

Liver Assessment in Patients with Osteoarthritis Taking Non Steroidal Anti Inflammatory Drugs Mainly (Diclofenac Acid) Within Two to Six Weeks of Treatment

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ABSTRACT:

BACKGROUND:

Non Steroidal Anti-Inflammatory drugs (NSAIDs) are used to treat musculoskeletal disorders, inflammation and to control pain. Virtually all (NSAIDs) are capable of producing liver injury ranging from mild reversible elevation of liver enzymes to severe hepatic failure.

OBJECTIVE:

To estimate the hepatic risk associated with the use of some NSAIDs.

SUBJECT AND METHOD:

80 osteoarthritic patients were on diclofenac acid (voltarin) tablets 75 mg, 60 of them were female and 20 were male, laboratory estimation of serum alanine aminotransferase (ALT), serum aspartate aminotransferase (AST), serum alkaline phosphatase activity and total serum bilirubin (TSB) were done. For comparison age and sex matched 96 apparently healthy persons serve as controls.

RESULTS:

27 (33.75 %) of the diclofenac treated patients had some impairment of liver function tests, 66.6 % of the liver injury found in patients aged more than 50 years and 88.8 % had occurred in females. hepatocellular injury characterize most NSAIDs induced hepatotoxicity.

CONCLUSION:

The frequency of Drug induced liver injury (DILI) in diclofenac treated patients is about 33.75%.DILI is more common in females and old age.

KEYWORDS: non steroidal anti-inflammatory drugs,drug induced liver injury

INTRODUCTION:

Drug induced liver injury encompasses a spectrum of clinical disorders ranging from mild biochemical abnormalities to acute liver failure⁽¹⁾. Non steroidal anti-inflammatory drugs (NSAIDs) are frequently used and among the most common drugs associated with DILI⁽²⁾.

DILI can be predominantly hepatocellular with rise in serum aminotransferases activity or cholestatic with predominant rise in serum alkaline phosphatase (ALP) activity or mixed injury in which both serum aminotransferases and ALP activity are elevated⁽¹⁾.Cytochrome P450 is the most important family of

drug metabolizing enzyme in the liver. It represent a family of closely related 50 isoforms, six of them metabolizes 90% of the drugs⁽³⁾. Genetic variation (polymorphism) in cytochrome P450 enzymes should be considered when patients exhibit unusual sensitivity or resistance to drug effects of normal dose⁽⁴⁾.

Classification of DILI

1. Direct hepatotoxic drug reaction (intrinsic, predictable): It is dose dependant and the latent period between exposure and liver injury is usually short (after several hours)⁽⁵⁾.

2. Idiosyncratic drug reaction: In this type, the hepatic injury is unpredictable, infrequent, and dose independent. The idiosyncratic drug reaction is thought to be immunological mediated Most drug reactions involved in the hepatotoxicity belong to this group⁽⁶⁾.

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Risk factors for DILI

Old Age, female gender, liver diseases, alcohol ingestion, genetic factors, drug formulation and other co morbidities⁽⁷⁾.

Pathophysiology and Mechanisms of DILI

Free radical that causes peroxidation of membrane lipids, distortion of cell membranes, activation of apoptotic pathways, activation of some enzymes in

the cytochrome P450 system such as *CYP 2E1* leading to oxidative stress, alteration in immune response, inflammation and cytokines (like interferon, interleukin, and tumor necrotic factor)^(8,10) all play role in the development of DILI.

There are certain criteria could be used for the diagnosis of DILI as in the following table.

Table 1: Criteria for Diagnosis of DILI⁽¹¹⁾

1	Abnormalities of liver tests	Rise in ALT, AST, or bilirubin between the upper limit of normal (ULN) and twice of its value.
2	Acute liver injury	An increase more than twice the ULN of ALT or combined increase in AST or ALP and total bilirubin provided one of them was twice the ULN.
3	Hepatocellular injury	An increase of more than twice the ULN in ALT or R more than 5 (where R is the ratio of Serum activity of ALT over ALP).
4	Cholestatic injury	An increase of more than twice of ULN in ALP alone or R less than 5.
5	Mixed injury	both ALT and ALP were increased more than twice the ULN and R is between 2-5

Clinical Assessment of Drug Induced liver Injury

A causal relationship between the use of the toxin or drug and subsequent liver damage has to be established. The onset (challenge) is usually within 5-90 days and a positive dechallenge is a 50% fall in serum aminotransferases activity within 8 days of stopping the drug. Re-challenge is usually ethically impossible and dangerous⁽¹²⁾.

Non Steroidal Anti-Inflammatory drugs (NSAIDs)

NSAIDs are drugs with analgesic, antipyretic and anti-inflammatory effects,

They recently gained attention as an effective therapy for tumor patients, as they have protective effects on colon cancer⁽¹³⁾. Long term use, reduces the risk of developing Alzheimer disease⁽¹⁴⁾. Despite their wide usage, it can cause serious hepatotoxicity. NSAIDs are used in OA since they improve pain and disability. NSAIDs decrease prostaglandin synthesis by inhibiting cyclo-oxygenase (COX) enzyme; the enzyme required for conversion of arachidonic acid to prostaglandin which is a mediator of inflammation⁽¹⁵⁾.

Hepatic biotransformation⁽¹⁵⁾

Phase1 in this phase NSAIDs are metabolized by the cytochrome P450 enzymes mainly (*CYP 3A* or *CYP 2C9* or both).

Phase2 in this phase NSAIDs are conjugated and excreted in the urine or the bile.

AIM OF THE STUDY:

To estimate the hepatic risk associated with the use of some NSAIDs.

SUBJECTS AND METHODS

Subjects:

Eighty patients aged (40-70years), who had been diagnosed as OA patients were recruited from Rheumatologic Consultation Department, Baghdad Teaching Hospital in the Medical city. Collection of the data was carried during the period October 2007 to February 2008. Chronic OA patients were only included (for 6 months or more).

History regarding type, dose, and duration of NSAIDs used by every patient were taken. 80 patients were on diclofenac (voltarin) 75mg tablet once daily, 60 of them were female and 20 were male. Duration of treatment was between two to six weeks, for comparison age and sex matched 96 apparently healthy persons served as controls, patients with other medical disorders or on other drugs were excluded, patients with previous liver function abnormalities also were excluded

METHODS:

It includes laboratory analysis of ALT, AST, ALP, and total serum bilirubin (TSB) estimation all measured colorimetrically, blood samples were drawn three weeks after starting voltaren treatment.

Student t-test was applied to compare the significance of the difference in the mean values of any two groups, $P < 0.05$ was considered statistically significant, while $p < 0.001$ was considered highly significant. The correlation coefficient [r] was used to describe the association between the different parameters studied;

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RESULTS:

27 (33.75 %) of the diclofenac treated patients had some impairment of liver function tests. 88.8% of DILI had occurred in females and 66.6 % of the liver injury found in patients aged more than 50 years. ALT was abnormally elevated in 20% diclofenac treated group, acutely elevated (more than twice the ULN) in 1.25%, while AST were abnormally elevated in 15% of diclofenac group and acutely elevated (more than twice the ULN) in 1.25% of diclofenac group, ALP was abnormally elevated in 13.75%, no acute

elevation were noted. While TSB was abnormally elevated in 1.25%, with no acute elevation. By comparing the mean of ALT, AST, ALP, and TSB of the diclofenac treated OA patients with their controls; they were significantly higher in the diclofenac treated patients and became highly significant ($P < 0.001$) in females and patients aged more than 50 years ($P < 0.001$). AST correlates positively with the duration of treatment, and positive strong correlations were found between the serum activity of AST and ALT.

Table 2: Comparison between liver enzymes abnormalities in diclofenac treated osteoarthritis patients aged more than 50 years and the control of the same age group.

Characteristics	Cases Mean \pm SD	Controls Mean \pm SD	P value
Number	43	66	
Females NO (%)	35 (81.39%)	45 (68.18%)	
Age	60.07 \pm 5.30	59.52 \pm 5.44	NS
ALT(IU/L)	11.8 \pm 8.54	5.45 \pm 3.46	<0.001
AST(IU/L)	10.65 \pm 6.32	6.29 \pm 2.04	<0.001
ALP(KA/dl)	11.86 \pm 7.24	7.30 \pm 2.69	<0.001
TSB(mg/dl)	0.805 \pm 0.27	0.621 \pm 0.22	<0.001

Table 3: Comparison between liver enzymes abnormalities in diclofenac treated osteoarthritis females and the control females.

Characteristics	Cases(females) Mean \pm SD	Control (females) Mean \pm SD	P value
Number	60	62	
Age (years)	54.27 \pm 8.42	55.65 \pm 7.63	NS
ALT(IU/L)	11.44 \pm 8.18	5.35 \pm 3.43	< 0.001
AST(IU/L)	10.58 \pm 5.77	6.40 \pm 2.13	< 0.001
ALP (KA/dl)	12.19 \pm 6.47	7.05 \pm 2.44	< 0.001
TSB(mg/dl)	0.875 \pm 0.27	0.659 \pm 0.23	< 0.001

DISCUSSION:

The central role of the liver in drug metabolism set the stage for DILI. The incidence of hepatotoxicity associated with NSAIDs is low, but their wide spread use both prescription and over the counter makes it a clinically and economically important problem. Hepatotoxicity is considered a class characteristic of NSAIDs⁽¹⁶⁾. Nearly all NSAIDs have been implicated in causing liver injury. Diclofenac is reported to be more commonly associated with hepatotoxicity and the mechanism is thought to be immunological idiosyncrasy. Routine monitoring of liver function

tests have the highest likelihood of ascertainment of any liver function abnormalities, as hepatotoxicity may be asymptomatic⁽¹⁷⁾. In the present study 27 (33.75 %) of the diclofenac treated patients had impairment of some liver function tests which were asymptomatic and detected by laboratory analysis, this finding was comparable to that found by Bank and his Co-workers (1995)⁽¹⁸⁾ and Aithal and his Co-workers (1999)⁽¹⁹⁾. This study showed that 88.8% of DILI had occurred in females and 66.6 % of the liver injury found in

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patients aged more than 50 years, these findings are in agreement with Bareille *et al* (2001)⁽²⁰⁾ and Urs, *et al* (2007)⁽²¹⁾. They found that Females, age more than 50 years, autoimmune diseases and the use of other hepatotoxic drugs all increase the risk of DILI. The susceptibility of females to develop DILI may be due to differences in first-pass metabolism in the stomach, the elimination rate, or drug distribution volume in the body. In addition, estrogen has a major influence on increased proinflammatory cytokine production, which could be a major contributing factor to the increased risk of women to DILI. Most drug reactions occur in patients aged more than 50 years this may be due to increased frequency of drug exposure, multiple drug therapy, and age related changes in drug metabolism, diminished hepatic volume and blood flow. Old age associated with decreases disposition of drugs⁽⁶⁾.

ALT and AST were abnormally elevated (between the ULN and twice of its value) in 20% and 15% respectively of diclofenac treated patients, while ALP was elevated in 13.75%, this is in agreement with the result of a study done in France and Spain⁽²²⁾, to assess the hepatic risk associated with NSAIDs use. Our result is similar to that obtained in France, while that in Spain were much lower. This discrepancy between the countries may be explained by the use pattern or it may be due to genetic or environmental factors. ALT and AST were acutely elevated (more than twice the ULN) in 1.25% of diclofenac treated patients. Traversa and his colleagues (2003) found that the incidence of acute elevations was 1.5% in diclofenac treated patients⁽²³⁾, while Rostom, *et al* (2005) found the incidence to be 3.5%⁽²⁴⁾.

TSB and ALP activity showed no acute elevations and TSB were abnormally elevated in 1.25% of the patients. The acute elevations of serum aminotransferases with mild elevation of ALP and TSB give the picture of hepatocellular injury that characterize most NSAIDs induced hepatotoxicity⁽²⁵⁾, Since the most commonly reported hepatic adverse events were elevation in the serum aminotransferases activity that result from hepatocytes apoptosis or necrosis⁽²⁶⁾.

Human patients might become susceptible to diclofenac hepatotoxicity during modest inflammatory episodes. This appear more intriguing because most patients taking diclofenac for inflammatory related diseases such as rheumatoid arthritis and osteoarthritis. In fact OA had been associated with increased risk for diclofenac induced liver injury⁽²⁷⁾.

Inflammation is both a result and a susceptibility factor for drug toxicity, with an emphasis on the liver as a target organ⁽²⁷⁾.

By comparing the mean of ALT, AST, ALP, and TSB of the diclofenac treated OA patients with their controls; they were significantly higher in the diclofenac treated patients. Lacroix, *et al* (2004) found a significant association between liver disturbances and NSAIDs use⁽²¹⁾.

Mechanisms of diclofenac induced liver injury remain incompletely understood; mitochondrial injury leading to cell death had been proposed as a mode of hepatocellular injury

Polymorphism in genes encoding IL-4 and IL-10 had been identified in patients developing diclofenac induced liver injury⁽²⁸⁾. These polymorphisms cause less IL-10 which is anti inflammatory cytokines and more IL-4 which enhance hepatotoxic interactions between diclofenac and an inflammagen to which the patients might be exposed⁽²⁷⁾.

Other possible mechanisms include oxidative stress, polymorphism in CYP P450 enzymes and the formation of reactive drug metabolites⁽⁴⁾.

Positive strong correlations were found between the serum activity of AST and ALT, which suggest that both enzyme elevations are caused by the same mechanism. AST is found in greater amount in the hepatocytes than ALT but most of it is mitochondrial while ALT is cytoplasmic. Therefore in inflammatory - like condition where initially only the cytoplasmic membranes are damaged there is a release of both cytoplasmic enzymes in equal quantities, with more severe injury ;damage to the mitochondrial membrane will lead to the release of mitochondrial AST changing the proportion of the two enzymes⁽²⁹⁾.

In this study, AST correlates with the duration of treatment. This finding was observed before by Furst, *et al* (1993) who noted that the duration of treatment was a consistent determinant of AST elevations⁽³⁰⁾. Hepatotoxicity from NSAIDs can occur at any times during the treatment, but most commonly within 4-12 weeks of initiation of therapy⁽²⁾.

CONCLUSION:

The frequency of DILI in diclofenac treated patients is about 33.75%. DILI is more common in females, old age. Acute injury is usually hepatocellular in nature

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