Full Length Research Paper

Aspirin Associated Liver Insufficiency – The Optimal Dose of Aspirin in Liver Insufficiency

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Abstract. Acetylsalicylic acid (Aspirin) belongs to nonsteroidal anti-inflammatory drugs (NSAIDs). Numerous studies have proven that aspirin reduces the signs and symptoms of inflammation and exhibited a broad range of pharmacological activities, including analgesic, antipyretic and antiplatelet properties. Previous studies suggested that beside the pharmacological activities aspirin was also associated with the side effects and toxicity of various doses and in various formulations. The present study is performed to explore the effects of aspirin in various doses (75mg (EC), 100mg, 150 (EC)mg and 300mg) in different preparation (enteric coated (EC), non-enteric coated) on liver enzymes (Serum glutamic oxaloacetate transaminase (SGOT) and Serum glutamic pyruvic transaminase (SGPT)) followed by daily administration for 10 days and for 30 days. We found that the SGOT level was increased by all doses of aspirin after 30 days of treatment, this effect was most significant at 75mg (EC) and 100mg dose, whereas at 150mg (EC) and 300mg was not very significant. The level of SGPT was decreased by all doses regardless of duration of treatment, only 75mg (EC) dose increased its level after 30 days of treatment, suggesting 75mg (EC) aspirin could be hepatotoxic due to lessen of anti-oxidant effects, furthermore suggests that patients with hepatic insufficiency should not receive 75mg (EC) dose of aspirin.

Keywords: Aspirin, different doses, liver enzymes, SGOT, SGPT

1. INTRODUCTION

Aspirin was the first discovered member of nonsteroidal anti-inflammatory drugs (NSAIDs) (Warner, 2002). Aspirin, also known as acetylsalicylic acid, is a salicylate drug, is a synthetic compound with antipyretic, analgesic, anti-inflammatory, and antiplatelet properties (Awtry and Loscalzo, 2007). Rheumatic fever, Kawasaki disease remains one of the few indications for aspirin use in children (Hsieh et al., 2004).

Aspirin irreversibly inhibits prostaglandin-endoperoxide synthase 1 (PTGS1) and modifies the enzymatic activity of prostaglandin-endoperoxide synthase 2 (PTGS2). Normally PTGS2 produces prostanoids, most of which are pro-inflammatory. Aspirin-modified PTGS2 produces lipoxins, most of which are anti-inflammatory (Warner, 2002). Additionally, aspirin induces the formation of Nitric oxide (NO) radicals in the body. This reduces leukocyte adhesion, which is an important step in immune response to infection (Paul-Clark et al., 2004).

In children and adolescents, aspirin is no longer used to control flu-like symptoms or the symptoms of chickenpox or other viral illnesses, because of the risk of Reye's syndrome (Macdonald, 2002). Aspirin also raises the risk of hemorrhagic stroke and other major bleeding (Baigent et al., 2009), significant gastrointestinal damage even in the low doses used for cardiovascular protection (Yeomans et al., 2009). Avoid use in severe liver disease (Lacy et al., 2011), because liver toxicity is reported by aspirin (Bjorkman, 1998) days or weeks are required to develop hepatotoxicity (Zimmerman, 1981).

The potential of aspirin and salicylate to cause hepatotoxicity has been recognized in 1980 (Prescott, 1980). One more study showed that aspirin in high doses for the treatment of rheumatic fever in children caused liver toxicity (Karademir et al., 2003; Singh et al., 1992). Another study suggested that high dose aspirin therapy for the treatment of systemic lupus erythematosus developed hepatitis (Wolfe, 1974). Low-dose aspirin was associated with the lowest risk, and moderate doses caused a relatively high hemorrhagic event rate, especially with regard to
minor, gastrointestinal, total bleeding, and stroke (Serebruany et al., 2005). The goal of current study is to explore the effects of aspirin in various doses (75mg (EC), 100mg, 150 (EC)mg and 300mg) in different preparation (enteric coated (EC), non-enteric coated) on liver enzymes and explore the optimal dose of aspirin in patients with liver insufficiency.

2. MATERIALS AND METHODS

2.1. Selection of Animals

This study was carried out on 50 locally bred rabbits of either sex weighing from 900-1400 gram, purchased from local market rabbit supplier. Rabbits were caged in pairs in iron cage under controlled room temperature (21±1°C) and humidity (50-60%)(Qazi et al., 2014; Feroz et al., 2011)). All rabbits were fed on lucerna hey diet

2.2. Drugs

Aspirin 75mg (EC), 100mg, 150mg (EC) and 300mg were procured from local medical store and prepared dose in distilled water. Drug was administered by per oral route once daily to the treated groups and distilled water administered by per oral route once daily to the control group for the period of 10 days and 30 days.

2.3. Experimental Protocol

All rabbits were equally divided into 5 groups, each group comprises of 10 rabbits, one group was serving as control and other 4 groups were drugs treated. The experimental protocol was designed to administered different doses and different preparation of aspirin orally once daily for 10 days and 30 days.

All groups were received drug in following mode: (i) control group served with distilled water (ii) aspirin 75mg (EC) in a dose of 1.1mg/kg/day (iii) aspirin 100mg in a dose of 1.4mg/kg/day (iv) aspirin 150mg (EC) in a dose of 2.14mg/kg/day (v) aspirin 300mg in a dose of 4.28mg/kg/day. Before starting the dosing, blood samples were collected from control group through cardiac puncture. After 10 days and 30 days of dosing blood sample were collected so that different hematological parameters were determined (Alam and Najam, 2015). At the end of study all animals were sacrificed for the purpose of histopathological analysis of organs such as liver, heart and kidney.

2.4. Sample Collection

Blood sample (5ml) were collected in a gel tube through cardiac puncture after completion of dosing at 10 days and at 30 days, serum was separated out by centrifuging the blood sample in Human 14K (Germany) at 3000 rpm for 15 minutes. The separated serum was stored in 2-8 °C and within 3 hours all analysis was done by using Humalyzer (Human Germany), using standard reagent kits of Human Germany.

2.5. Statistical Analysis

Analysis were performed by 2 Way-ANOVA (2-way analysis of different variance) to see the effects of drug on various parameters. Result are represented in mean ± S.E. post-hoc comparison was performed by Newman-Keuls test and P<0.05 values were considered as significant.

3. RESULTS AND DISCUSSIONS

3.1. Result

Graph 1 and 2 showed the effect of different doses of aspirin on SGOT level. Data analyzed by two-way ANOVA (df = 1, 90) showed a highly significant effect of drug (F = 29.22, p<0.005) significant effect of days i.e. 10 days and 30 days (F = 7.87, p<0.05) and also a significant interaction between two variable factors (F = 3.10, p<0.05).

Post – hoc analysis by Newman keuls test showed non-significantly decreased in SGOT level by aspirin 75mg (EC) after 10 days and 30 days. SGOT level was increased highly significantly (p<0.0001) by aspirin 100mg after 10 days and increased significantly (p<0.005) after 30 days, whereas decreased significantly (p<0.01) by aspirin 150mg (EC) after 10 days and increased non-significantly after 30 days. SGOT level was increased non-significantly by aspirin 300mg after 10 days and 30 days.

Graph 3 and 4 showed the effect of different doses of aspirin on SGPT level. Analysis by two-way ANOVA (df = 1, 90) showed a highly significant effect of drug (F = 71.10, p<0.005), non-significant effect of days i.e. 10 days and 30 days (F = 7.87, p<0.00) and also a highly significant interaction between two variable factors (F = 30.83, p<0.005).

Post – hoc analysis by Newman keuls test showed highly significantly decreased (p<0.0001) level of SGPT by aspirin 75mg (EC) after 10 days and a highly significantly increased (p<0.0001) after 30 days. SGPT level was decreased highly significantly (p<0.0001) by aspirin 100mg, 150mg (EC) and 300mg after 10 days and 30 days.
Graph 1: Effect of different doses of aspirin on SGOT level with control after 10 days
Values are mean ± S.E. (n=10). Significant differences by Newman-Keuls test *p<0.01, **p<0.001/0.005 and ***p<0.0001 as compared to control rabbits, following two-way ANOVA df (1, 90).

Graph 2: Effect of different doses of aspirin on SGOT level with control after 30 days

Graph 3: Effect of different doses of aspirin on SGPT level with control after 10 days
Values are mean ± S.E. (n=10). Significant differences by Newman-Keuls test *p<0.01, **p<0.001/0.005 and ***p<0.0001 as compared to control rabbits, following two-way ANOVA df (1, 90).

Graph 4: Effect of different doses of aspirin on SGPT level with control after 30 days

3.2. Discussion

The present study explored the toxicological and pharmacological effects on liver enzymes by daily oral administration of different doses of aspirin 75mg (EC), 100mg, 150mg (EC) and 300 mg and in different preparation i.e. enteric coated and non-enteric coated for 10 days and 30 days. Previous studies have shown that the liver toxicity is reported by aspirin (Bjorkman, 1998), most liver diseases are characterized by the elevation of SGPT enzyme than SGOT but two exemptions in alcohol abuse and/or in cirrhosis are associated with higher SGOT level than SGPT level, often in a ratio of approximately 2:1 (Palmer, 2004). In our finding SGOT level was increased in all doses after 30 days of treatment but level was significantly increased with 75mg (EC) and 100mg. this effect could be due to the nitric oxide liberation and free radicals scavenging abilities of liver, in low doses these abilities of liver is decreased and leading to liver toxicity. This is supported by the statement that NO-aspirin is also available which could be both hepato protective and can control platelet aggregation (Fiourcci and Del Soldatto, 2003).

Liver transaminases (SGPT and SGOT) are useful biomarkers of liver injury in a patient with some degree of intact liver function (Johnston, 1999; McClatchey, 2002; Mengel et al., 2005). Since SGOT can also be elevated in other diseases affecting other organs, SGPT is considered more specific for liver toxicity. Fragge et al. (1960) stated that one third of their patients with heart failure had increased SGOT level (Fragge et al., 1960). Studies have reported that SGOT level raised in acute liver damage but is also
exist in red blood cell, skeletal and cardiac muscles, so SGPT elevated level are not specific to the liver damage so SGOT has also been used as a cardiac marker. Sometime SGOT to SGPT ratio useful in differentiating between causes of liver damage (Nyblom et al., 2004; Nyblom et al., 2006).

In our finding level of SGPT increased only by aspirin 75mg (EC) after 30 days and all other doses decreased its level irrespective of duration of treatment. This could be due to reducing the protection of lever to inflammation and lessen anti-oxidant action. No studies are found to support our finding. Studies have shown that the mechanism for aspirin caused liver injury is not clear. Aspirin produced hepatotoxicity as a cumulative phenomenon which requires days or week to develop. Patients with rheumatic diseases as well as children are mainly susceptible (Zimmerman, 1981). The potential of aspirin and salicylate to cause hepatotoxicity has been only recently acknowledged (Prescott, 1980). Aspirin in high doses for the treatment of rheumatic fever in children caused liver toxicity (Karademir et al., 2003; Singh et al., 1992). In our histopathological slides showed that there was a mild to moderate portal inflammation, micro vesicular steatosis and focal cellular swelling with cytolysis. The preparations which are enteric coated only have advantage to overcome the gastrointestinal (GI) adverse effects and other effects are not dependent on its coating.

4. CONCLUSION

In conclusion, the results of this exploratory study show that the long term use of 75mg (EC) could be hepatotoxic due to reducing its anti-oxidant activity, but in our finding aspirin 150mg (EC) may be given to patients with hepatic insufficiency and other G.I problems as it cannot alter the hepatic function significantly.

5. RECOMMENDATION

Further study should be carried out to observe the effects of combination of aspirin along with prasugrel, clopidogrel and other antioxidants on various parameters.

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