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Original Article

Assessment of Renal Parameters Following Combined Administration of Antihypertensive, Hypolipidemic and Hypoglycemic Drugs

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ABSTRACT

Introduction: Blood pressure, serum cholesterol and glucose levels are the age associated risk factors necessary to screen for controlling cardiovascular disorder. Multiple mediators are involved in pathogenesis of disease by different mechanisms. To target those pathological conditions multiple medicines yield is better therapeutic approach. Multi drug therapy for the management of multiple disorders among younger has different strategy than in elderly as many drugs may be less effective or less suitable for elderly patients. To minimize the risk of multiple drug administration associated toxicity treatment plans should to adjust accordingly.
Objectives: Drug interactions are of great concern because doctors and patients are usually unaware of toxicities due to simultaneous administration of drugs. Investigate of safe combinations should be necessary approach which are less likely to interact with each other. Several studies have been conducted previously to observe the toxic effects associated with the use of numerous combinations.
Method: In present study toxic effects on renal function were assessed following administration of individual and combination of drugs to rabbits for the period of two months. Renal function tests were done by using kit method and all values were compared with control by taking mean and standard error to the mean using one-way analysis of variance (ANOVA) followed by post hoc.
Results: Results of this study revealed that animals received individual drugs acarbose and glibenclamide and combination of metformin-amlodipine and atorvastatin showed significant decrease ($p<0.005$) in urea as compared to control rabbits. However animals received individual drugs lisinopril and losartan and combination of glibenclamide, losartan and Atorvastatin showed significant increase ($p <0.005$) in urea as compared to control animals.
Conclusion: Present study revealed significant nephrotoxicity with

poor kidney function in animals received combination of glibenclamide, losartan and atorvastatin, hence it may be suggested that this combination should be avoided in patients with compromised renal function and if is necessary than should be taken under proper medical supervision.

Keywords: Nephrotoxicity, Rhabdomyolysis, Interstitium, Thrombotic microangiopathy.

INTRODUCTION

Multiple drug administration is very common practice which sometimes induces significant toxic effects on the vital organ; hence present study was designed to determine cumulative toxicities of multiple drug administration. It has been seen that the incident of drug induced nephrotoxicity is more common in elderly patients as compare to younger and 20 percent of patient suffers from drug-induced renal failure[1-2].Patients suffering from multiple disorders like diabetes, hyperlipidemia and cardiovascular disorder are at higher risk of nephrotoxicity since exposed to multiple medications. Renal impairment is usually reversible after discontinuation of medication as stated in table 1[3-4].

Drug induced nephrotoxicity

The different mechanism of drug induced toxicity includes tubular cell toxicity, rhabdomyolysis, altered intra-glomerular hemodynamics crystal nephropathy, inflammation and thrombotic microangiopathy[4-6]. Complete knowledge about the medicine in use is essential for the prevention of associated renal toxicities[7]. Table 1 shows different drugs categories along with type of renal damage induce by them[8].

Altered intra-glomerular hemodynamics

The normal glomerular filtration rate (GFR) is about 120 ml per minutes. Urinary output and GFR of kidney are managed through afferent and efferent arterial pressure. Renal perfusion is depending upon PGs since dilate the arteries which allow more blood to flow through glomerulus[9].

All the drugs which alter circulating PGs can indirectly affect the inter-glomerular hemodynamics and urine output[4].

Tubular cell toxicity

Renal proximal tubules are responsible for reabsorbing glomerular filtrate and it is the more sensitive part to the toxic effect of drugs. Drugs usually impair mitochondrial function and interfere with tubular transport mechanism by forming free radicals[10].

Inflammation

Inflammatory changes in the glomerulus, renal tubular cells and interstitium leading to fibrosis and scarring[11].

Crystal nephropathy

Renal function impairment may results due to formation of drugs precipitate which make hurdle in urine flow. These crystals are insoluble therefore affect urinary output[3,12].

Rhabdomyolysis

Myoglobin and creatine kinase released during skeletal muscle injury cause

tubular obstruction and alteration in filtration rate resulting renal impairment[13-15].

Thrombotic microangiopathy

In thrombotic microangiopathy a platelet thrombi form in result of organ damage which moves in microcirculation and damage the renal system due to immune mediated reaction[16]. (See table 1.)

Risk factors in drug-induced renal impairment

Renal impairment due to drug occurs in some patients only in specific situation it is therefore necessary to take preventive strategies before prescribing a drug having potential to induce nephrotoxicity[19]. Following risk factors must be considered in patients before prescribing drugs[20].

- Age of the patient (all nephrotoxic have common risk at age older than 60 years)
- Other illnesses (e.g. Diabetes, Heart failure, Hypertension etc.) altered renal function
- Multiple exposure to nephrotoxic substances
- Underlying renal insufficiency where GFR is lower than 60 ml/mints
- Inherently nephrotoxic drugs (aminoglycoside, amphotericin B, Cisplatin and dyes).

MATERIALS AND METHODS

Animal selection and dosing

The study was carried out on hundred ten white, healthy male rabbits weighing from 1000-1500 grams. The study was conducted with the approval of Departmental Ethical committee (Department of Pharmacology, Faculty of Pharmacy). Animals were divided in eleven groups, each containing 10 animals. Apparent health of these animals was monitored during the conditioning period under the laboratory environment for a week before administration of drug specifically noticing loss of hair, diarrhea, edema, ulceration and lack of activity[21]. Rabbits were housed in cages individually, under controlled condition of temperature 23±2° C. Diet and water was provided ad libitum[22]. Ten groups of animals served as test groups and one group served as Control which was given normal saline equivalent to the volume of respective doses according to their body weight[23].

The dose was given once a day every morning according to the body weight of animals through oral route for 60 days (See table 2).

Blood samples of 5 ml were collected at the end of dosing period i.e. 60 days from heart through cardiac puncture in gel tube for biochemical assays of renal parameters stated below.

- **(a) Urea:** Urea in the serum was estimated by enzymatic colorimetric test[24].
- **(b) Creatinine:** Creatinine in the serum was estimated by Jaffe reaction method, photometric colorimetric test for endpoint measurement of creatinine[25,26].

RESULTS

Table 3 shows the comparison of urea and creatinine levels among control animals and animals kept on individual drugs and their combinations for a period of 60.

Animals kept on acarbose and glibenclamide revealed highly significant decrease in the levels of urea i.e. 16.66±0.21 mg/dl and 24.40±1.20 mg/dl with respect to control i.e. 51.75±2.75 mg/dl respectively. While animals kept on lisinopril and losartan revealed highly significant increase in the levels of urea i.e. 87.31±1.30 mg/dl and 92.24±2.43 mg/dl with respect to control. However, the animals did not show any significant change in the creatinine level. Conversely the animals kept on metformin, atorvastatin and amlodipine alone did not

revealed any significant alteration in both urea and creatinine level.

Animals received GlLAt combination did not reveal any significant alteration in renal parameters at the completion of dosing. On the contrary animals kept on GLoAt and MAAt combination revealed highly significant increase and significant decrease in the level of urea i.e. 103.02±2.15mg/dl and 38.54±1.31 mg/dl respectively as compare to control. However there was no significant change in the levels of creatinine in these animals. (See table 3.)

CONCLUSION

Present study did not reveal any significant nephrotoxicity in animals received metformin, atorvastatin, amlodipine alone as well as acarbose-lisinopril-atorvastatin (GlLAt) in combination with respect to control. However, animal received acarbose, glibenclamide, lisinopril and losartan alone as well as GLoAt combination showed highly significant increase in urea with respect to control. Rise in serum urea might be an indication of azotemia or poor kidney function. This effect might be the result of accumulation of nephrotoxic metabolite of these drugs which at certain concentration tends to precipitate in crystalline form in the renal tubule. Although animals received losartan and atorvastatin alone showed moderate vascular congestion upon microscopic examination of the renal tissue.

Result of present study reveals that the combination of acarbose, lisinopril and atorvastatin has been found to be safe than all other combinations, since it has found to be least damaging. However further investigation are necessary to reach at definite conclusion.

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Table 1. Drugs induced nephrotoxicity[17,18]

Drug category	Name of drugs	Renal damage
Analgesics	Acetaminophen	Chronic interstitial nephritis
	Aspirin	Chronic interstitial nephritis
	NSAIDs	Acute interstitial nephritis, Glomerulonephritis
Antidepressants	Amitriptyline	Rhabdomyolysis
	Fluoxetine	Rhabdomyolysis
	Lithium	Chronic interstitial nephritis, glomerulonephritis, rhabdomyolysis
Antihistamines	Doxylamine	Rhabdomyolysis
	Diphenhydramine	Rhabdomyolysis
Antimicrobials	Aminoglycosides	Acute interstitial nephritis, crystal nephropathy
	Penicillin's, cephalosporins	Tubular cell toxicity
	Sulfonamides	Acute interstitial nephritis
Chemotherapeutics	Cisplatin	Chronic interstitial nephritis, tubular cell toxicity
	Methotrexate	Crystal nephropathy
	Interferon-alfa (intron a)	Glomerulonephritis
Cardiovascular agents	Ace inhibitors	Altered intra-glomerular hemodynamics
	Ticlopidine	Thrombotic microangiopathy
	Statins	Rhabdomyolysis
Diuretics	Triamterene	Crystal nephropathy
	Loops	Acute interstitial nephritis
	Thiazides	Acute interstitial nephritis
Proton pump inhibitors	Omeprazole	Acute interstitial nephritis
	Lansoprazole	Acute interstitial nephritis
	Pantoprazole	Acute interstitial nephritis
Miscellaneous	Ranitidine	Acute interstitial nephritis
	Zoledronate	Tubular cell toxicity
	Pamidronate	Glomerulonephritis

Table 2. Description of groups and doses

Groups	Name of Drugs
Control	Normal Saline for control
1	Acarbose
2	Glibenclamide
3	Metformin
4	Lisinopril
5	Losartan
6	Atorvastatin
7	Amlodipine
8	Acarbose + Lisinopril + Atorvastatin (GlLAt)
9	Glibenclamide + Losartan + Atorvastatin (GLoAt)
10	Metformin + Amlodipine + Atorvastatin (MAAt)

Table 3. Comparison of renal parameters after 60 days administration of individual drugs and combinations

Parameters/Groups	Urea (mg/dl)	Creatinine (mg/dl)
Control	51.75±2.75	1.45±0.25
Acarbose	16.66±0.21**	1.35±0.54
Glibenclamide	24.40±1.20**	1.59±1.56
Metformin	50.32±2.01	1.68±2.43
Lisinopril	87.31±1.30**	1.20±0.01
Losartan	92.24±2.43**	1.38±1.87
Atorvastatin	52.64±2.12	1.04±1.32
Amlodipine	43.04±1.31	1.32±0.04
GlLAt	49.88±4.13	0.71±0.37
GLoAt	103.02±2.15**	0.74±0.67
MAAt	38.54±1.31*	1.10±1.04

n=10
Mean ± S.E.M
*p < 0.05 significant with respect to control
**p <0.005 highly significant with respect to control.