Pharmacophore

ISSN-2229-5402

Journal home page: http://www.pharmacophorejournal.com

Pharmacophore
an International Journal
ISSN 2229-5402

COMPARATIVE EVALUATION EFFECTS OF NAPROXEN, MEFENAMIC ACID AND PARACETAMOL ON LIVER ENZYMES

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ARTICLE INFO

Received:
03th Jun 2017
Accepted:
29th Nov 2017
Available online:
14th Dec 2017

Keywords: *Naproxen, Mefenamic Acid, Paracetamol, Nsaids, Liver Enzymes*

ABSTRACT

Regarding the prevalence of taking naproxen, mefenamic acid and paracetamol, the effects of these drugs on liver enzymes and comparing the effects of doses and the length of treatment, help to prevent liver damage, to the extent possible and to choose the least harmful treatment NSAIDs.
The aim of this study was to compare the effects of naproxen, mefenamic acid and paracetamol on serum levels of liver enzymes in Wistar rats. In this study, a comparison of the effect of naproxen with different doses of 40 and 10 mg / kg body weight, mefenamic acid at doses of 400 and 100 mg / kg body weight and paracetamol at doses of 60 and 15 mg / kg body weight in two periods Short-term and long-term effects on liver enzymes.
Data were compared using spss software. To evaluate the results, $p < 0.05$ was considered as the significant level of differences.
Based on the results obtained from the Duncan test and paired t-test, liver enzymes activity was significantly increased in most treatment groups compared to control, but did not show significant increase in naproxen treated groups. An increase in the alkaline phosphatase enzyme is due to its hepatic isozymes increase.
The results suggest that mefenamic acid with low doses and then high-dose paracetamol in the short-term have the highest elevations of liver enzymes, which can be due to damage to liver cells or liver metabolism. In addition, naproxen has the least harmful effect on the liver and has the least change in liver enzymes compared with the control group.

To Cite This Article: Parisa Alibek, Seyed Ali Asghar Moshtaghi, Seyed Hossein Hejazi, (2017), "Comparative evaluation effects of naproxen, mefenamic acid and paracetamol on liver enzymes", ***Pharmacophore, 8(6S),*** *e-1173391.*

Introduction

Nonsteroidal anti-inflammatory drugs are often used to relieve non-specific fevers and continue to play a role in reducing pain (1). These drugs are most commonly used in the treatment of acute and chronic inflammation. Among the high-consumption members of this class of drugs, naproxen (2), mefenamic acid and paracetamol, which are rapidly absorbed through the small intestine, can be metabolized to the liver by non-chemical agents, but at high doses of metabolism normal saturation and long periods. Under such conditions, these drugs are oxidative metabolized and become toxic metabolites such as NAPQI, which can conjugate with glutathione and reduce glutathione storage of liver cells. Subsequently, this toxic metabolite is bonded to vital proteins and fatty droplets of the liver cell membrane, resulting in the death of liver cells and necrosis of the liver (4, 3). Given the role of these drugs that play in the life and survival of humans, the hepatic malignant effects of these drugs that are sometimes irreversible and cause poor quality of life. This study therefore suggests that the

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effect of these drugs with different doses in multiple groups of rats on liver enzymes such as alkaline phosphatase (5), ALT, AST, and others. The analysis of the data can be a step towards clarifying the effects of pain relief and fever medications and providing useful solutions in this regard.

Materials and Methods

A statistical population including male Wistar rats was selected randomly from a large number of male rats. Thirty-five rats were kept in optimal conditions for up to 72 hours. Subsequently, they were divided into 7 groups of 5, 3 groups for short duration of 15 days and 3 groups for a long period of 45 days for treatment with the three drugs mentioned and from one group as a control used. 0.5 cc per drug per day, each rat in the related group, and in the control and control group, 0.5 cc of the serum of physiology was gavage. For the short-term group, a multiplier of normal dose was used to achieve the result; however, this did not increase the dose to a dose level, while the long-term dose was normal for the dose (Table 1).

Table 1 - Normal and toxic doses of the drugs studied

Selective dose (for short time) mg/kg	Toxic dose mg/kg	Normal Dose (Selective Dose for Long time) mg / kg	The name of the drug
40	**>100**	**10**	**Naproxen**
400	**> 800**	**100**	**Mefnamic acid**
60	**>15**	**15**	**Paracetamol**

Grouping rats

Group 1: Control group without medication, and only 0.5 ml oral gavage daily daily physiology in 45 days
Group 2: 0.5 mg daily gavage of naproxen solution at a concentration of 7600 mg / dL for 15 days
Group 3: Daily gluten 0.5 ml of mefenamic acid solution at a concentration of 760 mg / dL for 15 days.
Group 4: Daily gavage 0.5 ml of paracetamol solution at a concentration of 16000 mg / dL for 15 days
Group 5: Daily bovine 0.5 ml Naproxen solution at a concentration of 1900 mg / dL for 45 days
Group 6: Daily gavage of 0.5 ml mefenamic acid solution at a concentration of 19000 mg / dL for 45 days
Group 7: Daily gavage 0.5 ml of paracetamol solution at a concentration of 3000 mg / dL for 45 days

How to gavage rats

Using a gavage syringe that has a special curvaceous tip, the drug was injected. In this way, the volume of each drug concentration for each rat was thrown into the syringe after being completely shaken, and with all the more precision, the gelatin syringe was passed through the mouth and esophagus of the animal and the related solution was inserted directly into the stomach rats.

Using a gauze syringe that has a special curvaceous tip, the drug was injected. In this way, the volume of each drug concentration for each rat was thrown into the syringe after being completely shaken, and with all the more precision, the gelatin syringe was passed through the mouth and esophagus of the animal and the related solution was inserted directly into the stomach.

Blood sampling, serum separation and isolation

After the expiration of each of the short-term 15-day and long-term 45-day courses, each rat was anesthetized with 0.2 CC ketamine 10% and blood collection from each rat was taken using a 5cc syringe. After being poured into the test tubes, they were centrifuged at 3000 rpm for 20 minutes and their serum was separated. The abdominal cavity of each rat was split to see the liver and be reported if macroscopic changes in the liver tissue were made.

Each serum was evaluated for AST or SGOT, ALT or SGPT, ALP (alkaline phosphatase) (6) as well as GGT for confirmation of the effects of doses on the liver by the RA 1000 autoanalyser.

Analyze each serum and measure any of the liver enzymes(7)

AST measurement Method: The first solution containing 100 mmol of Tris buffer (pH = 7.8) was 200 mmol / L aspartate, 800 L / L of dehydrogenase and 800 L / L of dihydrogenase with the second solution containing: 2- Oxaloglutarate to Mmol 12 and mmol 0.18 of NABh2 in a ratio of 4 to 1 and 1000 ml of it are removed in a tube. We then mixed 100 ml of the serum sample and added it for 1 minute incubation. We read the light absorbance at 340 nm in minutes 1, 2, and 3. We divide the total of 3 obtained by 3 into 3 and then multiply in 1746.

ALT measurement method: The first solution contained 100 mmol of Tris buffer pH = 7.5. 1200 u / l of LDH and 500mol / l of alanine, and the second solution consists of: mmol 15 of 2- oxalotrate and 18.8mmol of NADH, mixed in a ratio of 4 to 1, and the amount of 1000ml of it in a tube We cast Then the light absorbance was read after 1 minute incubation in minutes 1, 2, and 3. We calculated the average of these 3 numbers and multiplied by the number of 1985.

GGT Measurement Method: We had two solutions, the first one containing: Buffers with pH = 25/8 and 100 mmol / l, and the second solution was 2.9 mmol / L of L-gamma-glutamyl-3-carboxy-4-nitroanilide, which was 5 to 1 mixture and M 1000 from the tube.

Then add 100 ml of sample to the mixture well and incubate it for 1 minute. We then read the light absorption at 405 nm in minutes 1, 2, and 3, and multiply their mean in the standard concentration of 1309.

ALP Measurement Method: We incubated 1 ml of a ready-work solution or working solution in a cuvette and incubated for 5 minutes at 37°C. Ready-to-work solution contains paranitrofenil phosphate, which is an enzyme substrate and ethanolamine. Then add 20 ml of serum to Sample and simulates it well to mix. We then placed the cuvette in the device and measured the absorbance at 405 nm at 1, 2, and 3 minutes. The average was 3 times and we multiplied by 2257.

Results

For statistical analysis, the mean and standard deviation of each group were calculated and the significance level of the difference between the means was analyzed by means of analysis

One-way ANOVA, Duncan test was used to evaluate one-way variance.

1 -Aspartate aminotransferase

The results show that AST activity in all treatment groups except short-term naproxen has significantly increased compared to the control group (Figure 1).

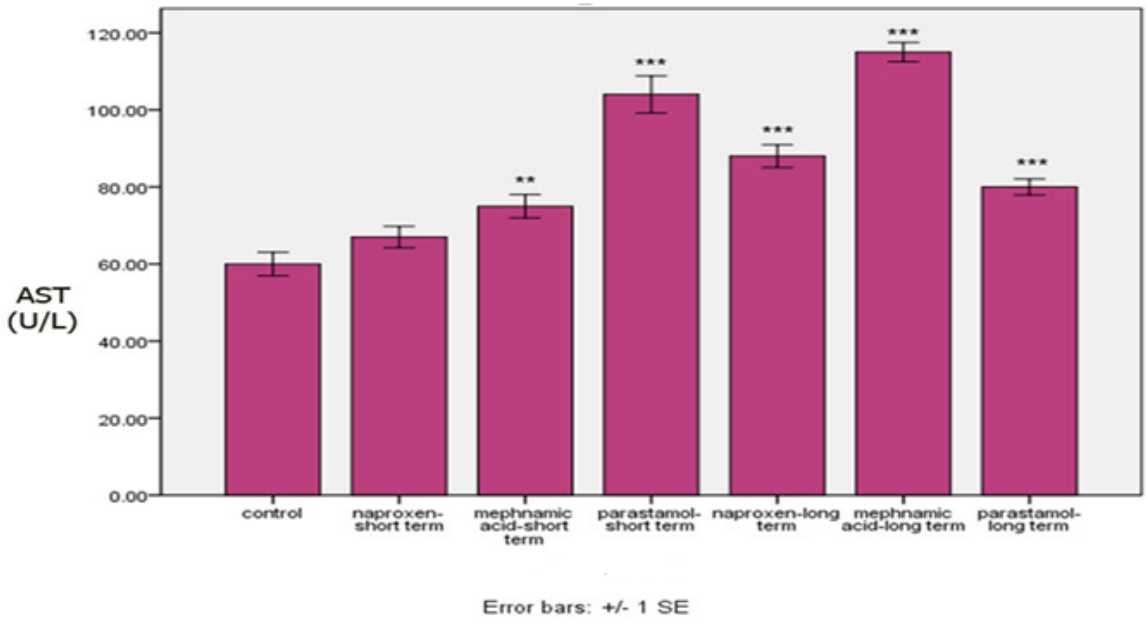

Figure 1. Comparison of the mean of AST activity between treatment and control groups in two short and long term periods

2-Alanine aminotransferase

The results in the short and long term treatment groups showed a significant increase in the mean amount of alanine aminotransferase in all treatments other than the short term naproxen group compared to the control group (Figure 2)

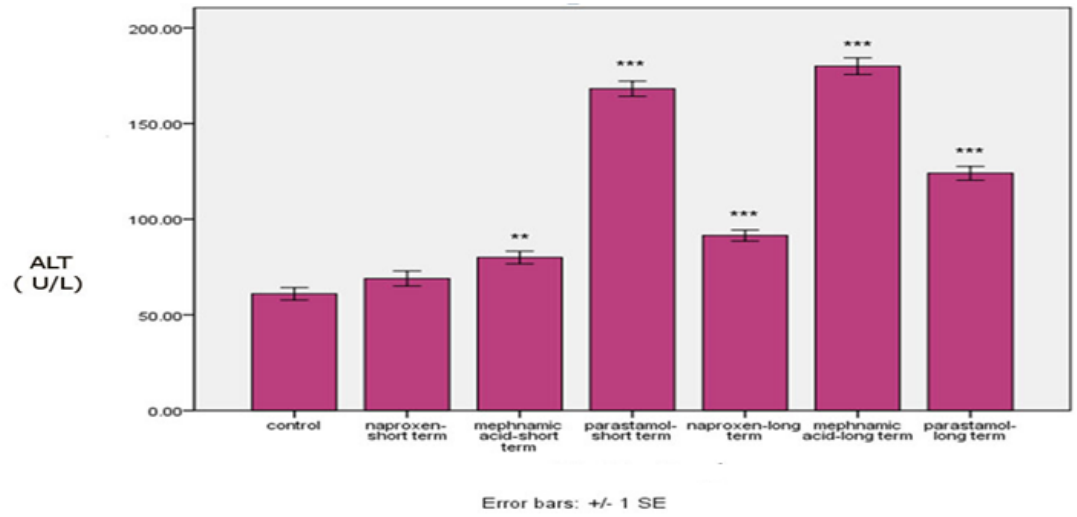

Figure 2. Comparison of the mean of ALT activity between treatment and control groups in two short and long term periods

3 -Gamma glutamyl transferase

The results showed a significant increase in the mean value of gamma-glutamyltransferase in the treatment groups with mefenamic acid and paracetamol in short and long term periods (Figure 3).

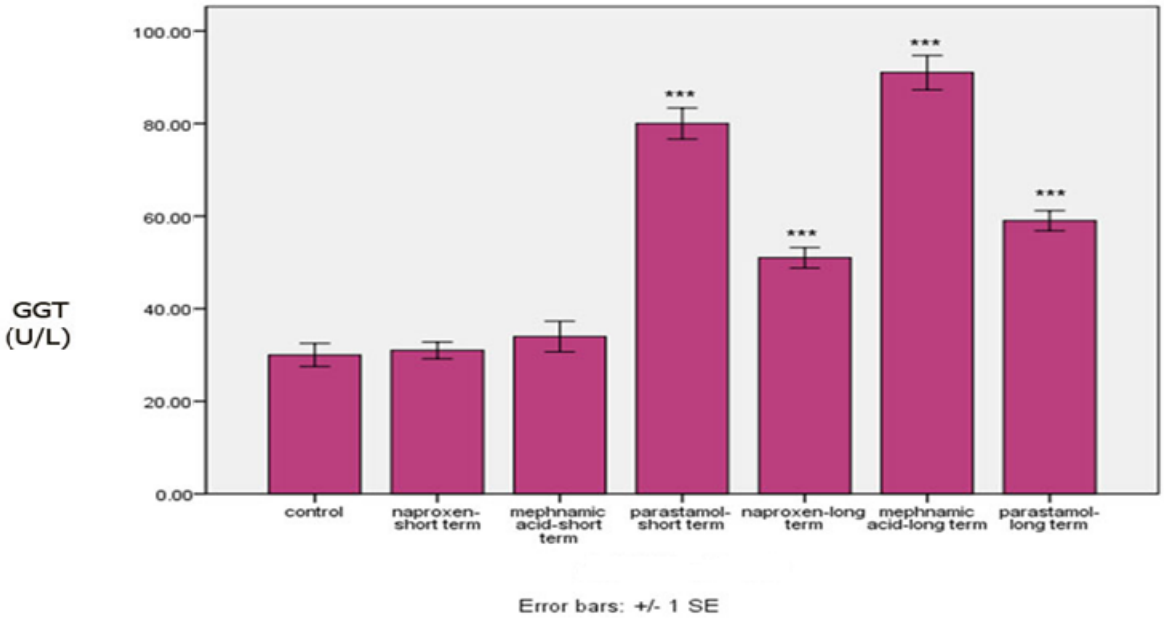

Figure 3. Comparison of the average GGT activity between treatment and control groups in two short and long term periods

4-alkaline phosphatase

The results indicated a significant increase in the mean activity of alkaline phosphatase in the treatment groups with mefenamic acid and paracetamol in short and long term periods compared to the control group.

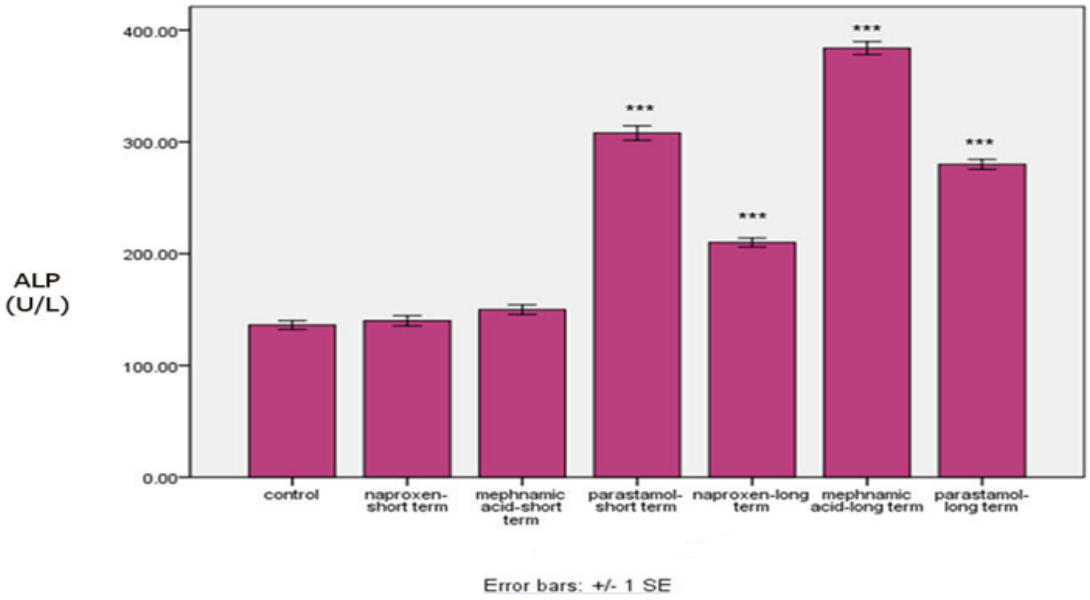

Figure 4. Comparison of the mean of ALP activity between treatment and control groups in two short and long term periods

The results of the comparison of the effects of naproxen, mefenamic acid and paracetamol in short and long term periods

To investigate the effect of mefenamic acid and paracetamol naproxen drugs on short and long term on liver enzymes, the effect of drug

Paired t-test was used in two different intervals of 15 days and 45 days, and their comparison chart it was drafted in two periods.

A: Aspartate aminotransferase

The activity of aspartate aminotransferase enzyme in short and long term periods is significantly different. (P <0.01). The effects of mefenamic acid and naproxen in the long term and paracetamol are more pronounced in the short term (Figure 5).

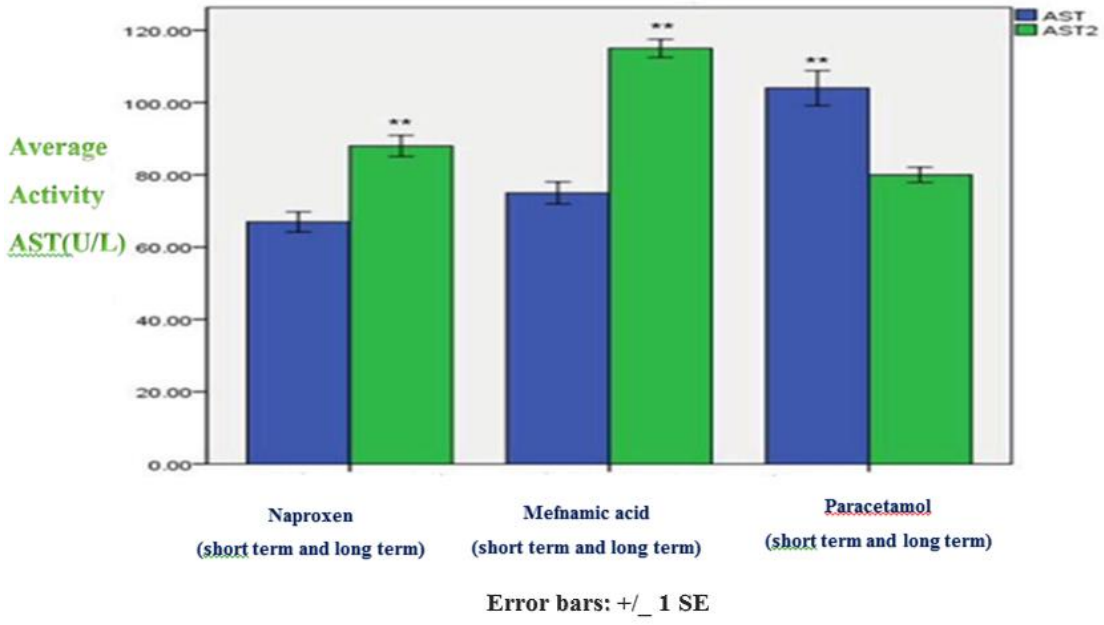

Figure 5. Comparison of the effects of naproxen, paracetamol and mefenamic acid in short and long term on AST activity

B: Alanine aminotranferase

The activity of enzyme alanine aminotransferase has a significant difference in both short and long term. (P <0.01) Mefenamic acid in the long term and then paracetamol in the short term and then long-term naproxen show the most enzyme activity (Figure 6).

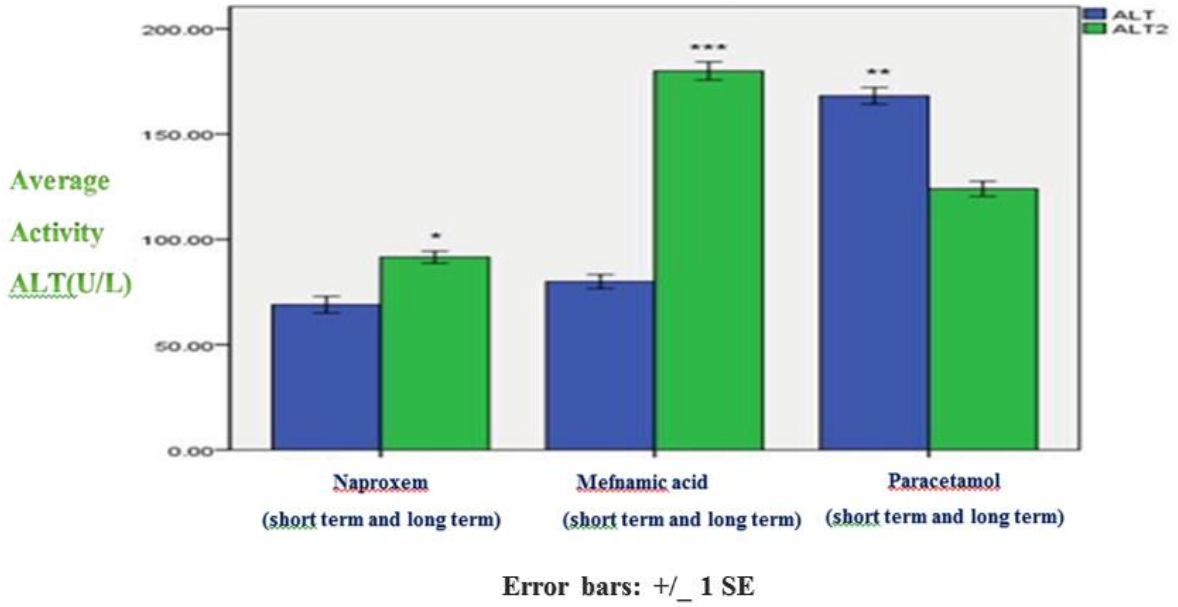

Figure 6. Comparison of the effects of naproxen, paracetamol and mefenamic acid in short and long term on ALT activity

C: Gamma glutamyl transpeptidase

The results indicate a significant difference in the activity of the gamma glutamyltransp peptidase enzyme in the short and long term.

According to Figure 7, it can be concluded that the highest activity of the gamma glutamyltransp peptidase enzyme in the long-term mefenamic acid group and short-term paracetamol is.

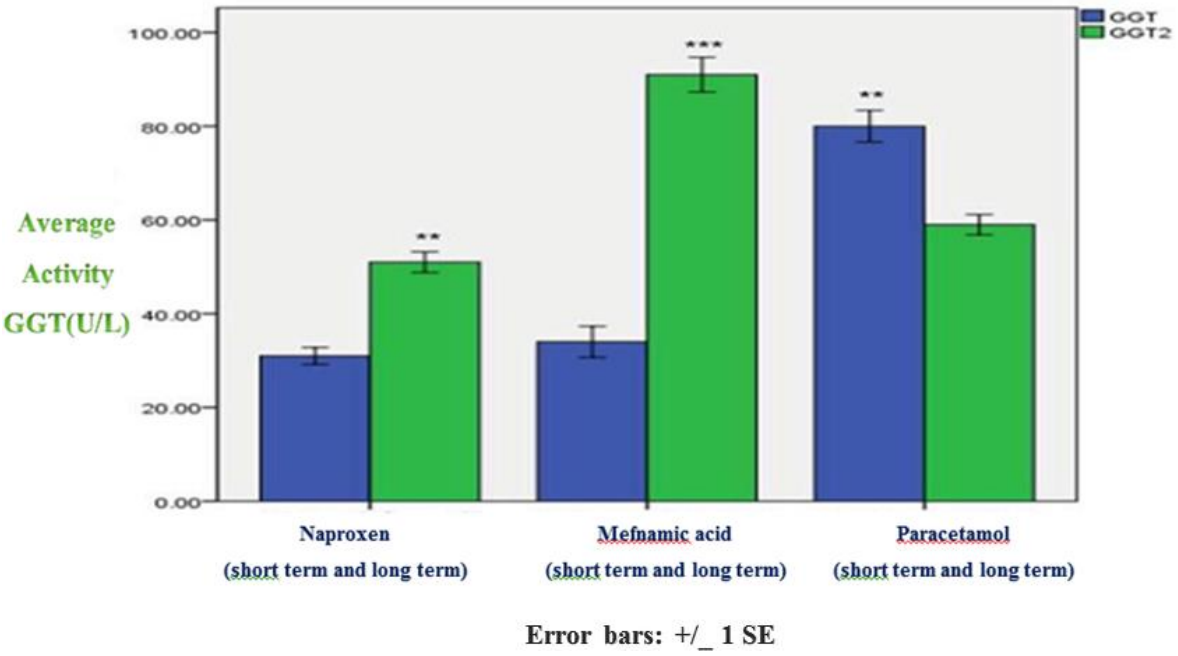

Figure 7. Comparison of the effects of Naproxen, Paracetamol and Mefenamic acid in short and long term on GGT activity

D: Alkaline phosphatase

Alkaline phosphatase activity is significantly different in both short and long term. According to Figure 8, the highest activity of alkaline phosphatase in the mefenamic acid and long-term naproxen group, and then the short-term paracetamol group, can be seen

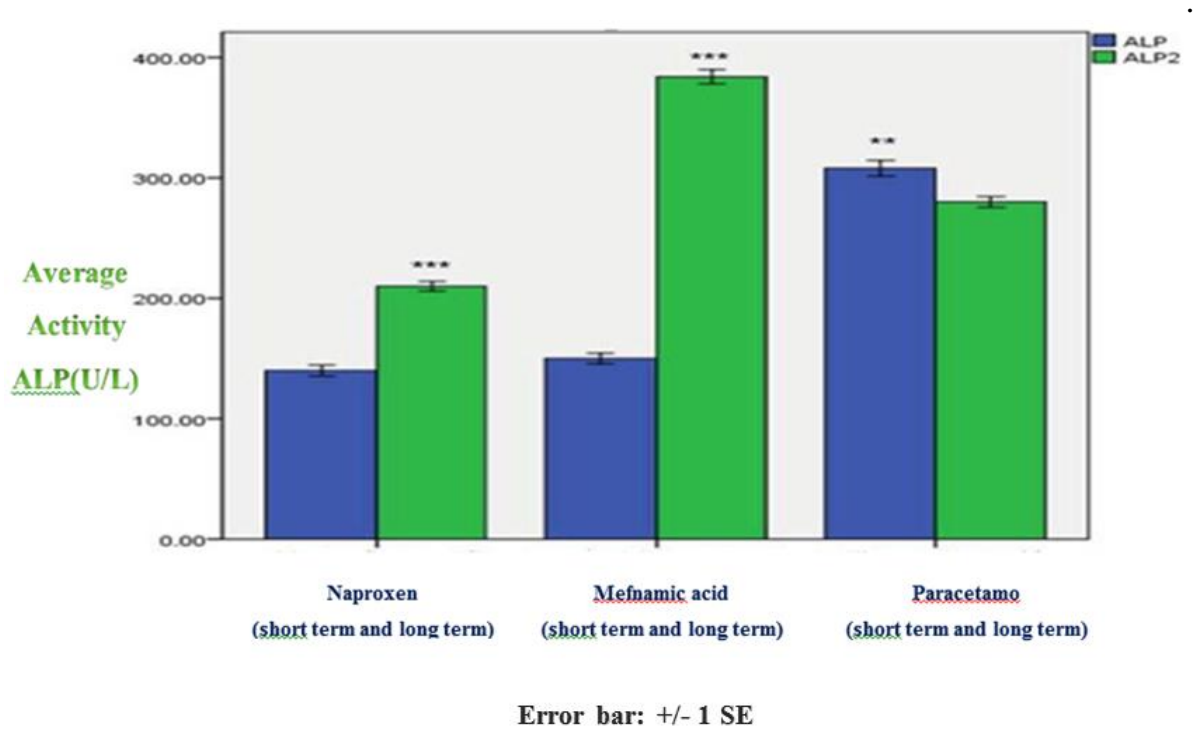

Figure 8. Comparison of the effects of Naproxen, Paracetamol and Mefenamic acid in short and long term on ALP activity

Discussion

The liver, as a vital organ of the body, is primarily responsible for the metabolism of substances of internal and external origin. One of the most important role of the liver is the elimination of drugs and toxins. Nonsteroidal anti-inflammatory drugs are often used to relieve non-specific fevers of joint and bone and muscle pain. These drugs are most commonly used in the treatment of acute and chronic inflammation (9, 8). As observed in the results, in the short-term naproxen group, the least change in liver enzymes was observed in comparison with the control group, so that the percentage change in aspartate aminotransferase (11.66), in alanine aminotransferase (11.11) In gamma glutamine, transpeptidase is 33.3 and alkaline phosphatase is 2.94. In the short-term paracetamol group, the highest percentage of changes in liver enzymes is observed in the control group. The percentage of changes in the control group for aspartate aminotransferase was 33.33, alanine aminotransferase 175/40, gamma glutamyl transpeptidase 166.66 and alkaline phosphatase 120 respectively. In the long-term naproxen group, there is less than 100% variation in the control group. These changes are for the aspartate aminotransferase enzymes 66/46, alanine aminotransferase 18/49, gamma glutamyltranspeptase 70, and alkaline phosphatase 54/41. While in the mefenamic acid group, the most percentage of changes in the activity of enzymes is compared to the control group. The percentage of changes in aspartate aminotransferase is 66.91, alanine aminotransferase is 19.08, gamma glutamyl transpeptidase is 33.23 and alkaline phosphatase is 18.38. Mefenamic acid has the potential to cause poisoning and liver necrosis, so care should be taken during use (10). For this reason, with the membrane rupture of the liver parenchymal cells, the enzymes in the hepatocytes are released into the bloodstream, resulting in an increase in the amount of these enzymes from the normal level in the serum.

Laurel et al. (2009) (11) state that liver factors AST and ALT show an hepatocellular necrosis in case of an increase, but increased GGT and ALP activity indicates a cholestasis injury. (12) In a study, he says, ALK activity increases in patients with colostatic liver disease. NSAIDs have many complications, and since the current study was based on naproxen, mefenamic acid, and paracetamol, it can be compared comparing naproxen to a long-term 45-day long dose and even a near-toxic dose (Multiplying dose) in the short-term 15 days has the least effect on liver and liver enzymes. If possible, do not use paracetamol at a dose close to the toxic and short-term dose, and mefenamic acid in the long-term, long-acting dose that has the most severe effects on the liver and liver enzymes.

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