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EFFECT OF CARDIOTROPHIN-1 ON THE ACUTE KIDNEY INJURY INDUCED BY GENTAMICIN

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INTRODUCTION

Drug nephrotoxicity is a very serious health and economic problem worldwide as it is the leading cause of intrinsic acute kidney injury (AKI). Gentamicin (G) is an aminoglycoside antibiotic widely used against Gram-negative infections whose most important side effect is its nephrotoxicity. Prevention of nephrotoxicity is an unmet therapeutic need, because although at a preclinical level, many molecules have been shown to exert protective effects of on G nephrotoxicity, either they have not progressed to the clinical setting or they have failed to demonstrate a clear protective effect after meta-analysis evaluation. Cardiotrophin-1 (CT-1) is a member of the IL-6 family of cytokines that seems to protect several organs such as the liver against toxic or ischemic damage. The purpose of this study was to assess the effect of recombinant human cardiotrophin-1 (HRCT-1) in the development of acute kidney injury caused by Gentamicin.

AIM

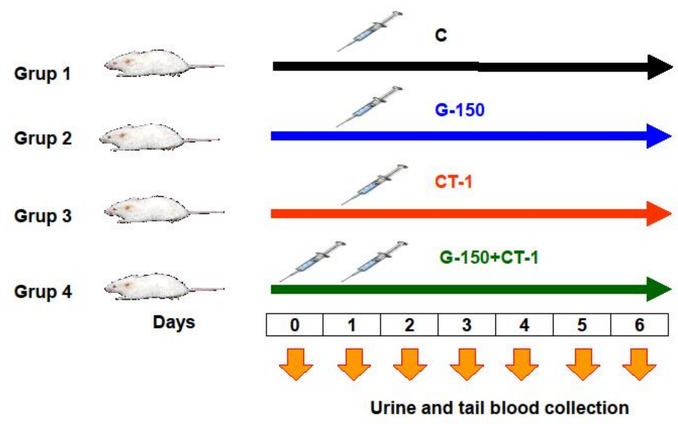
The purpose of this study was to assess the effect of recombinant human cardiotrophin-1 (HRCT-1) in the development of acute kidney injury caused by Gentamicin.

METHODS

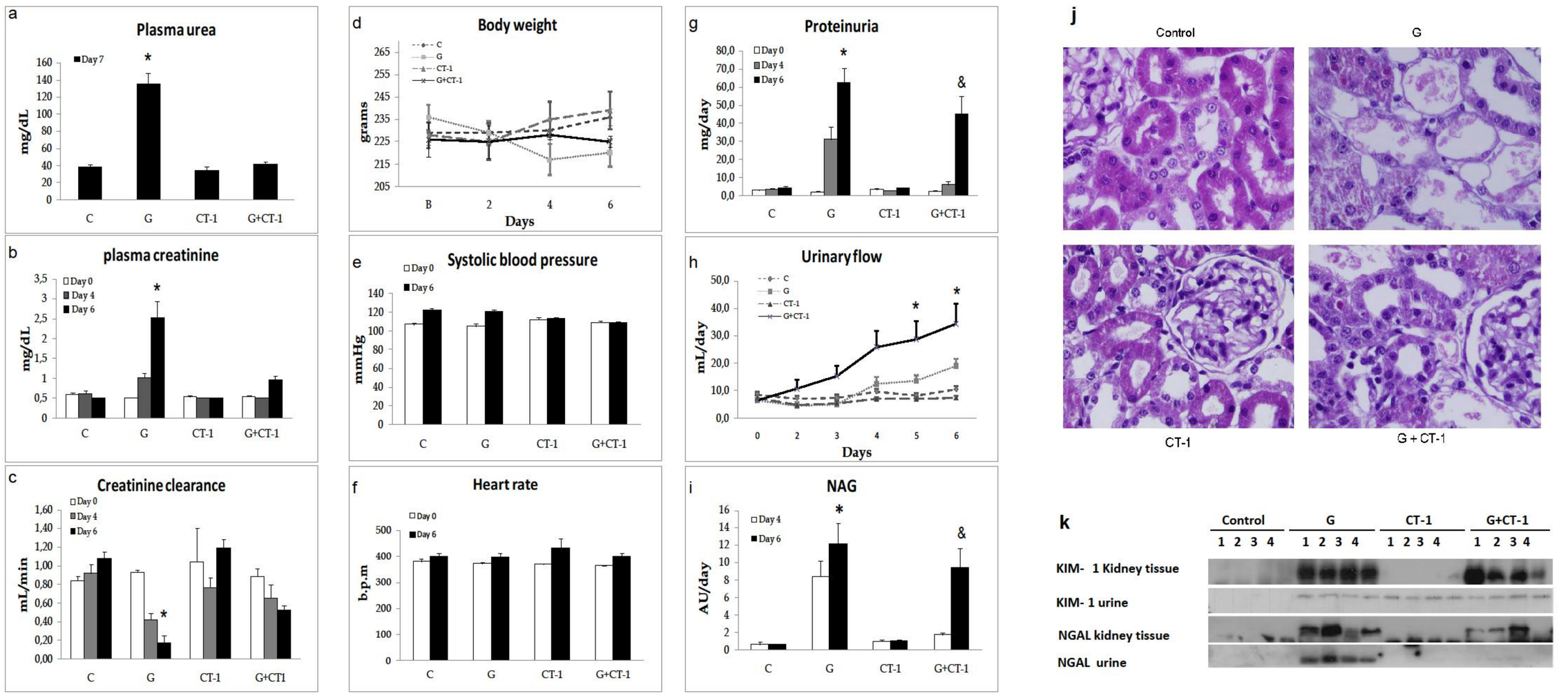
The study was performed in 24 male Wistar rats, divided in 4 experimental groups (6 animals/ group):

- Grup 1: Control group (C): rats receiving saline solution.
- Grup 2: Gentamicin group (G): rats receiving gentamicin (150 mg/kg/day, via intraperitoneal) for 6 days.
- Grup 3: Cardiotrophin group (CT-1): rats receiving HRCT-1 i.v. (100 µg/Kg/day) for 7 days.
- Grup 4: Gentamicin + Cardiotrophin group (G +CT-1): rats receiving gentamicin for 6 days and HRCT-1 the day before gentamicin administration and during 6 additional days (at the same doses as in single treatments).

SCHEMATIC REPRESENTATION OF THE EXPERIMENTAL DESIGN



RESULTS



Parameters of nephrotoxicity measured in the plasma and urine. Graphs represent determinations of plasma urea (a), plasma creatinine (b), creatinine clearance (c), body weight (d); systolic blood pressure (e); heart rate (f); proteinuria (g); urinary flow (h); urinary N-acetyl-glusoaminidase excretion (NAG, i); representative images of hematoxylin-eosin stained renal sections (j) and Western blot analysis of tissue and urinary excretion KIM-1 and NGAL (k).

In G group, there was an increase in plasma creatinine and urea and a decrease in creatinine clearance that were not observed in G+CT-1 group. In G group, it was observed a marked increase in urinary protein excretion that was markedly lower in the group that also received CT-1. Urinary excretion of AKI markers NAG), KIM-1 and NGAL) were markedly higher in G than in C or CT-1 groups. CT-1 + G group showed significantly lower excretion of NAG, NGAL, and KIM-1 than G group. Histological studies revealed that renal damage was less severe in G-CT-1 group that in G group.

CONCLUSIONS

Administration of CT-1 together with G prevents most of the AKI induced by the aminoglycoside. The results of this study have potential clinical application as a clinical trial with the goal of determining CT-1 safety, tolerability and early pharmacokinetics in volunteers is currently being conducted in Spain.

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