

Salicylic acid attenuates gentamicin-induced nephrotoxicity in rabbits

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Abstract: Gentamicin (GM) is a generally utilized as an antibiotic against dangerous and life threatening contaminations, yet its value is restricted by the development of nephrotoxicity. The present investigation was intended to decide the defensive impact of salicylic acid (SA) in gentamicin-induced nephrotoxicity in rabbits. Quantitative assessment of gentamicin-induced structural changes and level of functional modifications in the kidneys were performed by biochemical examinations keeping in mind the end goal is to decide the potential protective impacts of SA co-administration with gentamicin. Gentamicin was seen to cause a serious nephrotoxicity which was proved by a plasma urea, plasmacreatinine, plasma uric acid, plasma Na⁺, plasma K⁺, intra-erythrocyte Na⁺ and intra-erythrocyte K⁺ levels. On the other hand, simultaneous SA administration protected kidney tissue against the oxidative damage and the nephrotoxic effect caused by GM treatment. The outcomes from our investigation show that SA supplement lessens oxidative-stress related to renal damage by reducing oxygen free radicals in gentamicin-treated rabbits.

Keyword: Gentamicin, salicylic acid, renal function tests, electrolytes.

INTRODUCTION

Gentamicin (GM) is regularly prescribed in human clinical practices for treatment of gram-negative infections (Karahan *et al.*, 2005; Mwengee *et al.*, 2006). The value of GM is restricted by the development of nephrotoxicity. This reaction is severe to the point that the utilization of the medication must be ceased. Notwithstanding the presentation of more current and less lethal anti-biotic, GM is as yet utilized clinically as a result of its fast bactericidal activity, wide range action, synthetic strength, stability and minimal cost (Siegenthaler *et al.*, 1986; Matew *et al.*, 1992).

The components engaged with GM-induced cell damage are not plainly caught on. Notwithstanding, a few examinations showed that reactive oxygen species (ROS) might be critical attribute in GM-initiated nephrotoxicity (Bandy *et al.*, 2008). Irregular generation of ROS specifically harms a few macromolecules and actuates cell damage and necrosis via several mechanisms including peroxidation of membrane lipids, protein denaturation, and DNA damage (Balige *et al.*, 1998; Parlakpiner *et al.*, 2005). In like manner, the administration of several compounds with antioxidant activity has been successfully used to counteract or enhance GM-prompted nephrotoxicity (Stojilkovic *et al.*, 2012; Ali *et al.*, 2003)

In the previous couple of years, much intrigue has been laid on the role of naturally occurring dietary substances for the control and management of various chronic diseases, one such compound salicylic acid (SA) has been utilized since ancient times to give relief from discomfort and treat inflammatory conditions.

Salicylic acid is a phenolic compound present in plants, where it assumes a focal part in the development of local and systemic protection from pathogen infection (Dempsey *et al.*, 1994; Dungal 1998). Humans and animals acquire SA basically from natural products, daily foods, fruits, and vegetables. Increasing evidence shows that administrated SA can neutralize oxidative harm prompted by antagonistic conditions in animal (Guerrero *et al.*, 2007; Dinis-Oliveira *et al.* 2007), though the mechanisms underlying these effects remain unclear. It has been reported for SA that it has free radical-scavenging and iron chelation properties (Aruoma *et al.*, 1988). SA can influence the activation of transcription factors, specifically nuclear factor kappa B (NF-κB), accordingly mediating in apoptotic pathways (Yin *et al.*, 1998). It is likewise a hydroxyl radical scavenger in both experimental animals and humans who are encountering oxidative stress (Ghiselli *et al.*, 1992; Powell *et al.*, 1994).

The aim of the present study was therefore to investigate whether SA treatment prevents GM-induced nephrotoxicity. For this purpose, we have examined plasma urea, plasma creatinine and plasma uric acid levels in order to evaluate renal function. Plasma Na⁺, plasma K⁺, intra-erythrocyte Na⁺ and intra-erythrocyte K⁺ levels was examined to evaluate electrolyte homeostasis.

MATERIALS AND METHODS

Experimental protocol

Twenty four male rabbit (1200-1500g body weight) were purchased from local market (Karachi, Pakistan) for the study. Animals were acclimatized to the laboratory conditions one week before the start of experiment and caged in a quite temperature controlled room (23±4°C).

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Table 1: Change in body weight of different groups of rabbits over 21 days study period

Group	Initial Weight (gm)	Final Weight (gm)	Weight Gain (%)	Weight Loss (%)
Control	1300.83	1416.17	8.97 ± 1.76	--
Gentamicin	1316.67	1202.33	--	8.70 ± 0.78
GM+SA	1297.33	1231.50	--	5.08 ± 0.53
Salicylic Acid	1289.17	1341.00	3.90 ± 0.58	--

Table 2: The effect of salicylic acid on kidney weight of rabbits, plasma urea and creatinine levels of rabbits in Gentamicin induced nephrotoxicity

Parameters	Control	Gentamicin	GM+SA	Salicylic Acid
Kidney weight (gm)	9.08 ± 0.74	12.17 ± 0.52 ^(a)	9.25 ± 0.42 ^(b)	8.33 ± 1.13
Relative kidney weight	0.0064 ± 0.0003	0.0102 ± 0.0009 ^(a)	0.0075 ± 0.0003 ^(b)	0.0062 ± 0.0005
Plasma Urea (mg/dl)	28.17 ± 1.17	41.00 ± 1.26 ^(a)	27.83 ± 1.33 ^(b)	31.50 ± 2.26
Plasma Creatinine (mg/dl)	0.95 ± 0.19	3.17 ± 0.08 ^(a)	0.87 ± 0.05 ^(b)	0.88 ± 0.12
Plasma Uric Acid (mg/dl)	1.53 ± 0.03	2.35 ± 0.03 ^(a)	1.54 ± 0.02 ^(b)	1.55 ± 0.03

Table 3: The effect of salicylic acid on levels of Intra-erythrocytes Na⁺, Intra-erythrocytes K⁺, Plasma Na⁺ and Plasma K⁺ of rabbits in gentamicin induced nephrotoxicity

Parameters	Control	Gentamicin	GM+SA	Salicylic Acid
Intra-erythrocytes Na ⁺ (mmol/L)	14.7 ± 1.3	18.3 ± 1.9 ^(a)	14.8 ± 1.7 ^(b)	8.7 ± 0.5
Intra-erythrocytes K ⁺ (mmol/L)	180.0 ± 2.5	144.9 ± 6.8 ^(a)	174.2 ± 4.9 ^(b)	182.3 ± 6.1
Plasma Na ⁺ (mmol/L)	159.8 ± 10.6	141.5 ± 3.2 ^(a)	163.1 ± 2.0 ^(b)	166.6 ± 4.4
Plasma K ⁺ (mmol/L)	3.7 ± 0.1	5.2 ± 0.1 ^(a)	3.5 ± 0.2 ^(b)	3.7 ± 0.1

Data are shown as means ± SD

(a) P < 0.05 versus control group.

(b) P < 0.05 versus Gentamicin group.

Animals had free access to water and diet. The experiments were conducted with ethical guidelines of institutional ERB (Ethical Review Board No.2003) and internationally accepted principles for laboratory use and care in animal research (Health research extension Act of 1985). All efforts were made to minimize animal suffering and reduce the number of animals were used.

Study design

After a quarantine period of 7 days, 24 rabbits were randomly divided into four groups, each consisting of 6 animals.

Control group: Healthy untreated animals.

Gentamicin group: Received only gentamicin (80mg/kg)

Gentamicin + salicylic acid group: Received gentamicin (80mg/kg) + salicylic acid (80mg/kg)

Salicylic acid group: Received only salicylic acid (80mg/kg)

All groups were treated over a period of 21 consecutive days. Twenty-four hours after the administration of last doses of GM and SA, on 22nd day, rabbits were weighed and sacrificed.

Blood was sampled in lithium heparin coated tubes. Heparinized blood was centrifuged and plasma was separated for estimation of creatinine and urea. Kidneys

were excised, trimmed of connective tissues, rinsed with saline to eliminate blood contamination dried by blotting with filter paper and weighed.

Assessment of renal functions

Plasma samples were assayed for urea and creatinine. Urea was estimated spectrophotometry by the Oxime method (Butler *et al.*, 1981). Creatinine was estimated spectrophotometry by the Jeff's method (Spierto *et al.*, 1979). Uric acid was estimated spectrophotometry using kit method.

Assessment of electrolytes homeostasis

Estimation of Plasma Electrolytes: Plasma was analyzed for the estimation of sodium and potassium by flame photometry. Estimations of Intra erythrocyte sodium and potassium: Heparinized blood was centrifuged and plasma was separated. Buffy coat was aspirated and discarded. Erythrocytes were washed three times at room temperature by suspension in the magnesium chloride solution (112mmol/L), centrifugation at 4500 g at 4°C for 5 min and aspiration of the supernatant as described earlier (Fortes and Starkey, 1977). Final supernatant was retained for the estimation of intraerythrocyte sodium and potassium concentration. Neither electrolyte was detectable in the final wash. Washed erythrocytes were then used for the estimation of intraerythrocytes sodium and potassium (Tabssum *et al.*, 1996).

STATISTICAL ANALYSIS

Results were expressed as the mean \pm SD. Statistical significant difference was determined by one-way analysis of variance (ANOVA) followed by Tukey's post hoc test for multiple comparisons. Probability values (P) less than 0.05 were considered to be statistically significant.

RESULTS

The effect of salicylic acid on body weight, Kidney weight and relative kidney weight of rabbits in Gentamicin induced nephrotoxicity

The effect of salicylic acid on body weight of rabbits in Gentamicin induced nephrotoxicity

The effect of salicylic acid on kidney weight of rabbits in gentamicin induced nephrotoxicity

Kidney weights of rabbits were significantly increased (12.17 \pm 0.52gm) in the GM-treated renal injury group, when compared to the control group (9.08 \pm 0.74gm; P < 0.01). The increases induced by GM were prevented by SA administrations (GM + SA group). The kidney weights of rabbits were found similar in SA group as compare to that of control group (table 2).

The effect of salicylic acid on relative kidney weight of rabbits in gentamicin induced nephrotoxicity

Kidney to body weight ratio of rabbits was significantly increased (0.0102 \pm 0.0009) in the GM-treated renal injury group, when compared to the control group (0.0064 \pm 0.0003; P<0.01). The increases induced by GM were prevented by SA administrations (GM + SA group). The kidney to body weight ratio of rabbits was found similar in SA group as compare to that of control group (table2).

Assessment of renal function

The effect of salicylic acid on plasma Creatinine level of rabbits in gentamicin induced nephrotoxicity

Creatinine level of rabbits was significantly increased (3.17 \pm 0.08) in the GM-treated renal injury group, when compared to the control group (0.95 \pm 0.19; P<0.01). The increases induced by GM were prevented by SA administrations (GM + SA group). The Creatinine level of rabbits were found similar in the control and SA groups.

The effect of salicylic acid on plasma Urea level of rabbits in gentamicin induced nephrotoxicity

Urea level of rabbits was significantly increased (41.00 \pm 1.26) in the GM-treated renal injury group, when compared to the control group (28.17 \pm 1.17; P<0.01). The increases induced by GM were prevented by SA administrations (GM + SA group). The Creatinine levels of rabbits were found similar in SA group as compare to that of control group (table2).

The effect of salicylic acid on plasma uric acid of rabbits in gentamicin induced nephrotoxicity

Uric acid level of rabbits was significantly increased (2.35 \pm 0.03) in the GM-treated renal injury group, when compared to the control group (1.53 \pm 0.03; P<0.01). The increases induced by GM were prevented by SA administrations (GM + SA group). The Creatinine levels of rabbits were found similar in SA group as compare to that of control group (table 2).

Assessment of electrolyte homeostasis

The effect of salicylic acid on plasma sodium level

(mmol/L) of rabbits in gentamicin induced nephrotoxicity
Plasma sodium level was significantly decreased (141.5 \pm 3.2mmol/L) in the GM-treated renal injury group, when compared to the control group (159.8 \pm 10.6 mmol/L; P < 0.01). The decreases induced by GM were completely prevented by SA administrations (GM + SA group). Plasma sodium was increased in SA group as compare to that of control group (table 3).

The effect of salicylic acid on plasma potassium level (mmol/L) of rabbits in gentamicin induced nephrotoxicity

Plasma potassium level was significantly increased (5.2 \pm 0.1mmol/L) in the GM-treated renal injury group, when compared to the control group (3.7 \pm 0.1 mmol/L; P < 0.01). The increases induced by GM were completely prevented by SA administrations (GM + SA group). The plasma potassium level was found similar in the control and SA groups (table 3).

The effect of salicylic acid on intra erythrocyte sodium level (mmol/L) of rabbits in gentamicin induced nephrotoxicity

Intra erythrocyte sodium level was significantly increased (18.3 \pm 1.9 mmol/L) in the GM-treated renal injury group, when compared to the control group (14.7 \pm 1.3 mmol/L; P<0.001). The increases induced by GM were completely prevented by SA administrations (GM + SA group). The intra erythrocyte sodium level was found similar in SA group as compare to that of control group (table 3).

The effect of salicylic acid on intra erythrocyte potassium level (mmol/L) of rabbits in gentamicin induced nephrotoxicity

Intra erythrocyte potassium level was significantly decreased (144.9 \pm 6.8mmol/L) in the GM-treated renal injury group, when compared to the control group (180.0 \pm 2.5mmol/L; P<0.01). The decreases induced by GM were completely prevented by SA administrations (GM + SA group). The intra erythrocyte potassium level was found similar in SA group as compare to that of control group (table 3).

DISCUSSION

Aminoglycoside anti-infection GM is generally utilized for the treatment of serious gram-negative bacterial diseases (Reiter *et al.*, 2002). However, nephrotoxicity is a major complication of GM administration. Accordingly improvement of nephrotoxicity would upgrade its clinical utilization. A few methodologies including the utilization of chemical compounds have been utilized to lessen GM induced nephrotoxicity (Parlakpınar *et al.*, 2005; Cuzzocrea *et al.*, 2002). Phenolic compounds from dietary plants are known to be great scavengers of reactive oxygen species. In the previous couple of decades, an impressive and reliable measure of confirmation has shown that SA has antioxidant properties (Baltazar *et al.*, 2011; Colantoni *et al.*, 1998) though the mechanisms underlying these effects remain unclear.

Firstly, it has been reported that salicylates comprise free radical-scavenging and iron chelation properties (Auroma *et al.* 1988). Additionally, it has been exhibited that salicylate viably secures against gentamicin-prompted hearing misfortune in guinea pigs (Sha *et al.* 1999). Along these lines in the present examination, we evaluated whether the nephrotoxic impacts caused by intense organization of GM could be averted or improved by treatment with SA, a natural compound which has a solid cancer prevention agent property (Baltazar *et al.*, 2011). Thus in the present study, we assessed whether the nephrotoxic effects caused by acute administration of GM could be prevented or ameliorated by treatment with SA, a herbal compound which possesses a strong antioxidant property (Baltazar *et al.*, 2011)

The results of this study show that GM administration to rabbits produced a typical pattern of nephrotoxicity which was manifested by marked increase in kidney weight, relative kidney weight, plasma creatinine urea & uric acid levels and decrease in body weight. On the other hand, SA co-administration showed a significant decrease in kidney weight, relative kidney weight, plasma creatinine& urea levels and increase in body weight.

Mean body weight of the gentamicin treated group animals fell too by 8.70 percent. Comparable changes were observed by many other researchers following use of nephrotoxic dose of gentamicin (Morales *et al.*, 2010; Gossrau *et al.*, 1989; Erdem *et al.*, 2000). Body weight loss resulted from decreased oral intake that occurred following acidosis and increased catabolism associated with gentamicin induced acute renal failure (Ali *et al.*, 1992).

Kidney weight and kidney relative weight found elevated in gentamicin treated rabbits as compared to untreated group show nephrotoxic effect of gentamicin (Lakshmi *et al.*, 2009; Mehan *et al.*, 2017) which was attenuated by co-administration of salicylic acid.

The kidney plays a central role in the regulation the balance of body salt and water and then disordered regulation of renal functions is responsible for the altered balance of salt and water. In the present study, plasma electrolytes were disturbed significantly in gentamicin injected rabbits as compared with control rabbits. Lower value of plasma sodium indicates inability of kidney to conserve sodium. Haemodilution too may be involved in the fall of sodium value via excess of water intake and/or increase production of endogenous water, in turn, the reversed increases of potassium appeared to be due to reduced excretion of K⁺ aggravated by leakage of intracellular potassium into blood stream as a result of gentamicin induced lesions in renal tubular epithelium (Padmini *et al.*, 2012; Heibashy *et al.*, 1999; Heibashy *et al.* 2009). The obtained results may be due to kidney damage caused by the oxidative stress by increasing the formation of free radicals (Prahalthan *et al.*, 2012).

The curative effect of SA on the kidney markers can be attributed to its antioxidant property as it has been found that ROS may be involved in the impairment of glomerular filtration rate (GRF) (Hughes *et al.*, 1996). Low or moderate production of ROS plays a physiological role in several redox-responsive signaling pathways, for example, in defense against environmental pathogens, regulation of vascular tone by nitric oxide (NO), regulation of cell adhesion, and apoptosis (Valko *et al.*, 2007).

CONCLUSION

According to our biochemical findings administration of SA abolished nephrotoxic effects of GM. These findings indicate that SA supplementation may reduce GM-induced renal injury. We propose that salicylic acid modulates oxidative stress and associated potentially proinflammatory activity in the kidney. This may be via mechanisms linked to redox signaling, through an effective inhibition of proinflammatory factors and scavenging of ROS.

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