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Low Doses of Acetaminophen Prolonged Prothrombin Time and Increased International Normalized Ratio in Patients Receiving Long-Term Therapy

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Abstract

Objectives: Acetaminophen is one of the safest and effective antipyretic and analgesic medications. Long term administration of this medication appeared to interfere with the activity of two key enzymes of the vitamin K cycle. The primary end point of this study was to evaluate the chronic effect of acetaminophen on Prothrombin Time (PT) and International Normalized Ratio (INR) parameters.

Methods: Prospective, longitudinal , double-blind, placebo-controlled study was performed in Kurdistan region of Iraq, patients suffering from mild headache were prepared to take acetaminophen 500 mg twice daily for at least (8) months. PT, INR, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were measured for both patient and control groups before drug administration and then every month.

Results: The main consequence of the study was the difference in mean PT and INR between control group and group receiving acetaminophen long term therapy for 8 months. In patients on acetaminophen (1 g/day), the mean observed PT and INR were significantly elevated during therapy period. The significant differences in mean PT started from the second month of therapy (12.910 ± 0.098) in patients on acetaminophen versus (12.083 ± 0.077) in control participants (P<0.01). The maximum variations of mean PT was observed after eight months in patients on acetaminophen compared with the control participants (18.903 ± 0.184 vs. 12.300 ± 0.066, P< 0.01). Likewise the mean observed INR was significantly increased after the second month of treatment (1.123 ± 0.013) in patients on acetaminophen versus (1.006 ± 0.101) in control subjects (P<0.01). As well, maximum variations of mean INR observed after eight months in patients on acetaminophen compared with the control participants (2.084 ± 0.033 vs. 1.036 ± 0.008, P<0.01). There was a significant difference of mean ALT observed during the latest three months of study period in patients on acetaminophen compared with the control participants (P<0.01). However a significant value of both PT and INR in all patients rose markedly during the eight months of acetaminophen therapy.

Conclusion: The clinical findings of this study support that chronic administration of acetaminophen at low dose (Ig/day) induce a highly significant elevation of PT and INR parameters in all patients participated in this study.

Keywords: Acetaminophen; N-acetyl-para-benzoquinoneimine; Vitamin K cycle; Prothrombin time; International normalized ratio

Introduction

Acetaminophen is one of the most widely and commonly used analgesics and antipyretics worldwide. It is related to the large group of Non-steroidal anti-inflammatory drugs (NSAIDs) , but with distinct differences [1]. Acetaminophen is a weak inhibitor of COX-1which is responsible for prostaglandin biosynthesis and a very weak inhibitor of COX-2 that is tightly regulated the inflammatory conditions [1,2] .

In 1972, Flower and Vane [3] confirmed that acetaminophen inhibit the synthesis of prostaglandin mainly in the central nervous system, but less in peripheral tissue. Acetaminophen has ability to passage blood-brain barrier and inhibit the synthesis of prostaglandin, this inhibition has been considered to be the main action of acetaminophen [3-5]. However, acetaminophen has less peripheral adverse effects that associated with NSAIDs, such as stomach ulcers and impaired hemostasis [6].

At therapeutic doses, approximately 85% of acetaminophen metabolized by phase II conjugation to sulfated and glucoronidated metabolites, which then excreted in the urine [7]. Up to 10% of the drug metabolized through cytochrome P450 mixed function oxidase system (primarily by CYP2E1) into a toxic, highly reactive intermediate N-acetyl-para-benzoquinoneimine (NAPQI) [7-9]. Under normal condition, toxic intermediate NAPQI detoxified by hepatic glutathione to form inert nontoxic thiol metabolites [10]. In toxic doses of acetaminophen, the phase II conjugation system become saturated and the rate of NAPQI production proportionally increased due to more acetaminophen metabolized by hepatic CYP2E1 [7,9]. Furthermore, excessive NAPQI production depletes glutathione by 70 % causing hepatocellular injury [11].

The production of NAPQI in human body affects a number of metabolic pathways in the liver, and might inhibit vitamin k function [12]. The molecular function of vitamin K is to act as a cofactor for the enzyme gamma-glutamyl carboxylase that catalyzes the conversion of glutamyl residues (Glu) to g-carboxyglutamyl residues (Gla) in a variety of proteins referred to as vitamin K–dependent (VKD) proteins [13,14]. These VKD proteins include clotting factors II, VII, IX and X, are mainly synthesized in the liver and require gamma-carboxylation by vitamin K to be activated and conducted essential blood coagulation process [15].

Inhibition the activity of vitamin K dependent clotting factors causes disturbance and prolongation of PT [16]. Many evidence suggested that prolonged prothrombin time is consider to be a valuable early indicator of liver diseases, disorder of vitamin K cycle , and

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hepatic damage due to poisoning with acetaminophen [17,18].

PT is an important screening test used for diagnosis and estimation of hemostasis [19]. In 1982, The INR revised model was adopted for standardizing PT test and calibration of thromboplastin reagent of different species, this model calculated as follows [20]

$$INR = (\text{patient PT/mean normal PT})^{ISI},$$

where ISI indicated the International Sensitivity Index of the thromboplastin to perform the PT measurement [16].

The main purpose of this study is to evaluate the chronic effect of acetaminophen on both PT and INR parameters on patients receiving acetaminophen for long period of time, and to provide insights into possible biological mechanisms of acetaminophen and its metabolite NAPQI.

Materials and Methods

Subject and materials

This study is a prospective, double-blind, placebo-controlled, longitudinal study in which subjects enrolled between October (2013) to May (2014). Sixty patients, their ages are between (25-65) years old suffer from mild headache. Specialist decided to give them acetaminophen or placebo for long period of time. All patients gave written informed consent for participation in the study. Exclusion criteria were impaired renal function (Creatinine clearance<75 ml/min), bleeding and the use of medications like NSAIDs and Anticoagulants. Other exclusion criteria were history of alcohol intake, history of drug abuse, history of hepatic disease or elevation of serum transaminase level.

After providing informed consent, the 60 patients were randomized in two groups (Figure 1); the first group to be treated with acetaminophen, and the second one received placebo to consider as a control group. Both groups were followed up throughout eight months of the study. Treatment regimen consisted of taking one tablet of acetaminophen 500 mg twice daily. All patients underwent baseline (PT and INR) and hepatic transaminase test at the time of enrollment.

Every month, blood samples were taken for estimation of PT and INR in the 60 patients in order to find the extent of acetaminophen effect on these parameters, and also to evaluate if there was a significant difference in PT and INR in treated group compared with the control group. In addition to these parameters this study conducted to evaluate the effect of acetaminophen on serum hepatic transaminase level in both groups.

This study was carried out in the laboratories of the Rizgary Teaching Hospital and Al-wafaa Medical Center. The protocol was agreed by the Ethics committee of College of Pharmacy, Hawler Medical University (150513/9).

The total numbers of the patients in each group was 30 patients (15 women and 15 men) with their ages ranged between 25-65 years.

The study protocol is demonstrated in Figure 1.

Measurement of PT and INR

PT and INR were measured following the method of Neofotistos et al. [21] with slight modification. About 4.5 ml venous blood was drawn from each subject, and then transferred into a plain tube contain 0.5 ml of (3.8%) sodium citrate solution. after mixing the tube, centrifuged it for 10 minutes at 3000 rpm to separate the plasma. 1 ml of the plasma

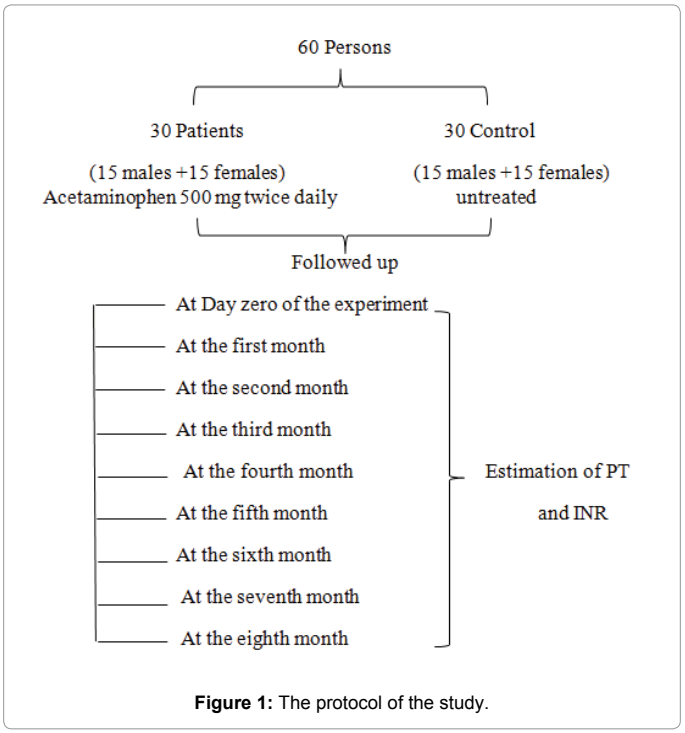

Figure 1: The protocol of the study.

was delivered into glass tube (khan tube), and then put this tube into CA-500 SERIES Automated Coagulation Analyzer to evaluate both PT and INR value. The international sensitivity index (ISI) of the tissue thromboplastin used was 1.62 for all data. This automated coagulation analyzers are capable of automatic delivery of reagents and plasma samples to the reaction cuvette, barcode sample identification, and then computerized the data of the samples to report the results on the screen of this device.

The normal rage of PT was 11-16 according to laboratory Bio-TP kit which used for determination of PT and INR in human plasma [22].

Measurement of aminotransferase (ALT and AST)

ALT and AST were measured according to the method of Bergmeyer et al. [23] with slight modification. Venous blood was collected from each subject, and then transferred into a gel barrier tubes. Centrifuged the tubes at 1500 × g for 10 minutes and put them in to Random Access Chemistry Analyzer (TARGA 3000) to estimate the serum level of ALT and AST.

Statistical analysis

All results are expressed as mean ± standard error of mean (SEM). The primary end point of the study was to determine the difference in mean PT and INR between acetaminophen and control groups at monthly intervals. All data was determined using a paired-samples T test (p values<0.01). Secondary end point was to determine the difference in mean PT and INR between treated and pretreated patients within the same group, using one way analysis of variance (ANOVA). P values, 0.01 were considered statistically significant. The Bonferroni multiple comparison tests were used to locate significant differences between treated and pretreated groups means. The third point of the study was to determine the significant difference in mean ALT and AST between acetaminophen and control groups using a paired-samples T test (p values<0.01).

Results

In this study the patients were enrolled between October (2013) to May (2014). Sixty patients were enrolled to take acetaminophen or placebo for 8 months. All patients underwent baseline PT test and INR value at the time of enrollment. All the observational results before taking the medication were within normal (PT= 11.886 ± 0.070, INR=0.979 ± 0.009, $P<0.01$). As well the observational results before taking placebo were within normal range also (PT= 11.990 ± 0.077, INR=0.992 ± 0.104, $P<0.01$).

The acetaminophen regimen was started early in 30 patients suffering from daily mild headache under the consultation of the specialist; they received acetaminophen 500 mg twice daily for 8 months. Likewise the control group which consists of 30 subjects received placebo for the same period of time.

Analysis of the primary end point during study period revealed a statistical significant increase in mean PT between acetaminophen and control groups. In patients on acetaminophen, the mean observed PT was increased after the first month of therapy (12.236 ± 0.087) *versus* (12.076 ± 0.072) in control subjects ($P<0.01$). But there was no significant difference between patient and control groups after the first month of therapy. However, the significant increase in mean PT was observed after cumulative administration of acetaminophen.

The changes in mean PT in patients on acetaminophen compared with the control group are shown in Table 1.

The mean observed PT was significantly increased started from the second month of therapy (12.910 ± 0.098) in patients on acetaminophen *versus* (12.083 ± 0.077) in control participants ($P<0.01$). While the maximum variations of mean PT was observed after eight months of therapy in all patients on acetaminophen compared with the control participants (18.903 ± 0.184 *vs*. 12.300 ± 0.066, $P<0.01$).

As well, all the 30 patients who took the medications were observed to have high INR. The mean observed INR was increased after the first month of treatment (1.028 ± 0.105) *versus* (1.005 ± 0.009) in control subjects. But, there was no significant difference between patient and control groups after the first month of therapy. However, the significant elevation in mean INR was observed after cumulative administration of acetaminophen.

The changes in mean INR in patients on acetaminophen compared with the control group are shown in Table 2.

The mean observed INR was also significantly increased from the second month of treatment (1.123 ± 0.013) in patients on acetaminophen *versus* (1.006 ± 0.101) in control group ($P<0.01$). Whilst, the maximal variations in INR observed after eight months of treatment in all patients on acetaminophen *compared with* the control participants (2.084 ± 0.033 *vs.* 1.036 ± 0.008, $P<0.01$).

The result of the study revealed that gradual increase of PT and INR estimated from the first to the eighth month of treatment. There was a significant difference in both PT and INR in patients received acetaminophen compared with control group.

The secondary point of the study was to determine the differences in mean PT and INR between treated and pretreated patients within acetaminophen group. In patients on acetaminophen, the value of PT and INR increased gradually from the first to the eighth month of therapy. The mean observed value of both PT and INR was none significantly increased after the first month of treatment. However, there was a statistical significant difference between treated and pretreated patients starting from 2nd to 8th month in both PT and INR parameters

The changes in mean of PT and INR in patients on acetaminophen compared to their pretreated values are previously shown in Tables 1 and 2.

The mean observed PT was significantly elevated from the 2ndto the 8th month (12.910 ± 0.098) to (18.903 ± 0.184) respectively, in patients on acetaminophen therapy *versus* (11.886 ± 0.070) in pretreated patients ($P<0.01$). Likewise, there was also a significant difference in INR value started from the 2nd to the 8th month (1.123 ± 0.013) to (2.084 ± 0.033) respectively, in patients on acetaminophen therapy *versus* (0.979 ± 0.009) in pretreated patients within the same group ($P<0.01$).

The one-way analysis of variance (ANOVA) for repeated measures detected a statistical significant difference of acetaminophen on both PT and INR parameters before and after acetaminophen therapy within the same group. Analysis of secondary point revealed that; there was a statistical significant difference in both PT and INR in patients received acetaminophen compared with the pretreated value.

The second part of the study was to investigate the chronic effect of acetaminophen at dose of (1 g/day) on the level of ALT and AST. All 60 patients underwent baseline serum ALT and AST at the time of enrollment. All the observational results before taking acetaminophen were within normal (ALT=19.366 ± 0.815, AST=18.666 ± 0.629, $P<0.01$)

In patient on acetaminophen, the mean observed ALT was increased after fifth month of therapy (24.600 ± 0.813) *versus* (21.633 ± 0.897) in control subjects ($P<0.01$). But there was no significant difference between patient and control groups after five months of therapy. However, the significant increase in mean ALT was observed from the sixth month in patients on acetaminophen (28.466 ± 0.860), *versus* (22.600 ± 0.909) in control participants ($P<0.01$). The maximum variations of mean ALT was observed after eight months of therapy in patients on acetaminophen compared with the control participants (42.533 ± 1.061*vs*.25.200 ± 0.919, $P<0.01$). The mean AST was not provided any significant change during eight months of therapy in both acetaminophen and control groups. Although, there was an increase in mean AST after eight months in patients on acetaminophen versus control groups (25.166 ± 0.648 *vs*. 23.766 ± 0.685, $P<0.01$), but this elevation was not significant.

The changes in mean ALT and AST in patients on acetaminophen compared with the control group are shown in Tables 3 and 4.

Discussion

Acetaminophen is one of the safest and effective antipyretic and analgesic medications, but with a very weak anti-inflammatory activity [24,25]. Unlike NSAIDs, acetaminophen largely lacks peripheral anti-inflammatory properties, suggesting that it is centrally inhibited prostaglandin synthesis [3,12]. Although it is safe when used frequently, but acetaminophen remain one of the most common toxicity cases that recorded in poisoning centers [7].

In this study, 60 participants were enrolled; 30 patients had taken acetaminophen 500 mg twice daily for long period of time and 30 subjects considered as control group. These randomized cases have been performed to evaluate the effect of acetaminophen and its metabolite NAPQI on both PT and INR parameters.

Our study demonstrates that an administration of acetaminophen

Period	Patient	Control
Pre-treat.(D0)	11.886 ± 0.070	11.990 ± 0.077
1M	12.236 ± 0.087	12.076 ± 0.072
2M	12.910 ± 0.098*	12.083 ± 0.077*
3M	13.806 ± 0.168*	12.133 ± 0.068*
4M	14.843 ± 0.076*	12.193 ± 0.073*
5M	15.686 ± 0.180*	12.186 ± 0.060*
6M	16.676 ± 0.193*	12.290 ± 0.072*
7M	17.570 ± 0.183*	12.283 ± 0.069*
8M	18.903 ± 0.184*	12.300 ± 0.066*

(All data are expressed as Mean±SEM; the significance was set at $p < 0.01$. Do=Day zero; M=Month)

Table 1: The chronic effect of acetaminophen on patient's PT as compared to the control group.

Period	Patient	Control
Pre-treat.(D0)	0.979 ± 0.009	0.992 ± 0.104
1M	1.028 ± 0.105	1.005 ± 0.009
2M	1.123 ± 0.013*	1.006 ± 0.101*
3M	1.251 ± 0.019*	1.013 ± 0.009*
4M	1.408 ± 0.026*	1.019 ± 0.009*
5M	1.538 ± 0.029*	1.020 ± 0.008*
6M	1.701 ± 0.326*	1.033 ± 0.101*
7M	1.854 ± 0.031*	1.033 ± 0.009*
8M	2.084 ± 0.033*	1.036 ± 0.008*

(All data are expressed as Mean±SEM; the significance was set at $p < 0.01$. Do=Day zero; M=Month)

Table 2: The chronic effect of acetaminophen on patient's INR as compared to the control group.

Period	Patient	Control
Pre-treat.(D0)	19.366 ± 0.815	19.266 ± 0.734
1M	19.433 ± 0.721	19.233 ± 0.742
2M	19.600 ± 0.665	19.533 ± 0.790
3M	20.300 ± 0.806	19.633 ± 0.850
4M	21.333 ± 0.860	19.966 ± 0.943
5M	24.600 ± 0.813	21.633 ± 0.897
6M	28.466 ± 0.860*	22.600 ± 0.909*
7M	34.366 ± 0.951*	23.966 ± 0.920*
8M	42.533 ± 1.061*	25.200 ± 0.919*

(All data are expressed as Mean ± SEM; the significance was set at $p < 0.01$. Do=Day zero; M=Month)

Table 3: The chronic effect of acetaminophen on patient's ALT level as compared to the control group.

Period	Patient	Control
Pre-treat.(D0)	18.666 ± 0.629	18.066 ± 0.563
1M	19.333 ± 0.671	18.433 ± 0.603
2M	19.566 ± 0.596	19.333 ± 0.620
3M	20.433 ± 0.594	20.133 ± 0.584
4M	20.766 ± 0.592	19.766 ± 0.901
5M	21.066 ± 0.613	20.566 ± 0.637
6M	21.766 ± 0.667	21.933 ± 0.594
7M	23.266 ± 0.637	22.133 ± 0.651
8M	25.166 ± 0.648	23.766 ± 0.685

(All data are expressed as Mean±SEM; the significance was set at $p < 0.01$. Do=Day zero; M=Month)

Table 4: The chronic effect of acetaminophen on patient's AST level as compared to the control group.

at dose of 1 g/day for eight months significantly elevates the value of PT and INR parameters. The significant elevation of these parameters described in all 30 patients on acetaminophen starting from the second month of therapy to reach maximum variation values at the end month of study. There were highly significant differences of both PT and INR in patients receiving acetaminophen versus control group.

The secondary point of this study revealed a significant difference in mean PT and INR in patients on acetaminophen compared with their pretreated values. Among those patients on acetaminophen, The PT and INR were statistically significantly increased from the second to the eighth month of therapy. While the value of these parameters not significantly changed with control group.

The result of this study confirmed that chronic administration of acetaminophen result in prolonged PT and high INR value in 30 patients compared with the control group that received placebo. This result indicates the validity of PT and INR to investigate the chronic acetaminophen therapy. The result of this study correlated well with the studies of Whyte and Thijssen [17,26] .

In fact, a significant increases of PT and INR following chronic therapy, was closely related to the mechanism of acetaminophen and its metabolite NAPQI. Repeating dose of acetaminophen result in plasma accumulation of the drug and this accumulation raises to a more than dose dependent increase in the amount of NAPQI formed [10]. The excessive generation of highly reactive toxic NAPQI depletes glutathione and is covalently bind to hepatocellular protein causing cell injury [7,11].

Whyte and colleagues [17] mentioned that acetaminophen and / or its metabolite NAPQ1 affect the function of vitamin K, and might inhibit its action. Vitamin K (vitamin K hydroquinone) while act a cofactor for gamma-glutamyl carboxylase, it catalyzes the conversion of Glu to Gla in a class of proteins referred to as VKD proteins [27]. This carboxylation is required for the functional activity of VKD proteins which play an essential role in blood coagulation process [28].

Thijssen et al. [26] has been reported that acetaminophen and its metabolite NAPQ1 effect the activity of 2 key enzymes of the vitamin K cycle which are gamma-glutamyl carboxylase (GGCX) and vitamin K-epoxide reductase (VKOR). The first enzyme GGCX catalyzes the posttranslational modification of glutamic acid to gamma carboxyglutamic acid which is essential for activity of VKD proteins [29]. The second enzyme is VKOR which responsible for reduction of vitamin K epoxide (KO) back to vitamin K hydroquinone (KH2) and regeneration of vitamin K cycle [28].

In this study, patients had taken acetaminophen for long period of time and the results showed a significant increase in PT value. This prolongation of PT may reflects the effect of NAPQI on the activities of vitamin K dependent protein, which are essential for blood coagulation [26,29]. However to examine the mechanism of this effects, many studies had been performed to conduct the effect of acetaminophen on blood coagulation parameters.

Whyte et al. [17] investigated the effect of acetaminophen on INR. The study showed that 143 patients having time-dependent increase in INR with acetaminophen overdose but without hepatic injury.

Another double-blind placebo-controlled study conductedin 2006 by Mahe et al. [30]. The study showed that 20 patients randomized to receive placebo or acetaminophen 1g 4 times daily. the result of the study indicated a significant increase of INR after 1 week of acetaminophen intake compared with placebo [30]. In both Whyte

and Mahe studies, there was a significant elevation in INR value after acetaminophen ingestion which related largely to the inhibition of vitamin K-dependent clotting factors [17,30].

Lopes et al. [12] investigations have performed that NAPQI effect on vitamin k cycle through deoxidizing vitamin K-hydroquinone, directly inhibiting Vitamin K-dependent carboxylase, and inhibiting the activity of VKOR enzyme. Therefore 3 sites of vitamin K cycle deteriorated in the presence of toxic metabolite NAPQI [12]. As well, Lopes et al. [12], showed another effect on vitamin K cycle by essential redox protein called thioredoxin. Many evidence indicated that thioredoxin is a molecule that reactivating VKOR enzyme [31]. However, the presence of oxidative stress species due to acetaminophen overdose, is impaired the activity of thioredoxin itself and consequently VKOR enzyme [12,26].

In addition to the critical effect of NAPQI on vitamin K cycle, this cycle was also affected by several metabolic pathways. Chronic administration of acetaminophen increases CYP2E1 induction which result in generation of reactive species called peroxynitrite (ONOO) [12,32]. Furthermore, while acetaminophen was used as CYP2E1 substrate, the expressing CYP2E1 within mitochondria was sufficient to produce reactive oxygen species and depleted the reduced glutathione [33]. All these intracellular events inversely affected the integrity of the vitamin K cycle [7,12].

In contrast to our study, there are many observational studies investigating that the interaction between acetaminophen and warfarin result in significant increase of INR values. However, the mechanism of this interaction is not clearly understood [26,34]. In 2005, a prospective study of Mahe and colleagues [35] randomized 11 patients on stable warfarin therapy to receive a random regimens of acetaminophen or placebo. The mean observed INR was significantly increased after 4 days and for the duration of the study in patients on acetaminophen, while it did not significantly change with placebo [35]. In 2007, another prospective study performed by Parra et al. [36] who tested the effect of acetaminophen in patients on stable warfarin therapy. This study also evaluated a statistical significant increase in mean INR in patient on acetaminophen compared with placebo [36]. From these prospective studies, we indicate that NAPQI affects the activity of vitamin K cycle regardless the presence of warfarin.

This study was also conducted the clinical effect of chronic administration of acetaminophen on hepatic aminotransferase (ALT and AST). In addition to the observed effect of acetaminophen on PT and INR, the level of ALT and AST was also affected by this medication. In this study we observed that the mean ALT was increased after five months of therapy, but this elevation was not significant. However the significant increase of mean ALT observed from the sixth to the eighth month in all patients on acetaminophen versus control participants. While, there were non-significant differences of mean AST in patients on acetaminophen therapy versus control group.

The result of our study investigated that an administration of acetaminophen at dose of 1 g/day for eight months significantly changes the value of ALT and to lower extent AST. Our findings are similar to the studies of Parra and Watkins [36-38]. The observed changes in ALT and AST regarded largely to the mechanism of acetaminophen and its toxic metabolite NAPQI. Excessive production of NAPQI irreversibly binds to the hepatic molecules and induces many deleterious effects [7,8,11]. Many observation studies reported that administration of acetaminophen 4 g/day for short period of time significantly elevated serum ALT level [37,38].

The current study evaluates the association between chronic administrations of acetaminophen and significant increase of PT, INR and ALT. The production of NAPQI is increased with patients taken acetaminophen for long period of time and/or acetaminophen overdose. The observational data approving that after repeating dose of acetaminophen is accumulated in plasma, which in turn raises the amount of highly reactive NAPQI to be formed [10]. NAPQI then appear its effect on the vitamin K cycle by inhibition the activation of GGCX and VKOR enzymes which support the carboxylation and together activate VKD proteins [39]. VKD proteins have an essential action in controlling blood coagulation process, therefore any defect in biological activity of these protein may disrupt the coagulation cascade process [13]. Evidence suggests that the mechanism of acetaminophen or its metabolites NAPQI on PT and INR parameters was largely due to reduction in the vitamin K-dependent clotting factors, specifically VII [17,30]. In addition to the inhibitory effect of NAPQI on vitamin K cycle, it has considerable effect in changing the level of aminotransferases after chronic administration of acetaminophen [7].

Conclusion

The results of our study support the statistical significant increase of PT and INR in patients received low doses of acetaminophen for long period of time. All patients on acetaminophen therapy developed a statistical significant elevation in these coagulation parameters. The precise mechanism of this elevation is largely related to the production of highly reactive toxic metabolite NAPQI after cumulative doses of acetaminophen. The data of the study suggest that chronic administration of acetaminophen even in low doses increase the risk of abnormal coagulation parameters. These findings may have important inclusions for clinical awareness of patients receiving acetaminophen for long period of time, and put them at risk of many metabolic disturbances in the liver.

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