Attenuation of Renal Ischemic Reperfusion Injury in Rats with DUR-928, a Novel, First-in-Class Therapeutic in Development for Renal Disease

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INTRODUCTION

DUR-928 (5-cholesten-3β,25-diol 3-sulfate) is a first-in-class, endogenous sulfated oxysterol that regulates lipid metabolism, inflammatory response, and cell survival.[1] It has been reported that this molecule protects against acute organ injury, including the kidney, and improved survival, from LPS-induced endotoxin shock and acetaminophen overdose/toxicity mouse models.[2,3] Therefore, the therapeutic effect of DUR-928 was investigated in a rodent model of acute kidney injury (AKI) induced by renal ischemia/reperfusion (I/R) injury.

MATERIALS & METHODS

- Renal ischemia was achieved in adult male Lewis rats (9-11 weeks of age) by transient occlusion of the left renal artery vein and ureter for 50 minutes. At reperfusion, the right kidney was removed.
- Rats were randomized into three treatment groups (Table 1). Intraperitoneal (IP) injections of 25 mg/kg DUR-928 or vehicle control were administered starting on either Day -1 or on Day 0 (day of surgery). The last dose was given on Day 4.
- Rats were followed through 7 days of observation after I/R injury. Blood was collected on Days -2 (baseline), 3 and 7 after surgery to measure serum creatinine and blood urea nitrogen (BUN) to evaluate renal function.
- Student's t-test was used to make statistical comparisons between the vehicle and the DUR-928 treatment groups on Days -2, 3 and 7.

REFERENCES

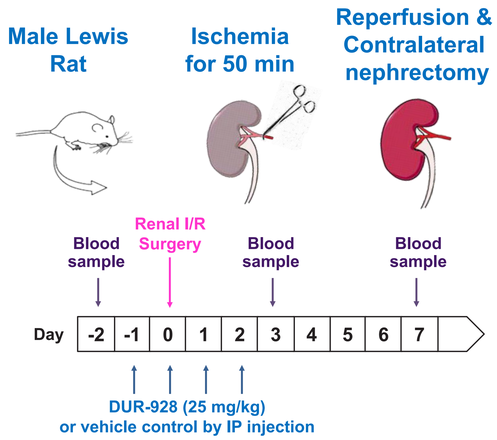
1) Ren, S; Ning, Y. Sulfation of 25-hydroxycholesterol regulates lipid metabolism, inflammatory responses, and cell proliferation. Am J Physiol Endocrinol Metab 2014. 15:E123-130.
2) Ning Y, Kim JK, Min HK, Ren S. Cholesterol metabolites alleviate injured liver function and decrease mortality in an LPS-induced mouse model. Metabolism 2017; 71:83-90.
3) Ren, S; Ning, Y; Kim, J; Min, HK; Brown, JE; Lin, W. Novel Oxysterol Sulfates Alleviate Injured Liver Function and Decrease Mortality in Mouse Models. HEPATOLOGY 2017; 666:S430A.

STUDY DESIGN

Table 1. Treatment Groups

Group	DUR-928 Dose (mg/kg/day)	Sample Size (n)	# of Injections or Doses	Start of Treatment
Vehicle	0	6	0	Day -1
DUR-928	25	11	4	Day -1
DUR-928	25	12	3	Day 0

Figure 1. Study Schematic



RESULTS

Figure 2. DUR-928 treatment lowers serum creatinine levels over study duration

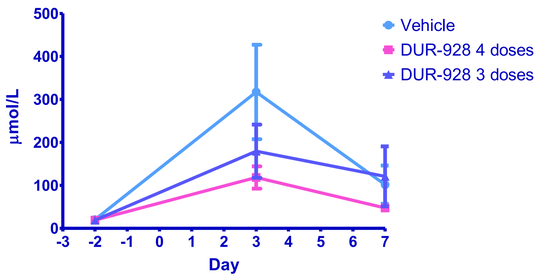


Figure 3. DUR-928 treatment lowers BUN levels over study duration

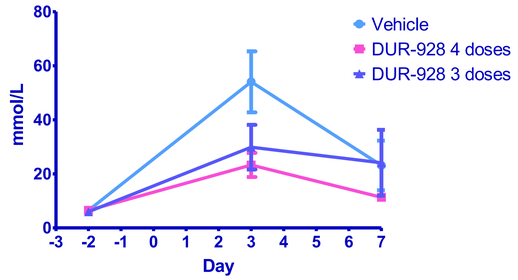


Figure 4. DUR-928 treatment significantly mitigates elevated renal I/R mediated serum creatinine levels on Day 3 compared to vehicle control

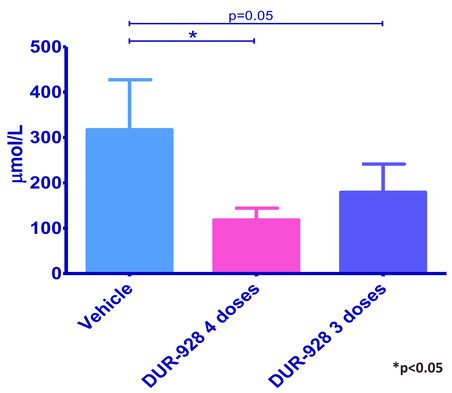
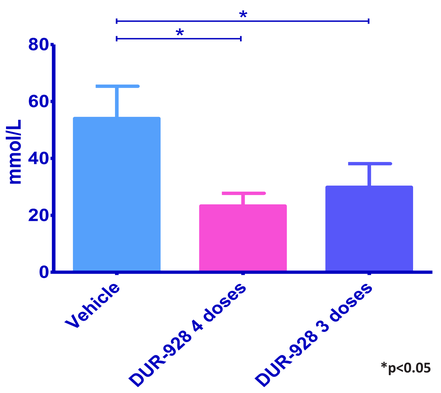


Figure 5. DUR-928 treatment significantly mitigates elevated renal I/R-mediated BUN levels on Day 3 compared to vehicle control



SUMMARY

- Induction of I/R injury in rats was successfully achieved. Serum creatinine and BUN levels peaked significantly on Day 3 compared to Baseline. Improvement of these measures was observed on Day 7 due to spontaneous self-recovery that is characteristic of this I/R injury model **(Figures 2 & 3)**.
- IP administration of 4 daily doses of 25 mg/kg DUR-928 resulted in significant reductions in serum creatinine and BUN compared to vehicle-treated rats on Day 3, suggesting improved renal function **(Figures 4 & 5)**.
  - DUR-928 treatment resulted in a 63% reduction in serum creatinine (118.4±85.9 µmol/L versus 317.3±296.6 µmol/L; $p<0.05$) and a 57% reduction in BUN (23.4±14.8 mmoL/L versus 54.0±27.7 mmol/L; $p<0.05$) compared to vehicle on Day 3.
  - Similar results were found with 3 daily doses of DUR-928, with a 43% reduction in serum creatinine ($p=0.05$) and 45% reduction in BUN ($p<0.05$), compared to vehicle **(Figures 4 & 5)**.

CONCLUSIONS

- DUR-928 administration prior to injury (4 doses) or at the time of injury (3 doses) in this rodent model of renal I/R injury resulted in significant and similar reductions of markers of AKI compared to control.
- The current study highlights the potential of DUR-928 to attenuate kidney injury in an acute setting and supports the continued evaluation of DUR-928 in renal disease.

CONFLICT OF INTEREST DISCLOSURE

- The authors are employees of DURECT Corporation and may hold company stock/options.
- This presentation includes discussion of an investigational drug product in Phase 2 development.

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