Influence of acetaminophen at therapeutic doses on surrogate markers of severity of acute viral hepatitis

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SUMMARY

Objectives — Data on the influence of acetaminophen intake on acute viral hepatitis is scarce, but it could play a role in the worsening of this disease. The aim of this study was to determine whether the intake of acetaminophen at therapeutic doses affects the severity of acute viral hepatitis.

Methods — This was a prospective study concerning 37 consecutive patients hospitalized for acute viral hepatitis. Acetaminophen consumption and time since last intake were assessed by a questionnaire. Parameters of severity were studied in comparison to time related serum concentrations of acetaminophen.

Results — Patients hospitalized for acute viral hepatitis (18 male, 19 female patients) had a mean age of 29.2 ± 11.5 years. The causal virus was HAV (n = 23), HBV (n = 7) and other viruses (n = 8). The mean cumulated dose of acetaminophen was 7.7 ± 5.65 g. The daily dose did not exceed the therapeutic dosage and the mean was 1.95 ± 0.81 g (1-3 g). Patients who received 7.5 g of acetaminophen or more had a lower prothrombin index 52.4 ± 30.3% vs 74.2 ± 17.2% (P = 0.039), and a lower factor V 54.7 ± 33.2% vs 83.3 ± 19.6% (P = 0.033). Prothrombin index and bilirubinemia were negatively correlated with time related plasma acetaminophen concentrations.

Conclusions — The use of acetaminophen at therapeutic doses was associated with greater alterations of surrogate markers of the severity of acute viral hepatitis especially hepatitis A. This was related to cumulated dosages and correlated to the time related acetaminophen plasma concentrations. Acetaminophen use should be interrupted when acute hepatitis is suspected.

RÉSUMÉ

Influence de la prise d’acétaminophène à doses thérapeutiques sur les marqueurs de sévérité des hépatites virales aiguës

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Malades et méthodes — Il s’agit d’une étude prospective concernant 37 malades consécutifs hospitalisés pour hépatite virale aiguë. La quantité d’acétaminophène et l’intervalle de temps depuis la dernière prise étaient évalués par un questionnaire. Les paramètres de sévérité de l’hépatite étaient étudiés par la concentration plasmatique d’acétaminophène en fonction du temps écoulé depuis la dernière prise.

Résultats — Les malades hospitalisés pour hépatite aiguë virale (18 hommes, 19 femmes) d’âge moyen 29.2 ± 11.5 ans présentaient une hépatite aiguë A, B, ou autre chez respectivement 23, 7, et 8 malades. La dose cumulée moyenne d’acétaminophène par malade était de 7.7 ± 5.65 g. La posologie quotidienne moyenne était de 1.95 ± 0.81 g (1-3 g). Les malades qui avaient reçu une dose cumulée d’acétaminophène ≥ 7.5 g avaient un taux de prothrombine plus bas 52.4 ± 30.3% vs 74.2 ± 17.2% (P = 0.039), ainsi qu’un taux plus faible du facteur V 54.7 ± 33.2% vs 83.3 ± 19.6% (P = 0.033). Le taux de prothrombine et la bilirubinémie étaient corréllés négativement avec la concentration plasmatique d’acétaminophène.

Conclusion — L’utilisation d’acétaminophène à posologie thérapeutique était associée par une altération des marqueurs biologiques de sévérité des hépatites virales en particulier les hépatites A. Cette altération était liée à la prise cumulée d’acétaminophène, et corrélée avec la concentration plasmatique d’acétaminophène en fonction du temps écoulé depuis la dernière prise. La prise d’acétaminophène devrait être arrêtée quand le diagnostic d’hépatite aiguë est posé.

Introduction

Acetaminophen is used to treat symptoms such as pain and fever. Therapeutic plasma levels range from 10 to 30 µg/mL. Peak levels after therapeutic doses do not exceed 20 µg/mL and they do not accumulate with multiple daily dosing [1]. However, patients who develop severe liver injury and continue to ingest multiple doses of acetaminophen may accumulate the drug due to prolongation of the half life of acetaminophen [2]. In the clinical setting, therapeutic dosages should take into account several factors, including history of ethanol abuse as well as the underlying hepatic illness. Several cases of severe liver toxicity have been reported even when the drug was taken at normal doses in alcoholic patients [3-6]. Furthermore, acetaminophen overdose, either intentional or unintentional, plays a major role in the etiology of acute liver failure.

During the prodromal period of viral infections, there is a down regulation of the gene expression of major cytochrome P-450 enzymes through proinflammatory cytokines, such as...
interleukins, transforming growth factor beta1, human hepatocyte growth factor, and lymphocytotoxin. The resulting effect varies according to the involved cytokines and the specific cytokine P-450, eventually leading to either metabolite-mediated adverse drug reactions or alteration of the metabolism of the drug [7]. Thus, acetaminophen metabolism is altered during acute viral hepatitis, and this alteration persists during the convalescence phase and disappears only after complete recovery from hepatitis. The elimination phase of acetaminophen is protracted, whereas the peak plasmatic concentration following a single dose is not affected [8]. The evolution of plasma acetaminophen concentrations after multiple dosages has not been studied in this setting. In patients with liver failure and portal hypertension, the absorption of acetaminophen is faster especially in the presence of esophagogastric varices [9]. Patients with cirrhosis have a higher area under curve and lower clearance of acetaminophen [9]. Increased absorption may be related to portal hypertension whereas protracted elimination is mainly due to liver failure [9]. Data on the role of acetaminophen in the course of acute viral hepatitis is scarce, but it seems to contribute to liver injury. Many questions remain unanswered [2]. In a recent paper, it was shownthat fulminant hepatitis A was associated with female gender, the rapid elimination of HAV detected by PCR, genotype other than genotype 1A, and acetaminophen intake [10]. However, in multivariate analysis, the only two independent prognostic variables were increased bilirubin levels and low or undetectable viremia. Acetaminophen is currently used for fever especially during the prodromal period before acute viral hepatitis is suspected. Data from the Acute Liver Failure Study Group showed that acetaminophen was detected in the serum of 20% of patients with acute viral hepatitis. In these patients median alanine aminotransferase levels were higher than in patients who did not take acetaminophen [11]. In a recent review, it was suggested that the 24 hour intake of acetaminophen in patients with acute or chronic liver disease should be restricted to around 2 g/day, which is half the suggested maximal dose of 4 g/day [12].

The aim of our study was to assess whether the intake of acetaminophen at usual therapeutic levels is associated with increased severity in the course of acute viral hepatitis.

Patients and methods

Study population

This was a prospective study of 37 consecutive patients hospitalized for acute viral hepatitis of various etiologies between December 2002 and February 2004. The causes for hospitalization were either acute liver failure or oral intolerance. A standardized questionnaire evaluating the quantity of ingested acetaminophen since the beginning of the symptoms, the interval since the last intake, as well as the search for factors associated with increased acetaminophen toxicity, (alcohol use, prolonged fasting, and underlying liver disease). Prolonged fasting was defined as the absence of food intake for more than 60 g per week. Consumption was less than 60 g/week (n = 19, 51.4%) or absent (n = 18, 48.6%) in all our patients. None of our patients had chronic alcohol abuse or recurrent binges.

Etiology

Twenty-two patients had an acute hepatitis A, 7 an acute hepatitis B, and among 8, hepatitis was related to either EBV or CMV. Out of the patients presenting with hepatitis B, 4 were severe, of whom, 3 had a fulminant liver failure, with 2 deaths related to liver disease (table I). Eight patients had a severe hepatitis in the HAV group. With respect to EBV related hepatitis a single patient had an increased prothrombin index (table I).

Acetaminophen intake in patients with acute viral hepatitis

Thirty-two patients (86.5%) had taken acetaminophen. The quantity of acetaminophen and the interval since the last intake could be precisely established in 25 patients. Total consumption, the mean number of days of acetaminophen intake and the daily dose of acetaminophen was equivalent in all groups. Interval since the last intake was longest in patients with acute hepatitis B (table I). All patients received acetaminophen prior to hospitalization and/or to the diagnosis of acute hepatitis and did not receive any further dose once the diagnosis was established. The mean cumulated dose of acetaminophen was 7.7 ± 5.7 g ranging from 1.5 g to 28 g taken over a mean period of 4.2 ± 3.2 days ranging from 1 to 14 days. The mean daily dose was 1.9 ± 0.8 g and extreme doses ranged from 1 g/day to 3 g/day. There were no patients with acute hepatitis without acetaminophen intake. Mean plasma acetaminophen concentrations were 32.3 ± 15.7 mg/L. Mean interval since the last intake was 33.5 ± 23.7 hours. When the interval was ≥ 24 hours, the mean plasma acetaminophen concentration was 34.8 mg/L, whereas when the delay was < 24 hours, the mean plasma concentration was 27.9 mg/L. This difference was not statistically significant. On the other hand, all patients (11/25) with a prothrombin index < 60% had acetaminophen detectable in plasma after a delay ≥ 24 hours. None of the patients with severe acute hepatitis had an interval of < 24 hours since the last intake. For
patients with prothrombin index $\geq 60\%$, 9 patients were detected within 24 hours, and 5 after 24 hours. When the interval was $\geq 24$ hours, 68.7% had severe hepatitis whereas 31.3% had non severe hepatitis ($P < 0.001$).

**Prothrombin index in relation to acetaminophen concentrations**

The Log (Ln) of the plasma concentration of acetaminophen and the time interval since the last intake were negatively correlated with the prothrombin index. This correlation was found in patients with acute hepatitis A. There was no statistically significant correlation in either of the groups of patients with acute hepatitis B nor EBV or CMV related hepatitis (figure 2).

On the other hand, the product of the mean serum concentration of acetaminophen times the time interval since the last intake was 61.2 when the prothrombin index was less than 60% and 30.9 when the prothrombin index was above 60% ($P = 0.001$) (table II). This difference was found in the acute hepatitis A group and could not be analyzed in the hepatitis B group since all the patients had a prothrombin index $< 60\%$ in this subgroup. There was no significant difference in patients with CMV or EBV related hepatitis.

The cumulated dose of acetaminophen in our population was $20.6 \pm 7.7 \text{ g}$. Patients who received $7.5 \text{ g}$ of acetaminophen or more had a lower prothrombin index, and a lower factor V activity. It should be noted that none of the patients exceeded the recommended dose of acetaminophen. There was no difference in aminotransferase levels, AST or ALT for the cumulated dose of acetaminophen (table III).

Two patients died from fulminant liver failure related to HBV infection. Both had a cumulated acetaminophen consumption of more than 7.5 g, and these patients had the highest product of the serum concentration of acetaminophen times the interval elapsed since the last intake in our studied population, with respectively 90.0 and 129.7. This product was respectively $41.0 \pm 21.2$ and $109.9 \pm 28.1$ for spontaneous recovery and for death (table II).

**Bilirubin relation to acetaminophen concentrations**

Patients who received $7.5 \text{ g}$ of acetaminophen or more, had a tendency to have higher bilirubin levels but this was not statistically significant. The product of the mean serum concentrations of acetaminophen times the interval since the last intake in our studied population, with respectively $28.1$ for spontaneous recovery and $21.2$ and $49 \pm 13.3$ respectively for bilirubin and prothrombin index (figure 1) (table II).

### Table I

<table>
<thead>
<tr>
<th></th>
<th>HAV</th>
<th>HBV</th>
<th>Other viruses</th>
</tr>
</thead>
<tbody>
<tr>
<td>N = 32</td>
<td>N = 7</td>
<td>N = 8</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>$24.9 \pm 5.7^{*}$</td>
<td>$43.2 \pm 20^{†}$</td>
<td>$36 \pm 14.5^{*}$</td>
</tr>
<tr>
<td>AST (IU/mL)</td>
<td>$2061 \pm 1655^{*}$</td>
<td>$1839 \pm 2018$</td>
<td>$511 \pm 389^{*}$</td>
</tr>
<tr>
<td>ALT (IU/mL)</td>
<td>$2796 \pm 2060^{*}$</td>
<td>$2668 \pm 3028$</td>
<td>$683 \pm 420^{*}$</td>
</tr>
<tr>
<td>GGT (IU/mL)</td>
<td>$259 \pm 104$</td>
<td>$172 \pm 84$</td>
<td>$223 \pm 178$</td>
</tr>
<tr>
<td>Alk. Phosphatase</td>
<td>$203 \pm 92$</td>
<td>$157 \pm 65$</td>
<td>$150 \pm 46$</td>
</tr>
<tr>
<td>Bilirubin µmol/L (IU/mL)</td>
<td>$91.2 \pm 80.6^{†}$</td>
<td>$195.3 \pm 166.9^{†}$</td>
<td>$40.8 \pm 47.8^{*}$</td>
</tr>
<tr>
<td>Prothrombin index (%)</td>
<td>$66.6 \pm 21.5^{†}$</td>
<td>$34.2 \pm 20.5^{†}$</td>
<td>$78 \pm 15.8^{*}$</td>
</tr>
<tr>
<td>Factor V (%)</td>
<td>$77.5 \pm 26.8^{†}$</td>
<td>$47.8 \pm 41.3^{†}$</td>
<td>$83.8 \pm 21.6^{*}$</td>
</tr>
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<td>Severe or (Fulminant hepatitis)</td>
<td>8 (0)</td>
<td>4 (3)</td>
<td>1 (0)</td>
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<tr>
<td>Hepatic encephalopathy (death)</td>
<td>0 (0)</td>
<td>3 (2)</td>
<td>0 (0)</td>
</tr>
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<td>Acetaminophen intake (data with known time elapsed since last intake)</td>
<td>$20 \pm 16$</td>
<td>$3 \pm 3$</td>
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<td>Quantity of ingested acetaminophen (g)</td>
<td>$5.0 \pm 3.6$</td>
<td>$5.1 \pm 5.9$</td>
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<td>Number of days of intake</td>
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<td>$8 \pm 5.3$</td>
<td>$5.2 \pm 4.5$</td>
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<td>Daily dosage (g)</td>
<td>$1.8 \pm 0.9$</td>
<td>$1.5 \pm 0.5$</td>
<td>$2.2 \pm 0.4$</td>
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<tr>
<td>Interval since last intake (hours)</td>
<td>$33.5 \pm 22.8^{†}$</td>
<td>$64 \pm 25^{†}$</td>
<td>$18.3 \pm 8.9^{*}$</td>
</tr>
<tr>
<td>Serum concentration of acetaminophen (mg/L)</td>
<td>$33.4 \pm 16.9$</td>
<td>$37.9 \pm 21.7$</td>
<td>$25.4 \pm 4.6$</td>
</tr>
</tbody>
</table>

* = HAV versus other virus, $P < 0.05$.

† = HAV versus HBV, $P < 0.05$.

‡ = HBV versus other virus, $P < 0.05$.  

Linear regression analysis showed a relation between plasma bilirubin concentrations with the time related concentration of acetaminophen. Statistical significance could not be reached for subgroups of viral hepatitis (figure 2).

**Time related acetaminophen concentration with relation to evolution**

In patients with hepatitis B, the mean Ln of the plasma concentration of acetaminophen and the interval of time since the last intake were respectively 64.3 and 109.8 in patients with a favorable outcome or death related to acute liver failure (P < 0.05). The mean product was respectively 42.8 and 30.3 in patients with acute hepatitis A and hepatitis of other etiologies. No deaths occurred in these two groups.

**Discussion**

Acetaminophen is a well-recognized cause of acute liver failure when taken in doses above 150 mg/kg/day (> 10 g). The potential for hepatotoxicity after acute overdose is best predicted from the Rumack-Matthew nomogram [14]. In certain settings and in particular in alcoholic patients, severe hepatotoxicity may occur after ingestion of as little as 4 g in 24 hours. Recent severe fasting was also considered a predisposing factor in patients with acetaminophen hepatotoxicity who had taken only 4 to 10 g in 24 hours [15]. The role of acetaminophen in increasing the severity of acute viral hepatitis was shown in patients with fulminant hepatitis A where the consumption of acetaminophen was a poor prognostic factor [10]. The dose that aggravates liver function tests has never been described, and in our series, the cut-off point of the cumulated dose was 7.5 g. AST and ALT levels were identical regardless of the ingested amount of acetaminophen. The prothrombin index and factor V were more altered in the group of patients who had taken more than 7.5 g. It is noteworthy that 85% of our patients consumed acetaminophen prior to hospitalization, making the comparison with a non-acetaminophen group difficult since the number of patients in this group is very low. Furthermore, in our experience, almost all patients with severe acute hepatitis or fulminant liver failure had consumed acetaminophen at some moment during the prodromal phase.
There is controversial evidence on the efficiency of acetylcysteine treatment for non-acetaminophen-induced acute liver failure [16]. Some of the controversy might be explained by a susceptibility to low dose acetaminophen in some patients, and its role in aggravating liver failure. Acetylcysteine could be beneficial in this subset of patients.

Criteria for the severity of acute viral hepatitis include INR or prothrombin ratio, serum bilirubin and prothrombin index. The prothrombin index INR may be affected by multiple factors including liver failure, chronic cholestasis, acetaminophen, N-acetyl-cysteine [17-19]. Acetaminophen may decrease the prothrombin index in patients with acetaminophen poisoning without hepatic injury. This effect is proportional to the ingested dose and to the nomogram-based risk [18]. It is due to a decrease in the function of factor VII but not to the amount of antigenic factor VII in exposed patients [18]. In our patients, the ingested amount of acetaminophen was within therapeutic range and the mean cumulated dose was 7.7 g, which is low in comparison to described doses affecting the prothrombin index. Furthermore, the plasma concentration of acetaminophen was lower than concentrations seen in acetaminophen intoxications, and it is not known if such concentrations affect the prothrombin index. Finally, the drop in the prothrombin index was correlated with a decrease in factor V suggesting that the latter was probably mainly related to the severity of hepatitis. N-acetylcysteine treatment was reported to decrease the prothrombin index in all patients [17]. In our patients, all plasma acetaminophen dosages were performed prior to the start of N-acetylcysteine perfusion. In a recent study, the detection of plasmatic acetaminophen-containing protein adducts showed that unrecognized acetaminophen

Fig. 1 – Line Chart representing mean Log acetaminophen plasma concentration x time interval since the last intake in relation to Prothrombin index and bilirubin in all patients. A = bilirubin < 60 µmol/L and prothrombin index > 60%, B = bilirubin ≥ 60 µmol/L and prothrombin index ≥ 60%, C = bilirubin < 60 µmol/L and prothrombin index < 60%, D = bilirubin ≥ 60 µmol/L and prothrombin activity < 60%. Differences were statistically significant (P < 0.05) excepted for B versus C (P = 0.09).

Représentation graphique du Log de la concentration plasmatique d’acétaminophène x le temps écoulé depuis la dernière prise en fonction du taux de prothrombine et de la bilirubine plasmatique. A = bilirubine < 60 mmol/L et TP > 60 %, B = bilirubine ≥ 60 mmol/L et TP ≥ 60 %, C = bilirubine < 60 mmol/L et TP < 60 %, D = bilirubine ≥ 60 mmol/L et TP < 60 %. Les différences étaient statistiquement significatives sauf pour B versus C (P = 0.09).

Fig. 2 – Graphic representation of the regression curves of Log (Ln) plasma acetaminophen concentration with respect to severity parameters of acute hepatitis showing overall population and HAV patients with respect to prothrombin index and bilirubin.

Représentation graphique des courbes de régression du produit du Log de la concentration plasmatique d’acétaminophène x le temps écoulé depuis la dernière prise en fonction du taux de prothrombine et de la bilirubine dans la population globale et chez les malades atteints d’hépatite aiguë A.
poisoning might account for 20% of acute liver failure of unknown etiologies [19, 20]. This technique might be interesting for detecting the influence of acetaminophen in acute viral hepatitis.

The increase in serum bilirubin observed in viral hepatitis is also a marker of severity. However, increased serum bilirubin can interfere with the enzymatic and chromogenic reactions involved in the acetaminophen dosing methods. Acetaminophen was detected in specimens from hyperbilirubinemic patients without a history of recent acetaminophen exposure. Dilution of hyperbilirubinemic specimens produces a correction of apparent acetaminophen concentrations. The threshold for interference of bilirubin with acetaminophen dosage is < 85 µmol/L [21].

In conclusion, Acetaminophen might be toxic even when used at therapeutic dosages in the patients with acute viral hepatitis, in particular acute hepatitis A. In our patients, time related plasma concentrations of acetaminophen was correlated to bilirubin levels and the prothrombin index which are surrogate markers for the severity of acute viral hepatitis. Acetaminophen should be discontinued and avoided once the diagnosis of acute hepatitis is established.

REFERENCES