ANG-3777, a Hepatic Growth Factor Mimetic, Attenuates Mercuric Chloride-Induced Renal Dysfunction and Mortality in Rats

Narayan P[1] and Goldberg ID[1]

[1] Angion Biomedica Corp., Uniondale, NY-11553

Background

Hepatocyte Growth Factor (HGF) is an endogenous protein released in response to organ tissue damage. It is a natural ligand of the c-MET receptor, which is also upregulated in response to tissue injury. HGF stimulation of c-MET has been shown to decrease renal epithelial apoptosis and tubular necrosis, and to augment proliferation and renal regeneration in animal models of toxin induced acute kidney injury (AKI)[1,2,3,4]. ANG-3777 is a small-molecule mimetic of hepatocyte growth factor (HGF). In *in vitro* models, ANG-3777 has been shown to reduce apoptosis and stimulate cell proliferation. The objective of these studies was to evaluate the effects of ANG-3777, across a range of doses, on mortality (Study 1) and renal function (Study 2) in an animal model of toxin-induced AKI with mercuric chloride ($HgCl_2$).

Methods

Studies were conducted following an approved Institutional Animal Care and Use Committee (IACUC) protocol.

Animals. Adult male Sprague-Dawley (SD) rats (approximately 275 g), purchased from Charles River Laboratories.

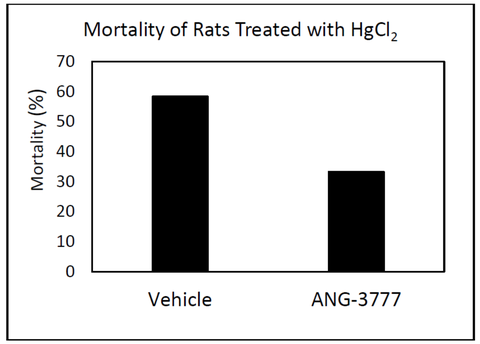
Study 1: Mortality. Twenty-four adult male SD rats were randomized to treatment with ANG-3777 (n=12) or Vehicle (n=12). Animals in the vehicle group were pretreated via IP injection with 0.5 mL solution of 50% PEG 300 [w/v]; 10% polysorbate 80 [w/v]; and 40% PBS [w/v]. Animals in the treatment group were injected with 2.0 mg/kg ANG-3777. Within 1 hour after study drug administration, all animals were injected with a high dose of $HgCl_2$ (5.0 mg/kg, IP in 0.5 mL saline). Vehicle or ANG-3777 treatment was repeated 18 hours afterwards. Mortality was determined at 24 hours post HgCl2 treatment.

Study 2: Renal function multi-dose: Eighty-seven adult male Sprague-Dawley (SD) rats were randomized to no treatment (Normal, n=2), Vehicle (same formulation as Study 1, n=19), or ANG-3777 (0.22 mg/kg, n=12; 0.66 mg/kg, n=18; 2 mg/kg, n=12; 4 mg/kg, n=12; or 12 mg/kg, n=12). On Day 0, rats were pretreated with IP ANG-3777, IP vehicle, or no pre-treatment. On Day 1, rats were again treated with IP ANG-3777 or placebo and 1 hour after study drug administration, the ANG-3777 and Vehicle animals were dosed with 3.0 mg/kg HgCl2. On Day 2 (20 hours post HgCl2 treatment and 4 hours prior to sacrifice), rats were again administered ANG-3777 or vehicle. Animals were sacrificed on Day 2. Blood samples were taken from the aorta immediately prior to sacrifice for measurement of renal function parameters: serum creatinine (SCr) and blood urea nitrogen (BUN).

Results

Study 1. Twenty-four hours after treatment with $HgCl_2$, 33.3% of the animals in the ANG-3777 treatment group had died, versus 58.3% in the Vehicle group (χ^2=1.51, p=0.22).

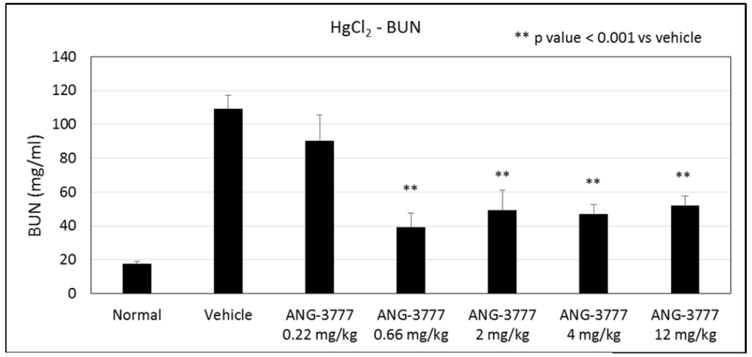
Figure 1. 24-hour mortality by treatment group: ANG-3777 vs. placebo.



Note: Mortality was 4 of 12 in the ANG-3777 treatment group and 7 of 12 in vehicle.

Study 2. On Day 3 of treatment, 2 days after renal insult with $HgCl_2$, rats receiving doses of ANG-3777 $\geq$ 0.66 mg/kg had significantly lower BUN (Figure 2) and SCr (Figure 3) than rats treated with vehicle.

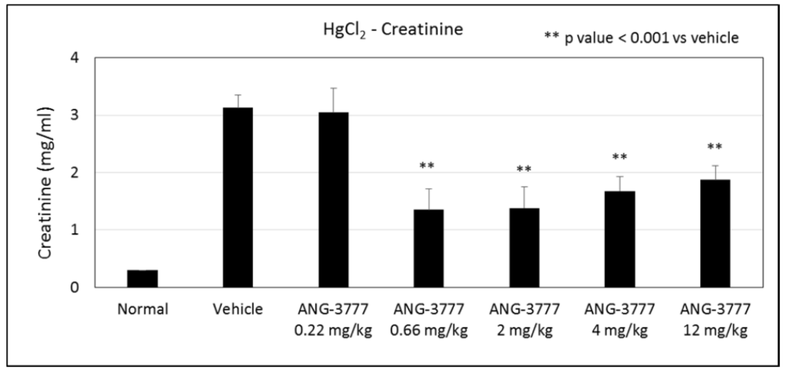
Figure 2. Blood urea nitrogen 2 days after renal injury by treatment group: ANG-3777 (multiple doses) vs vehicle vs normal*.



* Error bars represent SEM

Results (2)

Figure 3. SCr 2 days after renal injury by treatment group: ANG-3777 (multiple doses) vs vehicle vs normal*.



*error bars represent SEM

Conclusion

In SD rats with $HgCl_2$–induced AKI, those treated with ANG-3777 had:

1. Numerically greater survival at 24-hours
2. Statistically significant improvements in measures of renal function (BUN and SCr) at doses ≥ 0.66 mg/kg.

These results demonstrate that administration of ANG-3777 can protect against renal injury induced by nephrotoxic agents. Research translating these effects into treatment of human AKI are ongoing.

References

1. de Souza Durao M Jr, Razavickas CV, Goncalves EA, Okano IR, Camargo Sm, Monte JC, dos Santos OF, The role of growth factors on renal tubular cells submitted to hypoxia and deprived glucose. *Ren Fail.* 2003, 25, 341-353.
2. Igawa T, Matsumoto K, Kanda S, Saito Y, nakamura T. Hepatocyte growth factor may function as a renotropic factor for regeneration in rats with acute renal injury. *Am J Physiol.* 1993, 265, F61-69.
3. Miller Sb, Martin Dr, Kissane J, Hammerman MR, Hepatocyte growth factor accelerates recovery from acute ischemic renal injury in rats. *Am J Physiol.* 1994, 266, F129-34.
4. Dhanapriya J, Gopalakrishnan N, Arun V, et al. Acute kidney injury and disseminated intravascular coagulation due to mercuric chloride poisoning. *Indian J Nephrol,* 201,;26(3):206–208.