CODEN [USA]: IAJPBB ISSN: 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES

http://doi.org/10.5281/zenodo.1490594

Available online at: http://www.iajps.com Research Article

DRUG INDUCED NEPHROTOXICITY: GENTAMYCIN VERSUS RIVAROXABAN IN ALBINO RAT MODEL

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Abstract:

To compare the renal effects of Rivaroxaban and gentamycin in albino wistar rats this Experimental study was conducted in animal house Tando Jam Agricultural University and Pharmacology department Isra University Hyderabad from June 2015-December 2015. Male Albino wistar rats(n=30) randomly selected and purchased from Karachi and divided into 3 equal groups. Control Group (Group A), Gentamycin treated (Group B) and Rivaroxaban treated (Group C). A single daily dose of gentamycin (80mg/kg/day) was given by intra peritoneal route for 10 days and Rivaroxaban (10mg/kg/day). Blood samples were collected and analyzed for serum urea and creatinine on day 0 , 7and 14 under standard conditions using centrifuge and Hitachi analyzer. Data analysis was accomplished by using 21st version of the SPSS (Statistical Packages for Social Sciences) .The mean of weight, serum urea and creatinine of groups A, B and C, was compared by ANOVA. P-value <0.05 was considered as level of significance. We found Weight of study groups A, B and C at day 0 was 237.80±19.75, 249.10±23.59 and 239.90±20.76respectively with no significant difference (p-vale o.448) but the same was found significant at 7th and 14th days p-values 0.00002 and 0.00008 respectively. Similarly serum urea and creatinine were non -significant among all three groups initially but found highly significant after 7 and 14 days with p-values for urea 0.814, 0.00004 and 0.00003 and p-value for creatinine 0.367, 0.00001 and 0.00005 among groups A,B and C at days 0,7and14 respectively.

***Conclusion**: Rivaroxaban is less nephrotoxic than gentamicin.*

Key Words: *Gentamicin, Rivaroxaban, Urea, Creatinine*

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Please cite this article in press Samreen Ali Pandhiani et al., ***Drug Induced Nephrotoxicity: Gentamycin versus Rivaroxaban in Albino Rat Model.,*** *Indo Am. J. P. Sci, 2018; 05(11).*

INTRODUCTION:

Acute kidney injury (AKI) is among the top causes of death in nephrology and drug induced nephrotoxicity accounts for a significant figures[1]. Decreased clearance of Nitrogenous waste products show the reduction in normal renal function consequently result into elevation of urea and creatinine blood levels so carry the diagnostic value[1]. It may take from hours, days to months to reduce GFR with multiple etiological factors like renal, pre-renal and post-renal[2].Drugs are among the renal category of etiologies and most challenging one. Reduction of renal perfusion resulting into ischemia is the main process for a variety of drugs like aminoglycosides, amphotericin B and cis-platinum[3]. Aminoglycosides group of antibiotics is frequently used to treat infections caused by Gram-negative bacteria and gentamicin is most commonly used in Pakistan followed by amikacin for the mentioned purpose[3]. Aminoglycosides (gentamycin) is taken up by the epithelial cells in proximal tubules possibly due to binding with the membrane acidic phospholipids that generates hydroxyl radicals which affects the DNA synthesis and Na/K-ATPase activity[3].Rivaroxaban got approval in2008 for its use as prophylactic measure in the prevention of venous thromboembolism[4]. The prophylactic use of Rivaroxaban for the prevention of thromboembolic processes is common specially the AF (atrial fibrillation), DVT (deep vein thrombosis) and PE (pulmonary embolism) (PE) and along with stroke treatment[5]. It is also used to prevent ACS (acute coronary syndrome) in adults at risk along with aspirin, the trend being more common in USA[6]. Rivaroxaban is orally bioavailable drug two third of which gets metabolized by liver while one third remains unmetabolized, half of the drug gets eliminated through kidney while the remaining follows the hepatobiliary route so it possess dual mode of elimination[7]. It exerts its anticoagulant effects by directly inhibiting the factor Xa which is the common step for intrinsic and extrinsic pathway[8,9].This current study was planned to explore the renal effects of the Rivaroxaban and to compare them with the known nephrotoxic agent as there were many controversies about rivaroxaban to be nephrotoxic.

Inclusion and Exclusion Criteria:

Albino male rats were purchased from Karachi animals through inclusion criteria of healthy and weighing 200-300 grams excluding the female, low weight and diseased rats.

METHODOLOGY:

Rats were kept in animal house of the Agriculture University Karachi Tando Jam in steel cages with in well ventilated environment and international protocols for temperature , day night cycle, diet and animal handling. Animals were divided into A, B and C groups having10 animals each. Standard chow diet along with ad libitum water was provided after tagging, weighing and keeping them in separate cages. After acclimatization for two weeks intra peritoneal injection of gentamicin injection was administered to group B animals at dose of 80mg/kg/day for 10 days. Group C was given Rivaroxaban 10mg tablet were given orally after grinding in mortar and dissolving in distilled water while group A was kept as control group on normal saline. Medicines were purchased from local pharmacy.

Collection of Blood Sample:

2 ml blood was drawn from the rats on 0 day, 2nd on 7th day and 3rd on 14th day by cardiac puncture under mild anesthesia (Ketamine 20mg with xylazine 2mg subcutaneously in order to minimize the pain and to decrease the potential of complications. Aseptic measures were taken. 22 guage needle with 3ml syringe was used for the procedure in order to minimize the risk of damage to the myocardium. Blood volume was replaced by fluid. Samples were analyzed in Laboratory of Veterinary Physiology and Biochemistry department, Sindh Agriculture University Tando jam for measuring the blood urea and serum creatinine by Hitachi analyzer 902 after centrifuging at 4000rpm for 5 min.

Statistical Analysis:

Data was analyzed on SPSS version 21 and ANOVA was used technique at p-value <0.05 as significant. Mean and SD were measured for weight, serum urea and creatinine and compared among group.

Results:

Body weight:

Weight of study groups A,B and C at day 0 was 237.80±19.75, 249.10±23.59 and 239.90±20.76 respectively with no significant difference (p-vale o.448) which shows the homogenousity of the study animal before the intervention. The weight was changed to a significant level after 7days from 264.1±21.08 and 215.20±11.05 to 271.5±19.96 (p-value 0.00002) ,while after 14 days it was 281.40±25.89 ,202.60±31.48 and 281.80 ±17.49 for groups A, B and C respectively (p value 0.00008).

Serum urea:

There was no significant difference in serum urea concentration in study groups at 0 day which was 5.74±2.01, 5.74±2.01 and 6.21±1.62 for group A, B and C respectively (p-value 0.814). Urea levels after 7 days were noted as 5.49±1.93,

16.62±3.29 and 5.88±1.95 in groups A, B and C respectively with highly significant p-value 0.00004. Similarly levels of serum urea in group A, B and C after 14 days were found as 6.91±2.38, 18.44±3.64 and 6.96±2.33 respectively (p-value 0.00003).

Serum Creatinine:

Creatinine as measured at 0 day was 0.43±0.30 in group A , 0.58±0.22 in group B and 0.58±0.28 in group C (Non-significant p= 0.367). It was 0.57±0.28, 1.88±0.38 and0.59±0.25 after 7 days among A,B and C groups respectively (Highly significant difference p=0.00001. The same parameter was much deranged in gentamycin induced group after 14 days which were as group A= 0.58±0.28, group B= 3.03±0.60 and group C = 0.63±0.25 with high significance level p=0.00005.

Table I. Study parameters before experiment in all group at 0 day (n=30)

S.No	Parameter	Group A (Control)	Group B (Gentamycin)	Group C (Rivaroxaban)	F-Value	P-Value
1	Weight	237.80±19.75	249.10±23.59	239.90±20.76	0.82	o.448
2	Urea	5.74±2.01	5.74±2.01	6.21±1.62	0.20	0.814
3	Creatinine	0.43±0.30	0.58±0.22	0.58±0.28	1.03	0.367

Table II. Study parameters before experiment in all group at 7th day (n=30)

S.No	Parameter	Group A (Control)	Group B (Gentamycin)	Group C (Rivaroxaban)	F-Value	P-Value
1	Weight	264.1±21.08	215.20±11.05	271.5±19.96	27.93	0.00002
2	Urea	5.49±1.93	16.62±3.29	5.88±1.95	65.22	0.00004
3	Creatinine	0.57±0.28	1.88±0.38	0.59±0.25	59.25	0.00001

Table III. Study parameters before experiment in all group at 14th day (n=30)

S.No	Parameter	Group A (Control)	Group B (Gentamycin)	Group C (Rivaroxaban)	F-Value	P-Value
1	Weight	281.40±25.89	202.60±31.48	281.80 ±17.49	31.73	0.00008
2	Urea	6.91±2.38	18.44±3.64	6.96±2.33	54.38	0.00003
3	Creatinine	0.58±0.28	3.03±0.60	0.63±0.25	117.44	0.00005

DISCUSSION:

Our finding regarding Gentamicin related nephrotoxicity were found consistent with research results of Ghafoor et al(2013) and Salgueiro SR et al(2015) both authors used similar dose (80mg/kg/day) but they also worked on some other parameters urine volume and urine albumin level what we could not[10,11]. Mc Dofie et al(2013) reported too similar level of nephrotoxicity following gentamicin administration in his experimental animals marked elevation in serum urea and creatinine levels[12].We could not find any nephrotoxic effects related to rivaroxaban at 10mg l70 kg human dose which was consistent with the findings of a human study by Keith A Fox et al (2011) who recommended rivaroxaban to be safe mild to moderate renal failure[13]. A case reported by Miguel Oliveira et al (2017) mentioned acute renal injury and sudden rise in serum urea, creatinine levels and marked hematuria in a previously normal patient that is inconsistent with our results[14]. No such other reports were documented before or after that which suggests that the particular patient might have some other reason behind the outcome or there may exist some genetic justification like genetic polymorphism. A case report submitted by Sylvia Haas et al (2016) was consistent with our findings when a 71year patient of AF (atrial fibrillation) with co-morbidities intentionally took 1940 mg (97 tablets) of rivaroxaban for suicide. laboratories investigations showed BUN 28 mg/dL and creatinine 1.2 mg/dl at a rivaroxaban concentration of 160 ng/ml with normal renal function and improved conservative therapy alone[15].There are no specific studies available on the nephrotoxic effects of rivaroxaban so for but it is recommended by many authors to monitor renal function during therapy with rivaroxaban and its dose should be reduced from 20-15mg when GFR is 15-49ml/min and to stop the same when the GFR fall below 15ml]16,17]. Possible explanation to no nephrotoxic effects for rivaroxaban in the current study may be the low dose used in our experimental work. Weight loss in the gentamycin treated group seems to be due to loss of protein in urine again not among the parameters of our current research while the same was non -significant in the rivaroxaban treated animals supporting none or minimal renal damage.

CONCLUSION:

Rivaroxaban (10mg) was not found nephrotoxic when compared with gentamycin

Recommendations: Study to explore the nephrotoxic effects of rivaroxaban at various recommended doses is recommended.

Interest Conflict: None

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