intravesical administration of ACR.

Methods: All studies were performed in accordance with UK Home Office Legislation. Thirty-two Female Sprague-Dawley rats (200-250g) were housed in reverse light/dark cycle. On the day of ACR treatment, rats were anaesthetised with isoflurane (2-5%), the bladder cannulated trans-urethrally and any residual urine withdrawn. ACR (400uL 2mM) or vehicle (VEH, sterile water) was instilled via the catheter and left in place for 30 minutes following which the bladder was flushed twice to remove all residual ACR. Animals were subsequently recovered in their home cage. The effects of acute (a single instillation on day 0 (D0)) and repeated (administered on D0, D3 and D6 of the study) ACR dosing were studied on micturition parameters.

Results:

Acute ACR	Baseline	D1	D2	D3
Frequency	6.7±0.8	18.7±2.3**	14.7±2.5*	7.3±1.0
Vol. per void	0.43±0.03	0.16±0.03***	0.24±0.03*	0.41±0.1

Table 1. Frequency and volume micturition data in the acute ACR or VEH treated rat

Repeated ACR	Baseline	D1	D4	D7
Frequency	8.4±1.1	24.5±11.8**	13.1±2.5	10.8±4.5
Vol. per void	0.39±0.07	0.06±0.004***	0.18±0.005**	0.4±0.11

Table 2. Frequency and volume micturition data in the repeated ACR or VEH treated rat

Data are expressed as arithmetic mean ± s.e.m. (*p<0.05, **p<0.01, ***p<0.001 vs. VEH). Statistical testing of total volume data was a repeated analysis of covariance. Frequency data analysis was conducted using a Poisson model at each time point. When the bladders from these studies were examined histologically after acute and repeated ACR treatment repair was already underway with evidence of urothelial regrowth and fibrobast activation.

Conclusion: Urological and histological evidence suggests bladder repair following ACR-induced cystitis.

1. Macedo F.Y. *et al* ., (2008) *Exp Toxicol Pathol.* **59** (6)425-30.
2. Guerios S.D. *et al*., (2008) *Am J Physiol Regul Integr Comp Physiol* **295**:R111-R122.