Increased oro-cecal transit time in grade I or II hepatic encephalopathy

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SUMMARY

The pathogenic mechanisms of hepatic encephalopathy remain to be elucidated. It has been suggested that a digestive motor disorder could promote the absorption of toxins produced within the lumen and thus enhance hepatic encephalopathy.

Aim — To evaluate oro-cecal transit time in cirrhotic patients with and without hepatic encephalopathy.

Methods — Hospitalized patients with alcoholic cirrhosis without encephalopathy and with spontaneous grade I and II encephalopathy were included. Severity of hepatic encephalopathy was assessed clinically and the Child-Pugh score was used to describe cirrhosis severity. Nine healthy volunteers constituted a control group. Oro-cecal transit time was measured with the sulfasalazine test.

Results — Twenty-eight patients (mean age 62.5 ± 8.5 years) were included. Ten had hepatic encephalopathy of unknown cause and 18 were free of hepatic encephalopathy. Oro-cecal transit time was significantly longer in patients with hepatic encephalopathy (641 ± 350 min) compared to patients without hepatic encephalopathy (298 ± 96; P < 0.05) and to controls (354 ± 90; P < 0.05). Oro-cecal transit time was comparable for each Child-Pugh score and was not different between the two grades of hepatic encephalopathy.

Conclusion — Oro-cecal transit time is longer in alcoholic cirrhosis patients with hepatic encephalopathy. This digestive motor disorder provides a partial explanation of hepatic encephalopathy of unknown etiology.

RéSUMÉ

Augmentation du temps de transit oro-caecal dans l’encéphalopathie hépatique de stade I ou II

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La physiopathologie de l’encéphalopathie hépatique est mal connue. Il a été suggéré qu’un trouble moteur digestif pourrait favoriser le passage systémique de substances intraluminales et ainsi favoriser l’encéphalopathie hépatique.

But — Mesurer le temps de transit oro-caecal chez les malades cirrhotiques sans ou avec encéphalopathie hépatique.

Matériel et méthodes — Étaient inclus les malades hospitalisés présentant une cirrhose alcoolique sans ou avec encéphalopathie hépatique d’étiologie indéterminée et de stade I ou II. Le temps de transit oro-caecal a été mesuré par le test à la salazopyrine chez les malades et 9 volontaires sains. La gravité de l’encéphalopathie et de la cirrhose (score de Child-Pugh) ont été évaluées.

Résultats — Vingt-huit malades (âge moyen 62,5 ± 8,5 ans) ont été inclus. Dix-huit n’avaient pas d’encéphalopathie hépatique et 10 présentaient une encéphalopathie hépatique sans cause retrouvée. Le temps de transit oro-caecal était significativement plus élevé dans le groupe encéphalopathie hépatique (641 ± 350 min) que dans le groupe sans encéphalopathie hépatique (298 ± 96; P < 0.05) et le groupe témoins (354 ± 90; P < 0.05). Le temps de transit oro-caecal n’était pas influencé par la gravité de la cirrhose et le grade de l’encéphalopathie hépatique.

Conclusion — Les malades avec une cirrhose alcoolique avec encéphalopathie hépatique ont un temps de transit oro-caecal allongé. Cette anomalie motrice digestive pourrait expliquer un certain nombre d’encéphalopathies hépatiques dites idiopathiques.

Introduction

Hepatic encephalopathy is a serious complication affecting at least 50% of patients with cirrhosis [1, 2]. This neuropsychiatric syndrome results from metabolic anomalies caused by liver failure and cavo-portal anatomoses [1-3]. Clinical manifestations range from psychomotor impairment to coma. The pathophysiological mechanisms underlying hepatic encephalopathy remain to be elucidated [2, 3]. Experimental models are inadequate because they correspond either to fulminant hepatitis or cavo-portal anastomoses but not cirrhosis-related hepatic encephalopathy. In humans, several events (digestive bleeding, sepsis, electrolyte disorders, sedation, liver failure) can favor hepatic encephalopathy, but the cause of certain episodes remains unknown [4]. Most of the compounds (or their precursors) currently recognized as potentially involved in the generation of hepatic encephalopathy come from food intake or are produced by the digestive tract bacterial flora (ammonia, mercaptans, short-chain fatty acids, aromatic amino acids, gamma-aminobutyric acid) [4-8]. Slow transit time might favor absorption of these compounds into the systemic circulation and consequently facilitate development of hepatic encephalopathy.

In the rat, it has been demonstrated that portal hypertension affects small bowel migratory motor complexes and also increases oro-cecal transit time [9]. In humans, Chesta et al. [10] demonstrated increased duration of small bowel motor complexes in cirrhotic patients, a finding favoring a small bowel motility disorder in this population. More recently, other studies in cirrhotic [11] or chronic alcoholic [12] patients have demonstrated increased oro-cecal transit time compared with controls. These results strongly suggest that cirrhotic patients have a slower...
small bowel transit time. Van Thiel et al. [11] published the only study suggesting a correlation between hepatic encephalopathy and increased oro-cecal transit time which could favor production of ammonia and other compounds involved in the development of hepatic encephalopathy.

We hypothesized that slower small bowel transit time could favor the development of hepatic encephalopathy in cirrhotic patients. The purpose of our study was to compare the oro-cecal transit time in patients with stable alcoholic cirrhosis with or without hepatic encephalopathy of unknown cause.

Material and methods

This prospective monocentre study without direct individual benefit was conducted in the hepatogastroenterology unit of the Caen University Hospital. It was conducted in compliance with the guidelines of the Helsinki convention on biomedical research in patients.

Patients

To be included in this study, patients had to have cirrhosis exclusively related to alcohol intake and either present encephalopathy of unknown cause or be free of encephalopathy. Exclusion criteria were: 1) age under 18 years, 2) presence of grade III or IV encephalopathy, 3) medications known to affect gastrointestinal transit time (prokinetics, laxatives, psychotropics, antibiotics for more than 8 days, opiates or other transit inhibitors), 4) history of allergy to salicylates and/or sulfamides, 5) diabetes mellitus, 6) digestive bleeding or infected ascites.

Controls

A control group of nine healthy volunteers free of chronic disease and taking no medication for two weeks prior to the test was recruited for measurement of oro-cecal transit time. This group was used to establish our pharmacology laboratory’s normal value for oro-cecal transit time [13].

Diagnosis of hepatic cirrhosis

Positive diagnosis of cirrhosis was established by two hepatologists (TD and MB) working independently. Agreement was necessary for patient inclusion. Criteria retained for the diagnosis of cirrhosis were clinical signs (hard liver enlargement with signs of portal hypertension and/or liver failure), laboratory results (serum albumin, prothrombin, factor V, bilirubin, thrombopenia, protein electrophoresis), ultrasound findings (segment IV atrophy, segment I hypertrophy, portal vein dilatation, ascites, splenomegaly), and endoscopy results (signs of portal hypertension). An alcoholic etiology was retained if the patient’s daily alcohol intake was greater than 30 g/day for more than 10 years and serology tests for hepatitis B and C virus, transferin saturation, serum antibodies (anti-mitochondria, anti-centromere, anti-smooth muscle, anti-nuclear, anti-reticulum, anti-soluble hepatic antigen), alpha-1 antitrypsin, and ceruloplasmin were negative [14].

The Child-Pugh score [14, 15] was used to assess cirrhosis severity: Child A, B, and C.

Evaluation of hepatic encephalopathy

The diagnosis of hepatic encephalopathy was based on clinical presentation and psychometry. The same clinician (MB) evaluated hepatic encephalopathy in all patients using the criteria proposed by Conn and Lieberthal [16] which describe five grades: grade 0 (absence of encephalopathy), grade I (mild alteration), grade II (moderate alteration), grade III (severe alteration) and grade IV (coma). Patients with grade II or IV encephalopathy were not retained for this study due to the risk of swallowing disorders.

Measurement of oro-cecal transit time

The sulfasalazine test was used to measure oro-cecal transit time [17, 18]. Briefly, after oral administration of sulfasalazine (1 g, Salazopyrine®), the compound progresses without absorption to the colon where colonic bacteria break the azo linkage releasing two molecules: 5-aminosalicylic acid (5-ASA), which is eliminated in the stools, and sulfapyridine, which is rapidly absorbed in the bloodstream and can be assayed. The time interval between ingestion of sulfasalazine and the appearance of sulfapyridine in blood samples is the time required for sulfasalazine to reach the cecum. This time is considered to be the oro-cecal transit time [19, 20].

High-performance liquid chromatography C18 (inverted-phase chromatograph; 12.5 cm Lichrospher RP 8 Merck column with a mobile phase of 85% distilled water and 15% mixture (methanol 88%, ethyl alcohol 10%, acetic acid 2%) effluent; 2 ml/min flow rate; 261 nm detection) [21] was used to assay sulfapyridine in serum samples after double chromatoform then sulfuric acid extraction in acid buffer medium. Six concentration points of sulfadiazine ranging from 1 to 15 mg/L were used to draw the internal calibration curve. Each patient was given 1 g sulfasalazine per os at 8 a.m. Blood samples were drawn at 4, 6, 8, 12, 24, 36, 48 and 72 hours to determine the absorption/elimination parameters: maximal blood concentration (Cmax), absorption constant (ka), elimination constant (ke), area under the curve (AUC), time lag to absorption (Tlag), maximal absorption time (Tmax). Oro-cecal transit time was given by Tlag, the latency time between ingestion of sulfapyridine and appearance of its metabolite in the bloodstream. Tmax, expressed in hours, was calculated from the sulfapyridine absorption/elimination curve.

Values obtained in patients were compared with normal values for our pharmacology laboratory established from the control group of nine healthy volunteers [13].

Statistical analysis

Student’s t test was used to compare discrete values. The chi-square test was used for percentage or two-class variables. Pharmacokinetic parameters were expressed as mean ± standard deviation. Analysis of variance was performed with the non-parametric Kruskal-Wallis test. Two-way analysis was performed with the Mann-Whitney test. P < 0.05 was considered significant.

Results

Patient characteristics

Twenty-eight patients (8 women, 20 men, mean age 62.5 ± 8.5 years) were included in the study group. All 28 patients had alcoholic cirrhosis and were hospitalized for the following reasons: ascites (N = 13), poor general health (N = 5), malaise of unknown cause (N = 3), hepatic encephalopathy (N = 2), jaundice (N = 2), epistaxis (N = 1), thrombopenia (N = 1), rib fracture (N = 1). The Child-Pugh score was: A (N = 7), B (N = 10), C (N = 11) (table I). Ten patients had hepatic encephalopathy of unknown cause.

Validation of the sulfasalazine test in the cirrhotic patient

Results are expressed by Child-Pugh score in figure 1. Severity of cirrhosis did not affect sulfapyridine Cmax (figure 1a). Conversely, elimination half-life increased significantly with cirrhosis severity (figure 1b). The AUC increased, though non-significantly, with severity of cirrhosis, indirectly reflecting increased elimination half-life (figure 1c). These pharmacokinetic data demonstrated that cirrhosis modifies the elimination curve and AUC of salazopyrine but does not influence Cmax or the absorption constant (ka) (personal data). These findings demonstrate that the

Table I. – Characteristics of the cirrhotic patients. (N = 28).

<table>
<thead>
<tr>
<th>Encephalopathy</th>
<th>N</th>
<th>Child Pugh</th>
</tr>
</thead>
<tbody>
<tr>
<td>Without encephalopathy</td>
<td>18</td>
<td>A = 7 B = 6 C = 5</td>
</tr>
<tr>
<td>With encephalopathy</td>
<td>10</td>
<td>A = 0 B = 4 C = 6</td>
</tr>
<tr>
<td>TOTAL</td>
<td>28</td>
<td>A = 7 B = 10 C = 11</td>
</tr>
</tbody>
</table>

Caractéristiques des malades cirrhotiques (N = 28).
Discussion

Our findings demonstrate that patients with cirrhosis due to alcohol with grade I or II hepatic encephalopathy exhibit a significantly longer oro-cecal transit time than their counterparts without hepatic encephalopathy. Patients free of hepatic encephalopathy had an oro-cecal transit time comparable to that of healthy controls. These results strongly suggest that there is a link between oro-cecal transit time and hepatic encephalopathy but not necessarily between oro-cecal transit time and cirrhosis.

We used the sulfasalazine test to measure oro-cecal transit time. This pharmacological method has the advantage of being applicable irrespective of the patient's health status. Other methods rely on scintigraphy results and require the implementation of complex techniques for a routine test [18]. The hydrogen breath test after ingestion of lactulose is another easily applicable technique. The hydrogen breath test and the sulfasalazine test provide well-correlated results, but the breath test appears to artificially give a slightly shorter time, leading to an apparent acceleration of transit time [23]. The appearance of sulfasalazine in the bloodstream is however perfectly correlated with its arrival in the cecum as has been demonstrated by numerous pharmacological studies [17, 18, 20, 24]. As there are few data in the literature on sulfapyridine absorption and elimination kinetics in cirrhotic patients, we examined the validity of this technique in this type of patient. Our results demonstrated that the sulfasalazine test is as reliable in the cirrhotic patient as in the healthy subject. We found that sulfapyridine absorption, the

sulfasalazine test can be used to measure oro-cecal transit time in cirrhotic patients in the same way as in healthy subjects.

Oro-cecal transit time

Oro-cecal transit times for cirrhotic patients with and without hepatic encephalopathy are presented in figure 2 together with the results obtained in healthy controls. Oro-cecal transit time was significantly longer in cirrhotic patients with hepatic encephalopathy than in cirrhotic patients without hepatic encephalopathy (641 ± 350 vs 354 ± 90 min respectively; P < 0.05). There was no significant difference between cirrhotic patients without hepatic encephalopathy and healthy controls (298 ± 96 vs 351 ± 90 min respectively; NS) (figure 2). Patients with grade I (N = 6) and grade II (N = 4) hepatic encephalopathy exhibited comparable oro-cecal transit times (617 ± 322 vs 676 ± 450 min respectively; NS). Child-Pugh score did not affect oro-cecal transit time (figure 3).

Fig. 1 – a) Sulfapyridine maximal concentration in µg/mL (mean ± SD) in the control group (5.6 ± 1.7) and in the cirrhotic group according to the Child Pugh score: Child A (5.8 ± 2.7); Child B (7.4 ± 2.6); Child C (5.8 ± 1.9). b) Sulfapyridine elimination half-life (mean ± SD) in the control group (576 ± 162) and cirrhotic patients according to the Child-Pugh score: Child A (834 ± 150); Child B (1182 ± 540); Child C (1476 ± 696). A significant difference was noted between the control group and cirrhotic patients with B or C Child score (* P < 0.05 compared with the control group). c) Control group sulfapyridine area under the curve in µg/mL/min (143.2 ± 47.8) (mean ± SD) and cirrhotic group sulfapyridine area under the curve according to the Child-Pugh score: Child A (203 ± 94); Child B (290 ± 198); Child C (270 ± 135).

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The small bowel transit time in patients with hepatic encephalopathy was significantly longer than in the control group and in cirrhotic patients without encephalopathy (641 ± 350 vs. 354 ± 90 and 298 ± 96 respectively; *P < 0.05 compared to the control group and to patients without encephalopathy).

principal parameter determining the test’s measurement of oro-cecal transit time, is not modified by cirrhosis.

We demonstrated that oro-cecal transit time is increased in cirrhotic patients with hepatic encephalopathy but is not in their counterparts without hepatic encephalopathy. These findings are in agreement with the report by Van Thiel et al. [11] who used scintigraphy to measure gastric emptying and the lactulose breath test to measure small bowel transit time in an unselected group of cirrhotic patients. They found that small bowel transit time was longer in patients with hepatic encephalopathy compared to those without. In a third group of patients with infra-clinical hepatic encephalopathy, they found an intermediary small bowel transit time. Gastric emptying times were not different between the three groups. These findings strongly suggest a link between small bowel transit time and the severity of hepatic encephalopathy. Moreover, treatment with neomycin combined with lower protein intake led to a small bowel transit time in patients with hepatic encephalopathy equivalent to that in patients without hepatic encephalopathy. We chose to study only patients with alcoholic cirrhosis because of the prevalence of this etiology in our recruitment and also because these patients form a homogeneous study group. Cirrhosis per se is one of several factors which can modify oro-cecal transit time. Wegener et al. [12] demonstrated increased small bowel transit time in chronic alcoholic patients and suggested that alcohol has a direct effect. However since their cohort included patients with and without signs of cirrhosis, alcohol cannot be incriminated as the sole factor. Others have also suggested that hepatotropic viruses, e.g. hepatitis B virus, could also influence gastrointestinal motility. Chen et al. [25] used the breath test to study oro-cecal transit time in patients with chronic hepatitis C with and without cirrhosis but were unable to demonstrate an effect of the virus on intestinal motility.

Our results do not allow determination as to whether oro-cecal transit time precedes hepatic encephalopathy or results secondary to encephalopathy. Slower intestinal motility could lengthen the time of contact between intestinal contents and the epithelium and thus favor absorption of neurotoxic compounds. Several candidate compounds could arise within the digestive tract (ammonia, mercaptans, short-chain fatty acids, aromatic amino acids, gamma-aminobutyric acid). Small bowel motility disorders favor microbial overgrowth [26, 27], which in turn favors bacterial translocation as well as synthesis and absorption of neurotoxic compounds normally synthesized in the colon. Small bowel bacterial overgrowth cannot be excluded in our patients, but its presence or absence would be insufficient to explain our results. Its presence would produce an artifact in the measurement of transit time since sulfasalazine would be more rapidly degraded into sulfapyridine by bacteria encountered in the small bowel (and not in the colon). Thus our measurement of oro-cecal transit time in patients with small bowel bacterial overgrowth would have been shortened artificially, which would have led to a less significant difference between patients and controls.

In summary, cirrhotic patients with grade I or II hepatic encephalopathy exhibit a significantly longer oro-cecal transit time. Our results demonstrated the existence of a link between small bowel motility disorders and hepatic encephalopathy in cirrhotic patients. These findings contribute to our understanding of the pathophysiology of hepatic encephalopathy and may be useful in developing treatment strategies. A new therapeutic approach based on the use of prokinetic agents would be worthy of evaluation.

REFERENCES