ORIGINAL PROF-622

# HEPATIC INSUFFICIENT PATIENTS;

## EFFECT OF ALPRAZOLAM THERAPY ON LFT's

***DR. AHMAD DANYAL**
***DR. ABIRA NAZIR**
***DR. KHALID MAHMOOD QURESHI**

*Assistant Professors of Pharmacology
Nishter Medical College Multan.

***Dr. Roohi Manzoor Khan***
Professor of Pharmacology
Nishter Medical College Multan.

**ABSTRACT**

Alprazolam is principally metabolized by the liver. The effect of alprazolam therapy on LFT's of fifteen hepatic insufficient patients, was assessed and compared with five control subjects. Alprazolam, in a dose of 0.25 mg, B.D., was given for 21 days to fifteen male and female patients, with age group from 24-42 years, having weight from 45-60 Kg, and compared with five control subjects. The mean values of direct bilirubin in control and hepatic insufficient patients were 0.25 mg% and 4.71 mg% on day zero, while on day 21, the values were 0.52 mg% and 4.42 mg%, respectively. Total bilirubin was 0.76 mg% and 6.28 mg% on day zero and 0.53 mg% and 5.54 mg% on day 21 in control and hepatic insufficient patients, respectively. The mean values of alkaline phosphatase (ALP) were 154.50 U/L on day zero and 169.20 U/L on day 21 in control group, while these were 626.40 U/L on day zero and 677.70 U/L on day 21, in hepatic insufficient patients. The mean values of serum glutamic pyruric trainsaminase (SGPT) were 26 U/L on day zero and 27.40 U/L on day 21 in control group, while these were 48.0 U/L and 60.60 U/L on day 21 in hepatic insufficient patients. From above data, it was concluded that long term alprazolam therapy have no effect on direct and total bilirubin but the values of ALP and SGPT increased.

***KEY WORDS:*** Alprazolam, Direct bilirubin, Total bilirubin, Alkaline phosphatase, Serum glutamatic pyruvate transaminase.

## INTRODUCTION

Alprazolam is a widely used triazolobenzodiazepine. It is used as anxiolytic and for treatment of panic disorders. The drug is metabolized primarily by hepatic microsomal oxidation, yielding alphahydroxy and 4-hydroxy alprazolam as principal initial metabolites[1].

In patients with cirrhosis, adequate treatment of insomnia and anxiety has remained controversial. Generally, hepatologists agree that in some cirrhotics ordinary doses of sedatives may lead to disorientation and coma[2].

Acute and chronic liver diseases have the potential to alter other determinants of drug disposition in addition to drug metabolizing ability. Quantitative and possible qualitative changes in plasma protein binding are well established in liver disease. Depending on the extent of any such changes, the systemic clearance and distribution of total drug may be affected. Increased volume of distribution was observed in the cirrhotics

which was not present when expressed in terms of unbound drug[3].

As liver diseases affect pharmacokinetics of alprazolam, so we have decided to evaluate weather the bilirubin, ALP and SGPT are also altered in long term therapy of alprazolam or remain unchanged.

## MATERIAL & METHODS

**Subjects:**
Five normal, healthy subjects (two males and three females) and 15 hepatic patients (8 male & 7 female) were selected for the study. The hepatic patients were diagnosed by typical clinical findings and biochemical laboratory tests. Age range was 24-45 years and weight range 45-60 Kg in both control and hepatic groups. All volunteers were informed about the aim of study who gave their written consent.

**Study Design:**
Tab. Alprazolam in a dose of 0.25 mg, (Tab.Xanax by Upjohn), P.O. was given twice a day in both groups. Alprazolam was started at day zero and continued in the same dose for 21 days.

Liver function tests were assessed on day zero and day twenty one. Serum bilirubin , both total and direct, was measured photometrically[4] on auto analyzer (Hitachi 2000). Kit No. 123927 was provided by the Boehringer Mannheim.

Alkaline phosphatase was measured (MacGilchrist et al., 1986) photometrically on auto-analyzer (Hitachi 2000). Kit No. 14858 was provided by Merck. Similarly SGPT was measured (MacGilcrist et al., 1986) photometrically on auto-analyzer (Hitachi 2000). Kit No. 3040113205, was provided by Eli Tech diagnostics. Statistical analysis was done by applying students (t) test.

## RESULTS

**Table-I. Table of LFT's in different groups on day 0 and 21.**

**i). CONTROL**

| | DAY 0 | | | | DAY 21 | | | |
|---|---|---|---|---|---|---|---|---|
| | Bilirubin (mg%) | | ALP(U/L) | SGPT(U/L) | Bilirubin (mg%) | | ALP(U/L) | SGPT(U/L) |
| No. | Direct | Total | | | Direct | Total | | |
| 1 | 0.26 | 0.69 | 143 | 21 | 0.30 | 0.78 | 182 | 29 |
| 2 | 0.22 | 0.60 | 113 | 30 | 0.31 | 0.28 | 101 | 31 |
| 3 | 0.16 | 0.51 | 156 | 13 | 0.79 | 0.32 | 187 | 21 |
| 4 | 0.14 | 0.36 | 245 | 47 | 0.21 | 0.89 | 188 | 38 |
| 5 | 0.51 | 1.64 | 115 | 19 | 1.00 | 0.41 | 188 | 18 |
| Mean | 0.25 | 0.76 | 154.40 | 26 | 0.52 | 0.53 | 169.20 | 27.40 |
| S.D. | 0.13 | 0.45 | 48.18 | 11.80 | 0.31 | 0.25 | 34.17 | 7.17 |
| S.E.M. | 0.05 | 0.20 | 21.50 | 5.29 | 0.14 | 0.11 | 15.28 | 3.20 |

**ii). HEPATIC PATIENTS**

| | DAY 0 | | | DAY 21 | | |
|---|---|---|---|---|---|---|
| | Bilirubin (mg%) | ALP(U/L) | SGPT(U/L) | Bilirubin (mg%) | ALP(U/L) | SGPT(U/L) |

| ii). HEPATIC PATIENTS | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| No. | Direct | Total | | | Direct | Total | | |
| 1 | 20.07 | 22.83 | 1340 | 11 | 7.18 | 8.03 | 509 | 23 |
| 2 | 1.10 | 2.35 | 171 | 33 | 1.80 | 2.20 | 308 | 40 |
| 3 | 3.87 | 4.08 | 328 | 29 | 1.70 | 3.88 | 348 | 38 |
| 4 | 6.53 | 8.28 | 752 | 68 | 6.99 | 9.02 | 798 | 65 |
| 5 | 3.70 | 5.28 | 289 | 48 | 10.03 | 10.08 | 886 | 92 |
| 6 | 3.82 | 4.23 | 852 | 72 | 3.52 | 4.88 | 728 | 80 |
| 7 | 1.97 | 2.98 | 728 | 61 | 2.12 | 3.70 | 829 | 71 |
| 8 | 3.03 | 4.89 | 802 | 42 | 2.03 | 3.28 | 938 | 80 |
| 9 | 3.57 | 5.02 | 878 | 55 | 4.02 | 4.49 | 869 | 60 |
| 10 | 2.48 | 4.38 | 429 | 43 | 1.78 | 3.29 | 385 | 48 |
| 11 | 6.48 | 7.29 | 512 | 41 | 6.89 | 8.39 | 582 | 48 |
| 12 | 2.83 | 3.82 | 582 | 62 | 1.98 | 2.22 | 628 | 78 |
| 13 | 4.30 | 8.04 | 628 | 72 | 0.05 | 1.02 | 289 | 43 |
| 14 | 4.80 | 5.82 | 784 | 51 | 5.01 | 6.82 | 889 | 52 |
| 15 | 2.13 | 5.02 | 321 | 32 | 11.20 | 11.80 | 1180 | 91 |
| Mean | 4.71 | 6.28 | 626.40 | 48.00 | 4.42 | 5.54 | 677.70 | 60.60 |
| S.D. | 4.35 | 4.71 | 290.10 | 16.92 | 3.22 | 3.14 | 259.00 | 20.23 |
| S.E.M. | 1.12 | 1.21 | 74.91 | 4.36 | 0.83 | 0.81 | 66.89 | 5.22 |

ALP. (Alkaline Phosphatase, SGPT. (Serum Glutamatic Pyruvate Transminase)

**Table-II. Comparison between different parameters in normal and hepatic patients.**

| No. | Parameters | DAY 0 | | | DAY 21 | | |
|---|---|---|---|---|---|---|---|
| | | Control | Hepatic | P value | Control | Hepatic | P value |
| 1 | D.Bil. (mg%) | 0.25±0.05 | 4.71±1.12 | < 0.01 | 0.52±0.14 | 4.42±0.83 | < 0.01 |
| 2 | T.Bil. (mg%) | 0.76±0.20 | 6.28±1.21 | < 0.01 | 0.53±0.11 | 5.54±0.81 | < 0.001 |
| 3 | ALP (U/L) | 154.40±2150 | 626.4±74.9 | < 0.001 | 169.20±15.28 | 677.7±66.8 | < 0.001 |
| 4 | SGPT (U/L) | 26.0±5.29 | 48.0±4.36 | < 0.001 | 27.4±3.20 | 60.6±5.22 | < 0.001 |

D.Bil. (Direct Bilirubin), T.Bil. (Total Bilirubin), ALP. (Alkaline Phosphatase), SGPT. (Serum Pyruvate Transaminase)

The mean values of direct and total bilirubin (mg%) on day zero, were 4.71±1.12 and 6.28±1.21 in hepatic patients and in controls, it was 0.25±0.05 and 0.76±0.20 respectively.

On day 21, the mean values were 4.42±0.83 and

5.54±0.81 in hepatic patients and in controls, it was 0.52±0.14 and 0.53±0.11 respectively. The mean values of ALP (U/L), were 626.40±74.91, on day zero and 677.70±66.89 on day 21, in hepatic patients and in controls. It was 154.40±21.50 on day zero and 60.60±5.22 on day 21, in hepatic patients and in controls, it was 26.0±5.29 on day zero and 27.40±3.20 on day 21 respectively.

## DISCUSSION

Drugs of the sedative/tranquilizer group are often needed in the treatment of inter-current problems in patients with hepatic insufficiency. The kinetics of most commonly used drugs in this group can be altered due to such diseases. Therapeutic efficacy and safety of such drugs can also be altered[6].

As clear from the obtained data, serum bilirubin (both total and direct), were not measured in hepatic insufficient patients which show that alprazolam therapy on this parameter. Infact it is decreased which show that these patients might have recovered from hepatic diseases spontaneously or with relevant treatment, nevertheless, it proved that prolonged treatment with alprazolam have no effect on serum bilirubin. In contrast ALP and SGPT increased tremendously during the course of 21 days regimen which initiate that these two enzymes are significantly altered in hepatic diseases and are even worsed by a course of benzodiazepines.

## CONCLUSION

Alprazolam therapy does alters liver enzymes like ALP and SGPT. If treatment is necessary in patients with impaired hepatic function, therapy should be initiated continuously to the extent that it is compatible with the degree of residual function of these organs and should be monitored very closely (Phillip. 1999).

## REFERENCES

1. Greenblatt DJ; Wright CE. Clinical pharmacokinetics of alprazolam. Therapeutic implications. Clin. Pharmacokinet. 1993; 24(6): 453-71.

2. Gul Bakti, Hans, VF; George K. Minder and Bircher, J. Mehanism of the excessive sedative response of cirrhotics to benzodiazepines: Model experiments with triazolam. Hepatology. 1987; 7(4): 629-638.

3. Kraus, JW; Desmond, PV; Marshall, JP; Johnson, RF; Schenker, S. Wilkinson, GR. Effects of aging and liver disease on disposition of lorazepam. Clin. Pharmacol. 1986; Ther. 24: 411-419.

4. MacGilchrist, AJ; Birine, GG. Cook, A. Scobie, G. Murray, T. Watkinson, G. Brobie, MJ. Pharmacokinetics and pharmacodynamics of intravenous midazolam in patients with severe alcoholic cirrhosis. 1986; Gut. 27: 190-195.

5. Philip W. Long. Internet Mental Health. 1999.

6. Thomas, GM. Soong, TC; Hans, Barryy. Renal disease, age and oxazepam kinetics. Clin. Pharmacol. Ther. 1981; 30(6): 805-809.

***Learn to obey before command.***

**Solon**