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Comparative Effectiveness of Cysteine, Lysine and Glycine to Fend Off Paracetamol-Induced Hepatic Insult

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Abstract

The aim of this study was to evaluate comparative effectiveness of cysteine, lysine and glycine to protect hepatocytes from toxic effects of paracetamol by monitoring liver function parameters in experimental rabbits. In this study design, animals were divided into two groups; Acute treated group and Chronic treated group. Each group was further divided into five sub-groups; Control Group (Group-I), Toxic group (Group-II), Cysteine treated group (Group-III), Lysine treated group (Group-IV) and Glycine treated group (Group-V). This study showed that cysteine, lysine and glycine markedly reduce the elevated liver enzymes in paracetamol induced hepatotoxic rabbits. In both acute and chronic toxicity study, there was a significant reduction in the level of liver indexes in cysteine and lysine treated group as compared to glycine treated animals. It is, therefore, concluded that cysteine and lysine have better clinical utilization as free redical scavengers as compared with glycine.

Keywords: Paracetamol; Hepatotoxicity; Cysteine; Lysine; Glycine

Introduction

Liver is an organ having both secretary and excretory functions. Most of synthetic and metabolic functions of liver are performed by hepatocytes. Hepatocytes play important role in the metabolism and storage of proteins, carbohydrates, fats, vitamins and hormones. Plasma proteins are also synthesized by liver parenchymal cells. Liver can both synthesize and remove cholesterol from body. Non-essential amino acids, when required, are also synthesized by liver [1,2].

Liver enzymes included SGOT (Serum glutamic oxaloacetic transaminase), SGPT (Serum glutamic pyruvic transaminase), ALP (Alkaline phosphatase) and LDH (Lactate dehydrogenase) are present within the cells of liver. These enzymes are released in circulation when hepatocytes damage or die. Plasma half-life of SGOT and SGPT is 16-18 hrs and 42-48 hrs respectively while the half-life of mitochondrial SGOT is 87 hrs. These enzymes act as marker of liver injury. Bilirubin is formed by enzymatic breakdown of haemoglobin in reticuloendothelial system. The plasma level of bilirubin also raised in case of liver impairment [3].

Paracetamol (N-acetyl p-aminophenol, 4-hydroxy acetanilide), also called acetaminophen, is commonly used analgesic and antipyretic drug. At therapeutic dose, it is the most safe and effective drug. When high dose of drug is taken accidentally or for suicidal attempt, then this toxic dose of paracetamol causes centrilobular necrosis in liver causing liver failure and finally death occur [4,5]. Oxidative stress, nitrotyrosine formation, inflammatory cytokines and mitochondrial permeability transition considered to be involved in paracetamol induced hepatotoxicity. Paracetamol is basically metabolized through conjugation with glucuronic acid and sulphate, but a minor pathway is also through Cyp4502E1 enzyme system which converts paracetamol to toxic metabolite N-acetyl -p -benzoquinone imine (NAPQI). NAPQI is detoxified through glutathione (GSH) pathway by the formation of glutathione conjugate. In case of over dose of paracetamol, high concentration of NAPQI is produced, which causes depletion of GSH stores. So this toxic metabolite reacts with –SH group of normal cell proteins and form paracetamol protein adducts and causing cell death [6,7].

Amino acids are having numerous protective effects which can help body to combat stress condition. They are abundantly present in protein rich diet such as poultry, eggs, wheat, broccoli, garlic, onions, red pepper, soyabean and nuts. N-acetylcysteine, a precursor of glutathione, is used to prevent paracetamol induced hepatotoxicity [8]. Glutathione is made up of three amino acids; glycine, glutamic acid and cysteine. L-Cysteine is a non-essential sulphur containing amino acid which can be synthesized in human body from amino acid methionine.In case of oxidative stress due to protein malnutrition or hepatic depletion of glutathione, cysteine restores gamma glutamyl cysteine ligase enzyme [9]. Cysteine, being a precursor of glutathione (GSH), possesses powerful antioxidant properties and acts as an extracellular reducing agent [10]. Lysine is also an essential amino acid and useful in heavy metals chelation, activation of protease enzymes, production of hormones and antibodies which strengthen the immune system [11]. Glycine is a non-essential amino acid because in human body it can be produced by liver from other amino acids. Glycine provides defense to body against variety of conditions such as sepsis, hemorrhage and attack of endotoxins. Glycine also protects the liver, kidney, skeletal muscles and heart against reperfusion injury due to ischemia, cold conditions various toxic compounds and drugs [12].

The main objective of this study was to determine the efficacy of various amino acids in paracetamol induced hepatotoxic animals. Cysteine, Lysine and Glycine were evaluated for their relative effectiveness in ameliorating hepatic damage caused by paracetamol, the most commonly prescribed analgesic and anti-pyretic drug.

Materials

Chemicals

Three types of amino acids, L-cysteine (Daejung), lysine (Fluka Granite) and glycine (Merck Pharmaceuticals) were used for this experimental study to check their hepatoprotective effect while paracetamol was used to induce hepatotoxicity. All solvents used are of analytical grade. Distilled water was obtained from the distillation plan in our laboratory.

Experimental animals

Albino rabbits weighing 1 to 2 kg were purchased from the local market. The animals were kept in the animal house of the Faculty of Pharmacy, University of the Punjab, Lahore. They were acclimatized for a period of one week before starting the experiment. The rabbit were fed fresh green fodder and water *ad libitum*.

Collection of blood

The rabbits were placed in a wooden box and the ear of rabbit was carefully shaved. The marginal vein of the ear was made prominent by rubbing the ear. A fine cut was made with sharp edged surgical blade and the blood was collected in centrifuge tube. The collected blood was kept in ice cold water for 10 minutes and was centrifuged for 15 minutes at 4000 revolutions per minute. Finally the serum was collected with the help of micro pipette in Eppendorf and labeled.

Experimental design

The rabbits were mainly divided into two groups; acute treated group and chronic treated group. Each group was further divided into 5 sub-groups and in each sub-group 6 rabbits (n=6) were included for each experimental study. Before treatment, all rabbits were investigated both physically and biochemically and only healthy rabbits were selected for study.

Acute Treated Group (ATG GROUP)

In each treatment sub-group, 6hrs after giving respective protocol, blood samples were drawn and changes in liver function test (LFT) parameters i.e. SGPT, SGOT, ALP, LDH, and total bilirubin (TB) were observed.

Group I (Control Group): This group was given distilled water through intragastric tubing.

Group II (Toxic Group): Paracetamol suspension prepared by dissolving 3g/kg paracetamol powder in water using tragacanth as suspending agent was administered to rabbits through intragastric tubing to induce acute hepatotoxicity.

Group III (L-cysteine Treated Group): L-cysteine (600mg/kg) was injected intraperitoneally10minutes before giving acute paracetamol toxic dose.

Group IV (Lysine Treated Group): L-lysine (10mg/kg) was injected intraperitoneally10 minutes before giving acute paracetamol toxic dose.

Group V (Glycine Treated Group): Glycine (800mg/kg) was administered orally through intragastric tubing10minutes before giving acute toxic paracetamol dose.

Chronic treated group

In this study group, each sub-group was treated with a course of thirty days of its respective protocol and then blood samples were drawn and changes in liver function test (LFT) parameters (ALT, AST, ALP, LDH, and total bilirubin) were observed.

Group I (Control Group): This group was given placebo (water) orally through intragastric tubing for 30 days.

Group II (Toxic Group): Paracetamol suspension, prepared by dissolving 75mg/kg/d paracetamol powder in water using tragacanth as suspending agent, was administered to rabbits through intragastric tubing for 30 days in animals with normal liver function tests.

Group III (L-cysteine Treated Group): L-cysteine (200mg/kg) was injected intraperitoneally to paracetamol treated rabbits during the last week of their 30 days toxicity protocol.

Group IV (Lysine Treated Group): L-lysine (3mg/kg) was injected intraperitoneally to paracetamol treated rabbits during the last week of their 30 days toxicity protocol.

Group V (Glycine Treated Group): Glycine (266.6mg/kg) was administered orally through intragastric tubing to paracetamol treated rabbits during the last week of their 30 days toxicity protocol.

Statistical analysis

Data was analyzed by using SPSS version 21.0. All the liver profile parameters were noted as standard deviation of the mean. Different experimental groups were compared by applying ANOVA post-hoc tukey's test using statistical tool SPSS® version 21. A statistical value of $p \leq 0.05$ was considered significant.

Results

Effects of paracetamol, L-Cysteine, Lysine and Glycine on hepatic profile in acute treated study

In acute toxicity study, toxic effects of paracetamol and protective effects of three amino acids including L-Cysteine, Lysine and Glycine were observed on SGOT, SGPT, ALP, LDH and total bilirubin levels (Table 1, Figure 1A). After applying statistical tools between toxic group(Group II) and control group (Group-1), a highly significant increase ($p<0.05$) in the levels of SGOT(84% ↑), SGPT (70% ↑), ALP(22% ↑), LDH (80% ↑) and total bilirubin (57% ↑) were observed in toxic Group. When Cysteine treated group (Group III) was compared with Toxicgroup (Group II), results showed highly significant decrease ($p<0.05$) in plasma level of SGOT (60% ↓), SGPT(41% ↓), ALP (63% ↓), LDH (73% ↓) and total bilirubin (59% ↓). Similarly Lysine treated group (Group IV) showed a significant decrease ($p<0.05$) in the plasma levels of SGOT (30% ↓), SGPT (61% ↓), ALP (49% ↓), LDH (73% ↓) and on total bilirubin (57% ↓) as compared to toxic group (Group II), but glycine treated group (Group V) did not show any significant ($p>0.05$) change in SGOT (18% ↓) level while significant decrease ($p<0.05$) in the level of SGPT (33% ↓), ALP (26% ↓), LDH (66% ↓) and total bilirubin (46% ↓).

Effects of paracetamol, L-Cysteine, Lysine And Glycine on hepatic profile in chronic toxicity study

In case ofchronic toxicity study, toxic effects of paracetamol and protective effects of three amino acids including L-Cysteine, Lysine and Glycine were observed on SGOT, SGPT, ALP, LDH and total bilirubin level (Table 2, Figure 1B). After applying statistical tools between toxic control group (Group II) and Control group (Group-1), significant increase ($p<0.05$) in the levels of SGOT (64% ↑), SGPT (103% ↑), ALP (15% ↑), LDH (23% ↑) and total bilirubin (33% ↑) were observed. Comparison of Cysteine treated group (Group III) compared with Control group (Group II) showed significant decrease ($p<0.05$) in plasma level of SGOT (25% ↓), SGPT(29% ↓), ALP (19% ↓), LDH (28% ↓) and total bilirubin (20% ↓). Similarly Lysine treated group (Group IV) showed a significant decrease ($p<0.05$)in the plasma levels of SGOT (21% ↓), SGPT (25% ↓), ALP (12% ↓) and non significant change in the level of LDH (23% ↓) and total bilirubin (17% ↓) as compared to positive control group (Group II). Glycine treated group (Group V) did not show any significant ($p>0.05$) change in SGOT

	SGOT (U/L)	SGPT(U/L)	ALP(U/L)	LDH(U/L)	TB(mg/dl)
Group I	19.4 ± 1.26	19.11 ± 0.83	67.7 ± 3.45	12.6 ± 2.04	0.75 ± 0.09
Group II	35.62 ± 3.17*	32.5 ± 2.59*	82.4 ± 3.21*	22.7 ± 1.51*	1.18 ± 0.14*
Group III	14.14 ± 2.17*	14.5 ± 0.6*	30.06 ± 1.6*	6.16 ± 0.94*	0.48 ± 0.09*
Group IV	24.9 ± 2.76*	12.85 ± 1.07*	42.3 ± 4*	6.2 ± 0.9*	0.51 ± 0.03*
Group V	29 ± 2.62	23.6 ± 1.13*	60.6 ± 1.56*	7.76 ± 1*	0.64 ± 0.07*

Table 1: Effects of l-cysteine, lysine, glycine on liver profile in paracetamol treated rabbits in acute treated study

1. Group I: Control Group, Group II: Toxic Group,Group III: Cysteine treated group, Group IV: Lysine treated group, Group V: Glycine treated Group
2. Values are represented as Mean ± SEM
3. * represents P<0.05
4. Group I is compared with Group II. Group II is compared with Group III, IV and V

	SGOT (U/L)	SGPT(U/L)	ALP(U/L)	LDH(U/L)	TB(mg/dl)
Group I	21.9 ± 1.35	19.08 ± 0.66	43.82 ± 1.37	19.7 ± 1.05	1.06 ± 0.21
Group II	36 ± 1.76*	38.64 ± 3.05*	50.4 ± 0.7*	24.25 ± 1.66*	1.41 ± 0.18*
Group III	27.05 ± 1.64*	27.62 ± 2.05*	40.9 ± 0.76*	17.3 ± 2.15*	1.13 ± 0.17
Group IV	28.5 ± 1.73*	28.92 ± 1.9*	44.17 ± 0.69*	18.61 ± 1.24	1.17 ± 0.15
Group V	29.4 ± 2.19	28.8 ± 1.96*	42.8 ± 0.58*	19.5 ± 1.27	1.18 ± 0.15

Table 2: Effects of l-cysteine, lysine, glycine on sgot level in paracetamol treated rabbits in chronic toxicity study

1. Group I: Control Group, Group II: Toxic Group, Group III: Cysteine treated group, Group IV: Lysine treated group, Group V: Glycine treated Group
2. Values are represented as Mean ± SEM
3. * represents P<0.05
4. Group I is compared with Group II. Group II is compared with Group III, IV and V

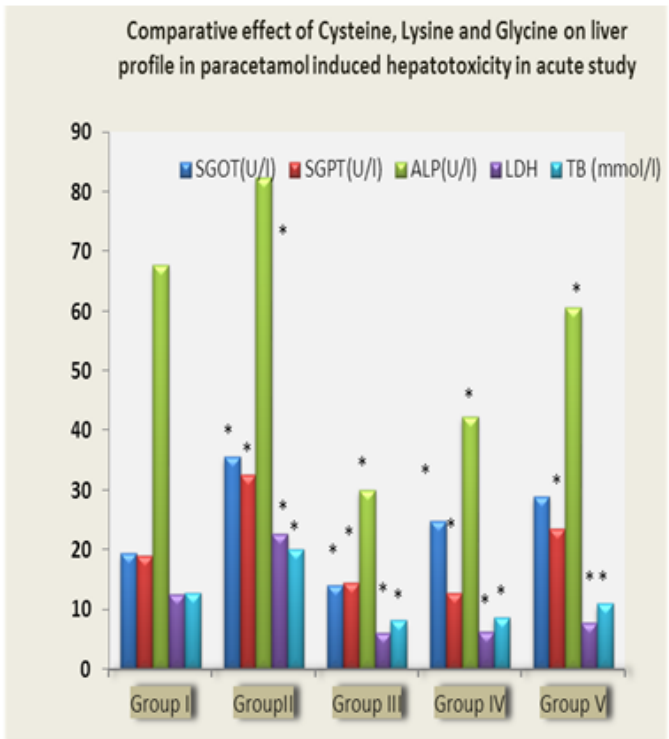

Figure 1A: Comparative effect of Cysteine, Lysine and Glycine on liver profile in paracetamol induced hepatoxicity in acute study.

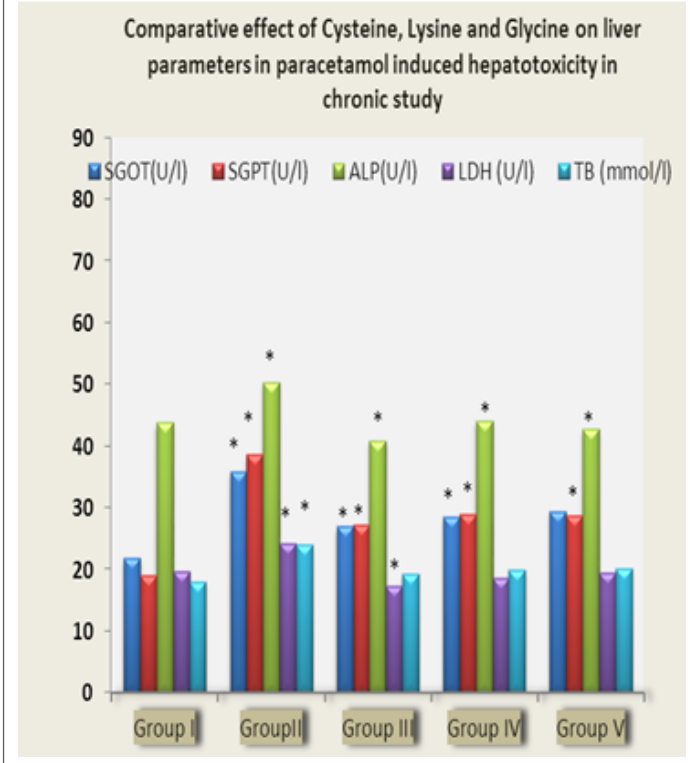

Figure 1B: Comparative effect of Cysteine, Lysine and Glycine on liver parameters in paracetamol hepatotoxicity in chronic study.

Dependent Variable	(I) Groups	(J) Groups	Acute		Chronic	
			Mean Difference (I-J)	Sig.	Mean Difference (I-J)	Sig.
SGOT	Group I	Group II	-16.16333*	.001	-19.56500*	.000
		Group III	5.31667	.563	-8.54000	.052
		Group IV	-5.54667	.523	-9.84000*	.019
		Group V	-9.57667	.078	-9.72333*	.021
	Group II	Group III	21.48000*	.000	11.02500*	.007
		Group IV	10.61667*	.041	9.72500*	.021
		Group V	6.58667	.355	9.84167*	.019
	Group III	Group IV	-10.86333*	.035	-1.30000	.991
		Group V	-14.89333*	.002	-1.18333	.994
	Group IV	Group V	-4.03000	.780	.11667	1.000
SGPT	Group I	Group II	-13.47167*	.000	-14.06467*	.000
		Group III	4.54000	.196	-5.09333	.272
		Group IV	6.26667*	.035	-6.59500	.090
		Group V	-4.50000	.203	-7.44333*	.044
	Group II	Group III	18.01167*	.000	8.97133*	.011
		Group IV	19.73833*	.000	7.46967*	.043
		Group V	8.97167*	.001	6.62133	.088
	Group III	Group IV	1.72667	.911	-1.50167	.973
		Group V	-9.04000*	.001	-2.35000	.876
	Group IV	Group V	-10.76667*	.000	-.84833	.997
ALP	Group I	Group II	-14.78500*	.012	-6.60833*	.000
		Group III	37.65000*	.000	2.92167	.153
		Group IV	25.40833*	.000	-.34000	.999
		Group V	7.10333	.448	.97667	.929
	Group II	Group III	52.43500*	.000	9.53000*	.000
		Group IV	40.19333*	.000	6.26833*	.000
		Group V	21.88833*	.000	7.58500*	.000
	Group III	Group IV	-12.24167*	.049	-3.26167	.090
		Group V	-30.54667*	.000	-1.94500	.520
	Group IV	Group V	-18.30500*	.002	1.31667	.818
LDH	Group I	Group II	-10.12983*	.000	-4.47667	.263
		Group III	6.44250*	.019	2.47167	.782
		Group IV	6.40417*	.019	1.15833	.983
		Group V	4.85017	.113	.25667	1.000
	Group II	Group III	16.57233*	.000	6.94833*	.027
		Group IV	16.53400*	.000	5.63500	.099
		Group V	14.98000*	.000	4.73333	.215
	Group III	Group IV	-.03833	1.000	-1.31333	.972
		Group V	-1.59233	.917	-2.21500	.841
	Group IV	Group V	-1.55400	.924	-.90167	.993
Total Bilirubin	Group I	Group II	-.43500*	.017	-.34100	.655
		Group III	.26500	.258	-.06767	.999
		Group IV	.23500	.370	-.10600	.993
		Group V	.10667	.916	-.10933	.992
	Group II	Group III	.70000*	.000	.27333	.808
		Group IV	.67000*	.000	.23500	.878
		Group V	.54167*	.002	.23167	.884
	Group III	Group IV	-.03000	.999	-.03833	1.000
		Group V	-.15833	.726	-.04167	1.000
	Group IV	Group V	-.12833	.849	-.00333	1.000

Table 3: Multiple comparision of treated groups in acute and chronic study

1. Group I: Control Group, Group II: Toxic Group, Group III: Cysteine treated group, Group IV: Lysine treated group, Group V: Glycine treated Group

* represents P<0.05

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(18% ↓) level,LDH (19% ↓) and total bilirubin (16% ↓) while significant decrease ($p<0.05$) in the level of SGPT (25% ↓), ALP (15% ↓).

Discussion

Drug induced liver injury (DILI) is a major limiting factor in use of drugs for therapeutic purpose. It is the most common disease condition of the liver [13]. The hepatotoxins have a unique pathway though which they damage liver cells. Individual factors also play a key role to make a patient susceptible for drug induced liver injury (DILI). By knowing these factors through advancement of toxicogenomics and proteomics, damage can be minimized [14]. A number of agents have already been marketed to prevent drug induced hepatotoxicity. Among them, amino acids play a central role in preventing cell damage. In this study, comparative effectiveness of cysteine, lysine and glycine to combat hepatotoxins was observed.

In Table 3, comparative study suggests that both cysteine and lysine are equally effective depending upon the pathways suggested below but glycine was not equally effective in reducing SGOT levels, however glycine plays an important role in hepatic inflammatory pathological conditions. In cysteine treated group (Group III), highly significant ($P<0.05$) decrease in the levels of SGPT, SGOT, ALP, LDH and bilirubin was observed in both acute and chronic toxicity study. Cysteine is required for synthesis of glutathione and PAPS (3-phosphoadenosine-5-phosphosulphate). PAPS is required for sulfation of paracetamol while glutathione is required for detoxification of NAPQI. So cysteine prevents paracetamol induced hepatotoxicity by shifting paracetamol metabolism towards safer side [15].Glutathione possess antioxidant property by reducing activity of reactive oxygen species. Cysteine also recovers the body from oxidative stress by increasing level of gamma glutamyl cysteine ligase enzyme which is required for glutathione synthesis [9]. Lysine treated group (group-IV) also showed a similar significant reduction in levels of SGOT and LDH, very significantly reduction in the level of SGPT while a highly significant reduction in ALP level. L-N^6-(1-iminoethyl)-lysine (L-NIL) is a lysine derivative. It has also been suggested that L-NIL acts on active site of iNOS enzyme and suppresses its activity. L-NIL prevents iNOS mRNA expression by inactivating NF-B, which regulates iNOS mRNA expression. The L-NIL also maintained GSH levels by reducing NO production in the liver because reactive nitrogen species are scavenged by GSH [16]. It also restores the perfusion of sinusoids. L-NIL also prevents the hepatic insult by reducing the bioactivation of paracetamol [17].

Treatment with glycine (Group V) showed a little different result as shown in (Table 3) and (Figure 1). In both acute and chronic study, only the level of SGPT was significantly reduced. Glysine being a part of Glutathione (GSH), a tripeptide of glutamic acid, cysteine and glycine, protects cells from free radical associated oxidative stress [18]. Glycine also improves survival in rat liver transplantation [19]. Glycine prevents phagocytosis, hepatocellular injury, fibrosis and apoptosis caused by intoxication with hepato toxic drugs [20]. Glycine also possesses antiperoxidative effects by restoring the activity of superoxide dismutase, catalase and glutathione peroxidase thus protecting cells from oxidative stress of NAPQI. Glycine also maintains lipid peroxidation (LPO) level of liver [1]. This study also confirms the role of glycine in maintaining the antioxidant activity of liver. In paracetamol induced hepatotoxicity, kupffer cells are activated resulting in release of cytokines. Glycine gated chloride channels are located on kupffer cells. Thus cytokines production is inhibited as glycine inactivates kupffer cells by hyperpolarizing cellular membrane. So glycine possesses anti-inflammatory activity and improves hepatic pathologic conditions [21]. Glycine also increases portal blood flow, production of bile, the hepatic microcirculation which improves cytochrome P450 activity and significantly reduces the levels of ALT,AST during hepatocellular injury [22].

Conclusion

It is inferred that cysteine, lysine and glycine markedly reduce the elevated liver enzymes in paracetamol induced hepatotoxic rabbits. In both acute and chronic toxicity study, there was significant reduction in liver enzymes in cysteine and lysine treated groups as compared to the glycine treated animals.

Conflict of Interest

It is declared that there is no conflict of interest.

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