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

Hepatocyte Growth Factor (HGF) is an endogenous protein released in response to tissue injury. 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 tissue injury and toxic acute kidney injury (AKI)1,2. ANG-3777 is a small-molecule mimetic of hepatocyte growth factor (HGF). 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 (HgCl₂).

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 HgCl₂ (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 (Study 1) and renal function (Study 2) in an animal model of toxin-induced AKI with mercuric chloride (HgCl₂).

Results

Study 1. Twenty-four hours after treatment with HgCl₂, 33.3% of the animals in the ANG-3777 treatment group died, versus 58.3% in the Vehicle group (χ²=1.51, p=0.22). In SD rats with HgCl₂–induced AKI, those treated with ANG-3777 had:

- Numerically greater survival at 24-hours

- 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


2. Statistically significant improvements in measures of renal function (BUN and SCr) at doses ≥ 0.66 mg/kg. In SD rats with HgCl₂–induced AKI, those treated with ANG-3777 had:

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Impact

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Results (2)

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

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

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

Conclusion

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References


