

Original Research Article

A clinical study on nimesulide hepatotoxicity

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ABSTRACT

Background: Hepatic injury can occur with the use of nimesulide, a non steroidal anti-inflammatory drug. This study was done to evaluate the hepatic and renal functions in patients with rheumatological complaints receiving nimesulide for 2 weeks.

Methods: Fifty patients with rheumatological complaints treated at orthopaedic outpatient clinic of a tertiary care centre with nimesulide 100mg twice daily were enrolled in this study. The sociodemographic details, details of comorbidities, history of use of alcohol or tobacco, indication for treatment with nimesulide etc. were recorded in a predesigned proforma. All patients were followed up for two weeks and reviewed at the end of each week for any gastrointestinal adverse effects, changes in blood routine, liver function tests and renal function tests. Data collected was entered in Microsoft Excel 2010, analysed and results were expressed as mean and standard deviation.

Results: Out of the fifty patients analysed, mean age was 39 years. 66 % were males. Among liver function tests, only serum albumin and serum aspartate aminotransferase (SGPT) were altered after treatment with nimesulide. Blood urea nitrogen, serum creatinine and blood routine remained normal. No gastrointestinal adverse effects were noted.

Conclusions: Nimesulide produced changes in serum albumin and SGPT levels without prominent gastrointestinal or renal adverse effects.

Keywords: Hepatotoxicity, Liver function, Nimesulide, Serum albumin

INTRODUCTION

Non steroidal anti-inflammatory drugs (NSAIDs) remain perhaps, the most widely prescribed drugs worldwide for pain and inflammation. Although widely used, what is missing is a comprehensive vision of the adverse effects of these agents and their impact on the health of the patients. The history of analgesics can be traced back to the year 1763 when willow bark was first used for the treatment of pain by Reverend Edmund stone. While many of the NSAIDs have equivalent efficacy, there is no doubt that they have different side effect profiles. It has been the endeavor of medical research right from the

1930s to achieve the goal of a “safer aspirin” as gastrotoxicity was a major limiting factor for its use. The pioneering efforts of Sir John Vane led to a more lucid understanding of the inflammatory processes and have made the cyclooxygenase (COX) enzymes the target of logical drug development. Discovery of COX isoforms and selective COX-2 inhibitors have finally succeeded in treating pain and inflammation with maximum benefits and minimum adverse effects.

Nimesulide, a COX-2 selective NSAID, is found to be effective in a variety of inflammatory conditions. It has potent anti-inflammatory, analgesic and antipyretic

properties. Higher COX-2 selectivity of nimesulide reduces the risk of gastrotoxicity. However, it is found to induce hepatic damage especially in elderly females who have consumed the drug for at least 1month. This is thought to be due to an idiosyncratic reaction resulting from an immunological response or altered metabolic pathway.¹

However, hepatic injury that occur as a sequelae to NSAID use is often reversible with stoppage of treatment.¹ COX inhibition can compromise renal functions also. In fact, many a time, hepatotoxicity and nephrotoxicity are seen to coexist.

Hence, this study was designed to evaluate the hepatic functions, renal functions and gastrointestinal adverse effects of nimesulide in patients with rheumatological complaints receiving the drug for a period of 2weeks.

METHODS

Fifty patients who were treated at the orthopaedic outpatient clinic of a tertiary care centre for rheumatological complaints with nimesulide 100mg twice daily for two weeks were enrolled in this study during April 2000 to September 2000, after taking informed consent.

The sociodemographic details, details of comorbidities, personal history related to the use of alcohol or tobacco, history of drug allergy and indication for treatment with nimesulide along with the dosage schedule were recorded in a predesigned proforma. All patients were followed up for two weeks with advice to report for review at the end

of each week. They were assessed for symptoms like acid eructation, heart burn, belching, nausea, vomiting, abdominal pain, hematemesis, melena, rectal bleeding, diarrhoea, jaundice, pruritus and rashes before starting treatment with nimesulide and then, at the end of 1st and 2nd week of therapy.

Investigation reports like blood routine, liver function tests, blood urea nitrogen and serum creatinine, which were done before and at 1st and 2nd week of therapy with nimesulide were also collected. Data collected was entered in Microsoft Excel 2010 and analysed. Results were expressed as mean and standard deviation.

RESULTS

The data of fifty patients enrolled in the study were analysed. The mean age was 39 years. 66% of the study population were males. 26% patients were from the urban population.

Family history of hypertension and diabetes mellitus was seen in 10% and 11.7% patients respectively. 6.7% patients gave a family history of bronchial asthma. 12% patients were hypertensive and on regular treatment. 4% each had diabetes mellitus and bronchial asthma. 10% gave a history of occasional alcohol use.

There was no history of drug allergy in any of the patients. Symptoms like acid eructation, heart burn, belching, nausea, vomiting, abdominal pain, hematemesis, melena, rectal bleeding, diarrhoea, jaundice, pruritus, rashes etc. were not statistically significant during and after treatment with nimesulide.

Table 1: Changes in Haematological parameters before and after treatment with nimesulide.

Parameter	Basal Wk and Wk 1 (Mean±SD)	P value	Wk 1 and Wk 2 (Mean±SD)	P value	Basal Wk and Wk2 (Mean±SD)	P value
Hb	12.5±1.44	0.098	12.2± 1.58	0.85	12.3±1.38	0.125
TC	7198.31±2812.07	0.68	7024.49±1877	0.487	7106.27±2298.17	0.92
Platelet count	4.3060±8.4573	0.897	2.7447±0.9587	0.624	6.3609±18.2073	0.487

Hb: Haemoglobin, TC: Total white cell count, Wk: Week

Table 2: Changes in Liver function tests before and after treatment with nimesulide.

Parameter	Basal Wk and Wk 1 (Mean±SD)	P value	Wk1 and Wk 2 (Mean±SD)	P value	Basal Wk and Wk2 (Mean±SD)	P value
Serum Bilirubin	0.715±0.204	0.469	0.751±0.280	0.879	0.715±0.151	0.959
Total protein	6.637±0.684	0.142	6.406±0.692	0.216	7.598±7.238	0.664
Serum Albumin	4.072±0.411	0.696	4.071±0.351	0.005	4.398±0.616	0.004
SGOT	45.97±23.62	0.255	49.19±26.64	0.706	47.46±27.03	0.66
SGPT	40.51±27.31	0.044	41.52±29.56	0.446	40.77±28.54	0.567
S. alk Phosphatase	117.63±51.5	0.922	112.40±45.31	0.608	111.23±61.43	0.463

SGOT: Serum glutamate aminotransferase, SGPT: Serum aspartate aminotransferase, S. alk phosphatase: serum alkaline phosphatase, Wk: Week

Table 1 depicts the changes in the haematological parameters (haemoglobin, total white cell count and platelet count) in the patients between the basal week and week 1, week 1 and week 2 and between basal week and week 2 of nimesulide therapy. The p values for the haematological parameters before and after treatment with nimesulide were not statistically significant (Table 1). The changes in the liver function tests from the basal values during the first two weeks of treatment with nimesulide are shown in Table 2. Serum bilirubin and Total protein values between basal week and week 1, between week 1 and week 2 and between basal week and week 2 were 0.469, 0.879, 0.959 and 0.142, 0.216, 0.664 respectively. Serum albumin was significantly decreased from the basal value in week 1 and week 2 (p value 0.005

and 0.004 respectively) as shown in Table 2. SGOT values were not elevated from the baseline values after treatment with nimesulide. However, there was a statistically significant elevation of SGPT values in the first week after treatment with nimesulide as indicated by a p value of 0.044 (Table 2). No significant alterations were seen in the serum alkaline phosphatase levels before and after treatment with nimesulide as depicted in Table 2. Table 3 shows the mean and standard deviation and p values of renal function parameters like Blood urea nitrogen and Serum creatinine between basal week and week 1, week 1 and week 2 and between basal week and week 2 after treatment with nimesulide. The p values of these renal parameters were not statistically significant before and after treatment with nimesulide.

Table 3: Changes in renal function parameters before and after treatment with nimesulide.

Parameter	Basal week and week 1 (Mean±SD)	P value	Week 1 and week 2 (Mean±SD)	P value	Basal week and week 2 (Mean±SD)	P value
Blood urea nitrogen	11.1±2.430	0.427	11.698±2.904	0.915	11.694±3.209	0.224
Serum creatinine	0.707±0.156	0.472	0.689±0.200	0.719	0.827±0.801	0.536

DISCUSSION

Nimesulide is an NSAID belonging to the Sulfonanilide group, selective for Cox-2.² In addition to cyclooxygenase inhibition and reduced prostaglandin synthesis, it also reduces generation of superoxide by neutrophils, inhibits synthesis of platelet activating factor and release of tumour necrosis factor, scavenges hypochlorous acid without affecting neutrophil function, decreases histamine release from tissue mast cells and inhibits the release of stromelysin and blocks metalloproteinase activity.³ The inhibition of prostaglandin synthesis is an important factor contributing to gastrointestinal toxicity. However, selectivity towards Cox-2 exerts better anti-inflammatory action with fewer gastrointestinal adverse effects.⁴

In this study, the data of fifty patients who were prescribed nimesulide 100mg twice daily for two weeks in the Orthopaedic Department of a tertiary care centre were analysed. The mean age was 39 years and 66% were males. Hypertension, diabetes mellitus and bronchial asthma were seen as comorbidities in very few patients. Gastrointestinal adverse effects were not noticed following treatment with nimesulide in this study. This may be because of its higher Cox-2 selectivity and better Cox-2/Cox-1 activity ratio.⁴ Moreover, since selective Cox-2 agents are weakly acidic, they avoid substantial accumulation in gastric mucosa also.⁵ A study on rat duodenum by Hirata et al, to study the gastrointestinal adverse effects of nimesulide and Indomethacin revealed

that no haemorrhagic lesions were provoked by nimesulide in rat duodenum.⁶

In this study, there were no significant changes in the haematological parameters (haemoglobin, total white cell count and platelet count) in the patients between the basal week and week 1, week 1 and week 2 and between basal week and week 2 of nimesulide therapy. Among the liver function tests, Serum albumin was significantly decreased from the basal value in week 1 and week 2 (p value 0.005 and 0.004 respectively) and SGPT values were significantly elevated (p value 0.044) in the first week after treatment with nimesulide. No significant alterations were seen in Serum bilirubin, total protein, SGOT and Serum alkaline phosphatase levels. In a study done at Argentina to evaluate the hepatotoxic potential of nimesulide, patients had presented with jaundice, pruritus and asthenia and all patients had evidence of drug induced acute hepatitis with predominant cholestasis and one patient had hepatocellular damage.⁷ But median time of onset of symptoms were 25 days and 50% of cases normalised their liver function tests in a median of 55 days.⁷ In contrast to this, only hypoalbuminemia and SGPT elevation was seen. This may be because of lesser exposure to nimesulide in present study (only for 2 weeks). In another study done in a 70 year old female, fatal hepatitis, hypoalbuminemia and renal failure were reported after consuming nimesulide for just 5 days.⁸ Fatal hepatitis was reported in a 66 year old lady in Spain who was prescribed nimesulide for an undefined connective tissue disorder with arthritis of right knee but

there was a delay of 8 months before development of hepatic failure.⁹ In patients with hepatic impairment, a dose reduction of four to five times is needed.¹⁰

Around 120 cases reports from a spontaneous reporting data in Italy suspected renal adverse effects in 11 patients who took nimesulide, out of which, 6 required hospitalisation.¹¹ In a study conducted in Switzerland, nimesulide when given as a tocolytic was reported to produce neonatal chronic renal failure.¹² However, in present study, renal function parameters like blood urea nitrogen and serum creatinine were not significantly altered before and after treatment with nimesulide.

CONCLUSION

Nimesulide, a sulfonanilide non steroidal anti-inflammatory drug, produced changes in Serum albumin and SGPT levels without significant gastrointestinal or renal adverse effects. However, further studies may be taken up to rule out definite hepatotoxicity in human beings following treatment with nimesulide.

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