A URINARY BIOMARKER FINGERPRINT DIFFERENTIATES AMIKACIN FROM GENTAMICIN NEPHROTOXICITY AND REVEALS DISTINCT UNDERPINNING PATHOPHYSIOLOGICAL MECHANISMS

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Introduction

Acute renal failure (ARF) is an extremely serious condition in which the renal excretory function abruptly falls within a few hours or days after an insult to the kidneys. Traditionally, ARF has been diagnosed using the RIFLE and AKIN international criteria, which focus on increments in serum creatinine. However, because of its limitations of late and unspecific diagnosis, a new generation of biomarkers is needed. There are multitudes of drugs which lead to ARF, as aminoglycoside antibiotics. Specifically, gentamicin and amikacin are still widely used against Gram-negative infections in spite of its nephrotoxicity.

Aims

We wonder if the renal injury induced by these antibiotics was distinguishable by traditionally or novel biomarkers, in order to improve handling of patients treated with aminoglycoside antibiotics.

Methods/ experimental design

We developed preclinical models of ARF induced by gentamicin and amikacin and studied both traditionally renal function markers and some of those potential novel biomarkers. Specifically, we treated Wistar rats with a nephrotoxic regime of six daily consecutive doses of 150 mg/kg/day gentamicin and nine daily consecutive doses of 500 mg/kg/day amikacin. Then we studied a urinary protein profile based on the analysis of the urinary excretion of selected biomarkers of renal injury: N-acetyl-β-D-glucosaminidase (NAG), bone morphogenetic protein 7 (BMP-7), plasminogen activator inhibitor 1 (PAI-1), neutrophil gelatinase-associated lipocalin (NGAL) and cistatin C.

Results

An experimental ARF was observed in both groups, characterized by similar increments in serum creatinine and histological injury. However, proteinuria levels were considerably different, being higher in gentamicin treated rats.

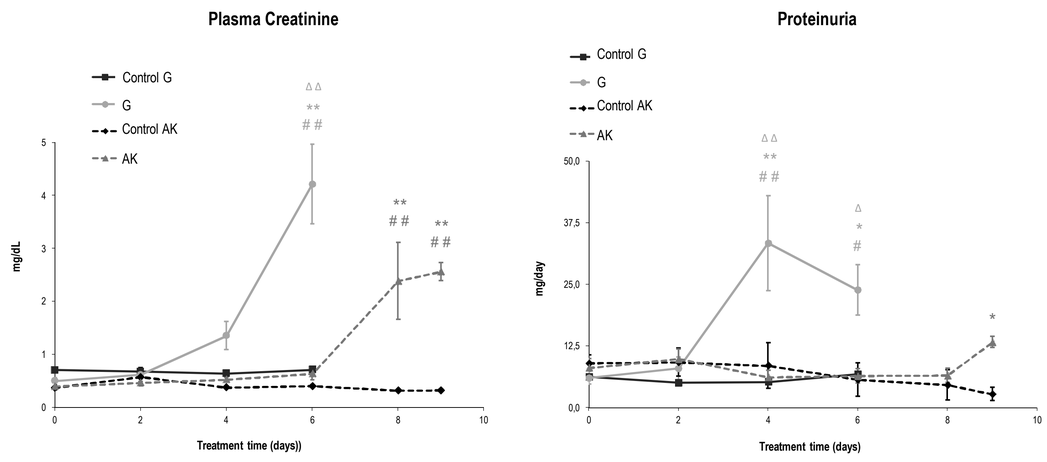

Figure 1. Characterization of the renal damage induced by gentamicin and amikacin. Wistar rats were divided into the following experimental groups: control G: rats treated intraperitoneally during 6 days with saline (0,9% NaCl) once daily; control AK: rats treated intraperitoneally during 9 days with saline (0,9% NaCl) once daily; G: rats treated with gentamicin 150 mg/kg/day; AK: rats treated with amikacin 500 mg/kg/day during 9 days. Time-course evolution of plasma creatinine concentration and proteinuria. Data are expressed as the average ±SEM *p<0.05 and ** p< 0.01 with respect to control groups; # p< 0.05 and ## p<0.01 with respect to its group day 0 (basal); Δ p<0.05 and ΔΔ p<0.01 with respect to AK.

Results

While rats treated with gentamicin showed an increment in all biomarkers, rats treated with amikacin only showed increments in cistatin C, while BMP-7, PAI-1 and NGAL levels were similar to control groups. Therefore, both models showed similar functional and structural damage characterized by traditionally biomarkers, but showed a different urinary protein profile.

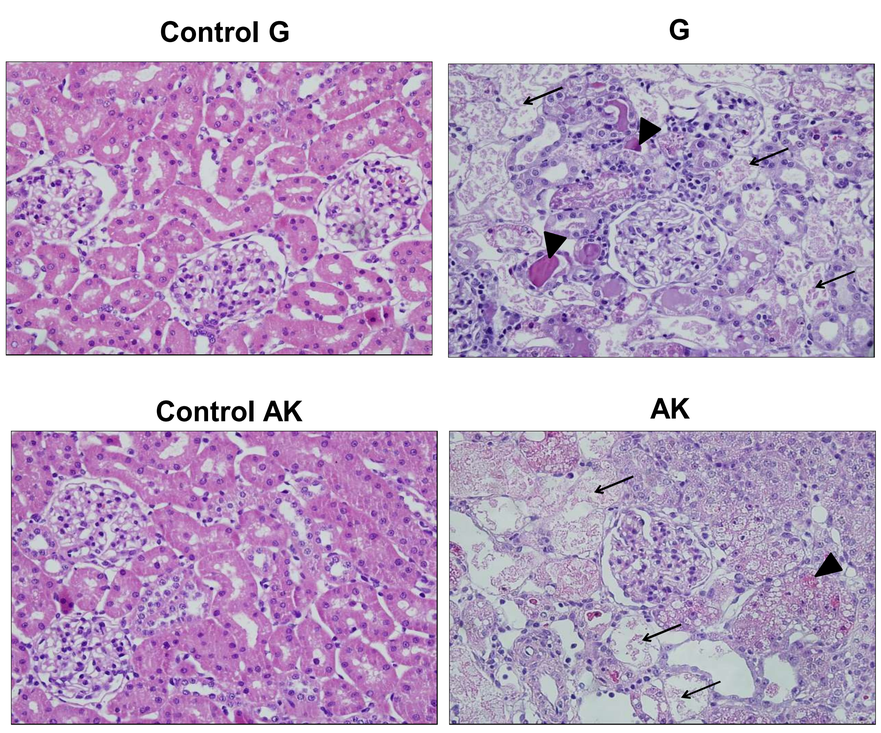

Figure 2. Renal effects after gentamicin or amikacin treatments. Representative images (400x) of the cortex of hematoxylin-eosin-stained renal section from following groups: control G: rats treated intraperitoneally during 6 days with saline (0,9% NaCl) once daily; control AK: rats treated intraperitoneally during 9 days with saline (0,9% NaCl) once daily; G: rats treated with gentamicin 150 mg/kg/day; AK: rats treated with amikacin 500 mg/kg/day during 9 days. Black arrows shown tubular necrosis and black triangle shown tubular obstruction.

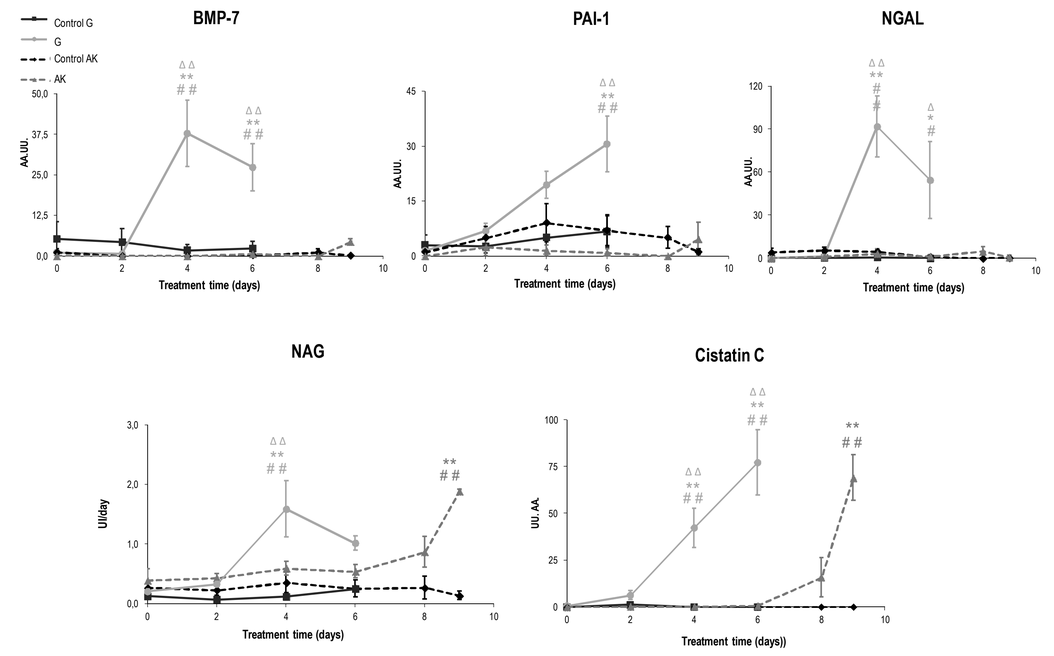

Figure 3. Time-course evolution of biomarkers expression. Densitometric quantification of the BMP-7, Cistatin C, NGAL, PAI-1 bands from three western blots carried out with the urine of three unselected rats and NAG expression . Wistar rats were divided into the following experimental groups: control G: rats treated intraperitoneally during 6 days with saline (0,9% NaCl) once daily; control AK: rats treated intraperitoneally during 9 days with saline (0,9% NaCl) once daily; G: rats treated with gentamicin 150 mg/kg/day during 6 days; AK: rats treated with amikacin 500 mg/kg/day during 9 days. Data are expressed as the average ±SEM *p<0.05 and ** p< 0.01 with respect to control groups; # p< 0.05 and ## p<0.01 with respect to its group day 0 (basal); Δ p<0.05 and ΔΔ p<0.01 with respect to AK.

Conclusions

These results suggest that severely damaged nephrons (probably clogged) do not tribute to the final urine. And that, before degeneration, sublethal tubular function in flowing nephrons is more affected by gentamicin than by amikacin. They could also lead to tailored diagnostics for the specific detection and monitoring of the nephrotoxicity of individual aminoglycosides.

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