Comparison of Hepatic Parameters Following Administration of Antihypertensive, Hypolipidemic and Hypoglycemic Drugs

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Abstract: The risk of additive effects of drugs has remained a continuous concern while prescribing more than one drug to a patient, and it becomes more of a problem when the patient suffers from various diseases simultaneously. In this reasearch the drug taking pattern of elderly patients was kept in mind and the antihyperlipidemic, oral hopoglycemic and antihypertensive commonly prescribed in combinations or as individual agents were given to the rabbits for period of two months and their effects on liver function tests were noted. As compared to control rabbits, Acarbose and Glibenclamide decreased Direct bilirubin (DBR), where as Lisinopril and Amlodipine increased it ($P<0.05$). Atorvastatin and Amlodipine increased Total bilirubin (TBR) ($P<0.05$). Acarbose and Metformin increased, where as Atorvastatin decreased Glutamic-Pyruvic Transaminase (GPT) ($P<0.05$). Metformin and Lisinopril decreased ($P<0.05$) where as Losartan increased ALP(alkaline phosphatase) ($P<0.005$). Losartan and Atorvastatin increased Gamma Glutamyl Transferase γ-GT ($P<0.005$).

Keywords: Hypoglycemia, hyperlipidemia, antihyperlipidemic, hypoglycemic, liver function tests.

INTRODUCTION

Older people take more drugs than younger ones since they are more likely to develop different kinds of disease affecting them chronically including hypertension, diabetes, hyperlipidemia and arthritis. All most in all chronic illness the medicines are used to manage disease for many years. While few medicines are taken by them for short period of time along with other drugs already in use for years, these are over the counter medicine either for pain, or infections. According to an average usually more than 4 medicines are taken for chronic illnesses while 2-3 non-prescriptions are also included with them, which develop possibility of serious life threatening toxicities [1].

Some of these drugs really work to improve health of older however; their side effects produce damaging effects to vital organ and system [2].

Hepatotoxicity

The major site for metabolism of drugs is the liver. Drugs taken by oral route undergoes through first pass metabolism in liver; it is therefore exposed to the initial compounds as well as their metabolites formed in liver increasing the threat for drug induced toxicities, however hepatic damages are not very common in patients. But some of the drugs may cause severe injury for example, hepatic failure induced by halothane is as high as 50% other drugs induce liver injuries including anti-tubercular, phenylbutazone and salicylates. All Industrial, laboratory, natural and herbal chemicals can induce hepatic toxicities, these agents are called hepatoxins. Thousands of chemical compounds produce injury to the liver which can be interpreted by examination of liver enzymes in blood [3]. 5% of the hospitalizations and more than 50% acute liver failure results due to drug induced hepatotoxicities increasing mortality and morbidity rate. Many drugs have been withdrawn from Market or having limitation for use due to the possibility of drug induce liver injury e.g. troglitazone, bromfenac, pemoline, tolcapone, trovafloxacin and benoxaprofen [4].

Drug Induced Hepatotoxicity

Drugs produce variety of liver injury some of the types are shown in Figure **1** and described below [5].

1. Interference with bilirubin levels: uptake, excretion and conjugation:

   Some of the drugs like rifampicin may interfere with the excretion, uptake and conjugation of bilirubin and may cause hyperbilirubinaemia [7].

2. Cytotoxic injury:

   Damage to the liver parenchyma [8].

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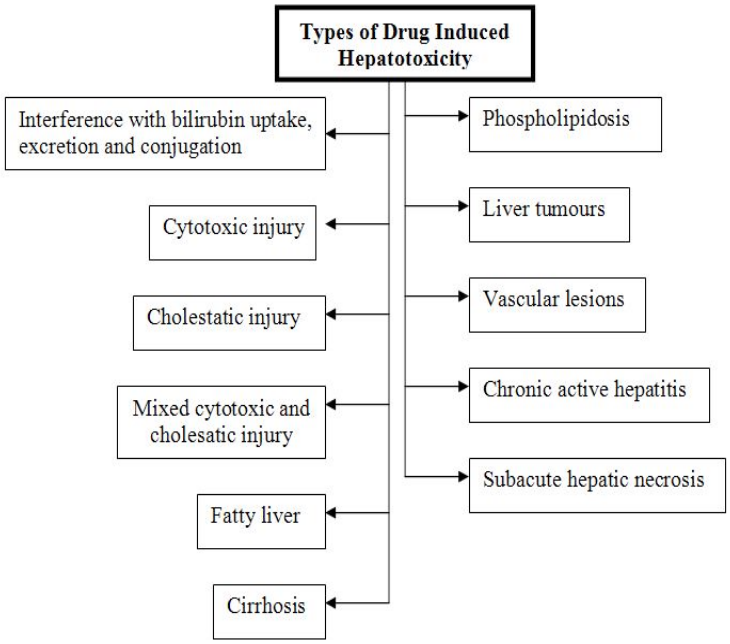

Figure 1: Types of Drug Induced Hepatotoxicity [6].

3. Cholestatic injury:

   This shows blockage in bile flow and jaundice which is similar to biliary obstruction. Less severe injury manifested as obstruction in bile duct resulting blockage in bile flow [9].

4. Mixed cytotoxic and cholesatic injury:

   Amino derivatives of salicylic acid may cause mix injury i.e. Cytotoxic hepatic damage along with cholestasis [10].

5. Fatty liver:

   Chronic liver injury where fat deposition occurs within the interstitial cell spaces but it is type of reversible injury [11].

6. Cirrhosis:

   Chronic liver damage where scar tissue replaces with healthy liver tissues resulting is blockage of blood flow to liver, the major causes of death [12].

7. Phospholipidosis:

   Characterized by filling of hepatocytes with fats [13].

8. Liver tumours:

   Neoplastic lesions like benign tumour (adenoma) and carcinom. Adenomas are associated with the use of anabolic steroids [14].

9. Vascular lesions:

   Occlusion in hepatic vein due to thromboembolism and it results in liver damage. Commonly it occurs due to the use of cortisteroids [15].

10. Chronic active hepatitis:

    Inflammatory necrosis of liver due to the use of drugs.

11. Subacute hepatic necrosis:

    A progressive bridging necrotic damage of liver with jaundice and cirrhosis in later stage due to the use of a herbal medicine like Chaparral Leaf as well as due to piroxicam and other drugs [13].

It is seen that women are more susceptible to drug induced toxicity than men but the reason is still unclear. several substances like phenobarbital, phenytoin, ethanol, grapefruit juice, and cigarette smoke induce hepatic enzymes and alter plasma levels of these drugs, resulting in extrahepatic adverse effects [7, 10]. Enzyme enhancers play major role in increasing hepatotoxicity, as substrate competition occurs when ethanol is used in combination with acetaminophen. Ethanol reduces rate of metabolism of acetaminophen to its byproduct those are toxic and harmful. Interaction of ethanol (the enzyme inducer) with acetaminophen enhances liver damage [11]. And when ethanol is withdrawn the enzyme cytochrome P-450 which was slowed down in presence of Ethanol enhances the formation of toxic metabolites.

Chance of hepatic injury further enhance due to the drugs affecting liver function if patient is already suffering due to chronic liver disease. In liver cirrhosis patients rate clearance of drug may be reduced up to 50 percent. Therefore, all medicine inducing hepatoxicity should be taken with extreme caution [16].

MATERIALS AND METHODS

Sample Collection

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

Biochemical Toxicity Testing

Blood samples collected in siliconised glass tube [17] and plasma was immediately separated out by centrifugation at 3000 rpm for 15 min to yield platelet poor plasma by Humax 14 K (Germany).

Hepatic Parameters

a. Bilirubin (Total and Direct – TBR and DBR)

Method

Bilirubin **(**Total and Direct) in the serum was estimated by photometric test [18].

b. Glutamic-Pyruvic Transaminase (GPT)

Method

GPT in the serum was estimated by kinetic method with reference to the International Federation of Clinical Chemistry [19].

c. Gamma Glutamyl Transferase (γ-GT)

Method

γ -GT in the serum was estimated by colorimetric method [20 and 21].

d. Alkaline Phosphatase (ALP)

Method

Method use to the recommendation of international Federation of Clinical Chemistry [22].

Statistical Analysis

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. Data was reported as mean ± standard error to the mean with 95% confidence interval and p-values were observed.

RESULT

Table **1** reveals the comparison of DBR, TBR, GPT, ALP, and γ-GT levels between control animals and animals kept on individual drugs for a period of 60 days.

Animals of group received **Acarbose** revealed significant decrease in DBR and significant elevation in GPT levels i.e. 0.20±0.02 mg/dl and 84.3±1.38µ/l with respect to control i.e. 0.50±0.45 mg/dl and 60.1± 0.31 µ/l respectively. Conversely there was no significant change in the levels o Animals received **Glibenclamide** showed significant decrease in DBR level i.e. 0.14±0.01and animals received Lisinopril and Amlodipine individually revealed significant elevation in DBR levels i.e. 0.73±0.03 mg/dl and 0.79±1.42 mg/dl with respect to control.

Animals received **Metformin** revealed highly significant increased and significant decrease in the levels of GPT and ALP i.e. 126.1±3.66 µ/l and 21.51±1.13 µ/l with respect to control i.e. 60.1± 0.31µ/l and 46±3.14 µ/l respectively. Similarly animals received **Lisinopril** and **Losartan** individually revealed significant decrease and highly significant increase in the levels of ALP i.e. 20.93±0.57 µ/l and 98.34±1.34 µ/l with respect to control, while animal received losartan also showed highly significant increase in the level of G-GT i.e. 41.08±0.03 µ/l with respect to control.

Animals received **Atorvastatin** individually showed significant increase and highly significant increase in the levels of TBR and G-GT i.e. 0.21±0.01 µ/l and 12.99±1.09 µ/l with respect to control, however, significant decrease in the level of GPT i.e. 44.21±2.86 µ/l with respect to control. While the animals received **Amlodipine** revealed significant elevation in the levels of DBR and TBR i.e. 0.79 ± 1.42 and 0.31±0.25 µ/l respectively with respect to control. Conversely there was no significant alteration in other hepatic parameters at the end of dosing.

DISCUSSION

Liver plays a major role in metabolizing and clearing metabolites from the body due to which chances of hepatic toxicity increases either when drugs are given in overdoses or in combinations. These toxicities are manifested by biochemical and histo-pathological changes [23]. Various biochemical markers such as

Table 1: Comparison of Hepatic Parameters Following 60 Days Administration of Individual Drugs

Parameters/Groups	DBR (mg/dl)	TBR (mg/dl)	GPT (µ/l)	ALP (µ/l)	γ-GT (µ/l)
Control	0.50 ± 0.45	0.07 ± 0.34	60.10 ± 0.31	46.00 ± 3.14	5.55 ± 0.46
Acarbose	0.20 ± 0.02*	0.11 ± 0.01	84.30 ± 1.38*	41.10 ± 1.86	5.70 ± 0.84
Glibenclamide	0.14 ± 0.01*	0.03 ± 0.02	73.70 ± 1.18	34.30 ± 1.98	4.04 ± 0.86
Metformin	0.35 ± 0.04	0.16 ± 0.04	126.10 ± 3.66**	21.51 ± 1.13*	5.65 ± 2.20
Lisinopril	0.73 ± 0.03*	0.08 ± 0.04	76.34 ± 1.90	20.93 ± 0.57*	7.98 ± 0.67
Losartan	0.40 ± 0.01	0.04 ± 0.12	74.0 ± 9.60	98.34 ± 1.34**	41.08 ± 0.03**
Atorvastatin	0.50 ± 0.10	0.21 ± 0.01*	44.21 ± 2.86*	34.20 ± 1.08	12.99 ± 1.09**
Amlodipine	0.79 ± 1.42*	0.31 ± 0.25*	59.65 ± 0.32	36.50 ± 0.01	7.56 ± 0.36

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

billirubin, GPT, ALP and γ-GT help to indicate liver damages [24].

In the present study animals received acarbose, glibenclamide, metformin, lisinopril, losartan, atorvastatin & amlodipine, as individual drugs they did not show any significant changes in over all biochemical indicators of hepatic toxicity. However there were some changes in few biochemical indicators of hepatic tocxicity such as animal received acarbose showed decrease in direct bilirubin level while the level of TBR was increased which was insignificant with respect to control. It is evident from several studies that either bilirubin is raised in hepatic disease or may be drug induced, which is reversed after discontinuation of the drug [25]. Similarly the level of GPT was also found to be decreased significantly in these animals. However the changes found may be of transient nature and may not be associated with any hepatotoxic effect of drugs [26].

Animal received glibenclamide did not show any significant change in hepatic enzymes except decrease in DBR it may be due to cholestasis as glibenclamide had potential to induce hepatotoxicity when used for long period, however such changes are infrequent and reversible [27].

Animals received metformin showed highly significant increase in GPT and significant decrease in ALP, although it has been reported in several studies that metformin help to attenuate the liver damage induce by certain other chemical [28] but can rarely cause hepatic injury which may be associated with prolong use of the drug [29].

Chronic use of losartan is associated with liver fibrosis, in present study losartan showed significant increase in ALP & γ-GT.

Atorvastatin is reported to be associated with liver injury on long term use [27-29]. The results of present study showed highly significant increase in γ-GT level and significant increase in TBR, however GPT levels were decrease significantly.

Amlodipine although rarely associated with liver damage but few reports which reveals that it is associated with reversible cholestatic liver injury [30]. While in present study group received amlodipine showed significant increase in DBR and TBR levels which may be associated with cholestatic liver damage while changes in the levels of rest of the enzymes remain insignificant [31].

CONCLUSION

It is concluded from the study that the drugs use for the treatment of diabetes, hypertension and hyperlipidemia are effecting liver functions therefore it is necessary to use these drugs with caution in patients having any hepatic dysfuntion or their hepatic funtion must be monitored during use of these drugs.

In continuation of this research, we will discuss effects of combinations of these drugs on liver function as well as histopathological changes in hepatocytes, in our next article.

REFERENCES

[1] Yamamoto BK, Moszczynska A, Gudelsky GA. Amphetamine toxicities: classical and emerging mechanisms. Ann NY Acad Sci 2010; 1187: 101-21. http://dx.doi.org/10.1111/j.1749-6632.2009.05141.x

[2] Santoso JT, Lucci JA 3rd, Coleman RL, Schafer I, Hannigan EV. Saline, mannitol, and furosemide hydration in acute cisplatin nephrotoxicity: a randomized trial. Cancer Chemother Pharmacol 2003; 52(1): 13-8. http://dx.doi.org/10.1007/s00280-003-0620-1

[3] McDonald GB, Frieze D. A problem-oriented approach to liver disease in oncology patients. Gut 2008; 57: 987-1003. http://dx.doi.org/10.1136/gut.2007.131136

[4] Bolesta S, Roslund BP. Elevated hepatic transaminases associated with telithromycin therapy: A case report and literature review. Am J Health Syst Pharm 2008; 65: 37-41. http://dx.doi.org/10.2146/ajhp070164

[5] Thomas MB, Abbruzzese JL. Opportunities for Targeted Therapies in Hepatocellular, Carcinoma. JCO 2005; 23: 8093-108. http://dx.doi.org/10.1200/JCO.2004.00.1537

[6] Juurlink DN, Andrade RJ, Lucena MI, *et al*. Drug-Induced Hepatotoxicity. NEJM 2003; 349: 1974-76. http://dx.doi.org/10.1056/NEJM200311133492021

[7] Usui T, Mise M, Hashizume T, Yabuki M, Komuro S. Evaluation of the Potential for Drug-Induced Liver Injury Based on *in vitro* Covalent Binding to Human Liver Proteins. Drug Metab Dispos 2009; 37: 2383-92. http://dx.doi.org/10.1124/dmd.109.028860

[8] DeSanty KP, Amabile CM. Antidepressant-Induced Liver Injury. Ann Pharmacother 2007; 41: 1201-11. http://dx.doi.org/10.1345/aph.1K114

[9] Xu JJ, Henstock PV, Dunn MC, Smith AR, Chabot JR, de Graaf D. Cellular Imaging Predictions of Clinical Drug-Induced Liver Injury. Toxicol Sci 2008; 105: 97-105. http://dx.doi.org/10.1093/toxsci/kfn109

[10] Petri N, Bergman E, Forsell P, *et al*. First-Pass Effects Of Verapamil On The Intestinal Absorption And Liver Disposition Of Fexofenadine In The Porcine Model. Drug Metab Dispos 2006; 34: 1182-89. http://dx.doi.org/10.1124/dmd.105.008409

[11] Clark CJ, Creighton S, Portmann B, Taylor C, Wendon JA, Cramp ME. Acute liver failure associated with antiretroviral treatment for HIV: a report of six cases. J Hepatol 2002; 36: 295-301. http://dx.doi.org/10.1016/S0168-8278(01)00291-4

[12] Carrillo-Jimenez R, Nurnberger M. Celecoxib-induced acute pancreatitis and hepatitis: a case report. Arch Intern Med 2000; 160: 553-54. http://dx.doi.org/10.1001/archinte.160.4.553

[13] Gonzalez de la Puenta MA, Calderon E, Espinosa R, Rincon M, Varela JM. Fatal hepatotoxicity associated with enalapril. Ann Pharmacother 2001; 35: 1492-92. http://dx.doi.org/10.1345/aph.1A055

[14] Capella D, Bruguera M, Fugueras A, Laporte J. Fluoxetine-induced hepatitis: why is postmarketing surveillance needed? Eur J Clin Pharmacol 1999; 55: 545-46. http://dx.doi.org/10.1007/s002280050671

[15] Graham DJ, Staffa JA, Shatin D, *et al*. ncidence of hospitalized rhabdomyolysis in patients treated with lipid-lowering drugs. JAMA 2004; 292(21): 2585-90. http://dx.doi.org/10.1001/jama.292.21.2585

[16] Conjeevaram HS, Kleiner DE, Everhart JE, *et al*. Virahep-C Study Group. Race, insulin resistance and hepatic steatosis in chronic hepatitis C. Hepatology 2007; 45(1): 80-7. http://dx.doi.org/10.1002/hep.21455

[17] Heyns AD, van den Berg DJ, Kleynhans PH, du Toit PW. Unsuitability of evacuated tubes for monitoring heparin therapy by activated partial thromboplastin time. J Clin. Pathol 1981; 34(1): 63-8. http://dx.doi.org/10.1136/jcp.34.1.63

[18] Jendrassik L, Grof P. Vereinfachte photometrische Methodern fur Bestimmung des Blutbilirubins. Biochemische Zeitschrift 1938; 81: 297-301.

[19] Bergmeyer HU, Bowers GN, Horder M, Moss DW. Provisional recommendation on IFCC methods for the measurement of catalytic concentrations of enzymes. Part 2. IFCC method for aspartat aminotransferase. Clin Chim Acta 1976; 70(2): 19-42. http://dx.doi.org/10.1016/0009-8981(76)90437-X

[20] Szasz G, Persijin JP. A kinetic colorimetric method for determination of G-glutamyl transpeptidase in serum. Zeitschrift fur klinische chemie und klinische biochemie 1974; 12: 228-32.

[21] Persijin JP, Van der silk W. A new method for determination of GGT. J Clin Chem Clin Biochem 1976; 4: 421.

[22] Tietz NW, *et al*. J Clin Chem Clin Biochem 1983; 21: 731-48.

[23] Cosgrove BD, Alexopoulos LG, Saez-Rodriguez J, Griffith LG, Lauffenburger DA. A multipathway phosphoproteomic signaling network model of idiosyncratic drug- and inflammatory cytokine-induced toxicity in human hepatocytes. Conf Proc IEEE Eng Med Biol Soc 2009; 5: 452-5.

[24] Jaeschke H, Gores GJ, Cederbaum AI, Hinson JA, Pessayre D, Lemasters JJ. Mechanisms of hepatotoxicity. Toxicol Sci 2002; 65(2): 166-76. http://dx.doi.org/10.1093/toxsci/65.2.166

[25] Sasaki T, Fujikane Y, Ogino Y, Osada K, Sugano M. Hepatic function and lipid metabolism are modulated by short-term feeding of cholesterol oxidation products in rats. J Oleo Sci 2010; 59(9): 503-7. http://dx.doi.org/10.5650/jos.59.503

[26] Ina Bergheim LG, Anne Davis M, Lambert JC, *et al*. Metformin Prevents Alcohol-Induced Liver Injury in the Mouse: Critical Role of Plasminogen Activator Inhibitor-1. Gastroenterology 2006; 130(7): 2099-12. http://dx.doi.org/10.1053/j.gastro.2006.03.020

[27] Ansede JH, Smith WR, Perry CH, St Claire RL 3rd, Brouwer KR. An *in vitro* assay to assess transporter-based cholestatic hepatotoxicity using sandwich-cultured rat hepatocytes. Drug Metab Dispos 2010; 38(2): 276-80. http://dx.doi.org/10.1124/dmd.109.028407

[28] Adeneye AA, Benebo AS. Oral metformin-ascorbic acid co-administration ameliorates alcohol-induced hepatotoxicity in rats. Nig Q J Hosp Med 2007; 17(4): 155-9.

[29] Nammour FE, Fayad NF, Peikin SR. Metformin-induced cholestatic hepatitis. Endocr Pract 2003; 9(4): 307-9.

[30] Segura J, García-Donaire JA, Ruilope LM. Calcium Channel Blockers and Renal Protection:Insights from the Latest Clinical Trials. J Am Soc Nephrol 2005; 16: S64-S66. http://dx.doi.org/10.1681/ASN.2004110969

[31] Zinsser P, Meyer-Wyss B, Rich P. Hepatotoxicity induced by celecoxib and amlodipine. Swiss Med Wkly 2004; 134: 201.

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