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

Afshan Siddiq1,*, Rafeeq Alam Khan2 and Afaq Ahmed Siddiqui3

1Department of Pharmacology, Faculty of Pharmacy, University of Karachi, Pakistan
2College of Medicine, Department of Basic Medical Sciences, King Saud bin Abdulaziz University of Health Sciences, King Abdulaziz Medical City Jeddah, Kingdom of Saudia Arabia
3Department of Pharmaceutical Chemistry, Faculty of Pharmacy, University of Karachi, Pakistan

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 research the drug taking pattern of elderly patients was kept in mind and the antihyperlipidemic, oral hypoglycemic 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 hyperbilirubinemia [7].

2. Cytotoxic injury:
   Damage to the liver parenchyma [8].
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 cholestatic 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 hepatotoxicity 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±1.38 μ/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 of Animals received Glibenclamide showed significant decrease in DBR level i.e. 0.14±0.01 and 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± 0.31 μ/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. 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
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 toxicity 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**


