Enhanced sedative efficacy and delayed recovery in propofol anesthesia in a rat model of hepatic cirrhosis

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Abstract: Purpose: The sedative efficacy of propofol anesthesia is enhanced in patients with hepatic cirrhosis. Establish a rat model to investigate the efficacy of propofol. Methods: 100 healthy Sprague-Dawley rats were divided into three groups and administered Phenobarbital sodium, carbon tetrachloride and ethanol solution for 0 (control), 9 (mild cirrhosis, M1), or 12 (severe cirrhosis, M2) weeks to induce hepatic cirrhosis. Propofol was infused via the caudal vein and the ED$_{50}$ of the sedative effect and the recovery time were assessed according to the loss and recovery of the righting reflex. The effect of propofol on circulating cells and platelets, blood biochemistry and neurotransmitter content of the brain were measured. Results: Cirrhosis was achieved in 25 of 35 M1 and 27 of 45 M2 rats. The propofol ED$_{50}$ was significantly lower in M1 and M2 (5.8 ± 1.2 and 4.8 ± 1.1 mg/kg, respectively) than in control rats (6.2 ± 1.1 mg/kg, $P < 0.05$), and the time to recovery of righting reflex was significantly longer in M1 and M2 (370.0 ± 108.2 s and 501.6 ± 100.1 s, respectively) than in control rats (275.0 ± 90.3 s, $P < 0.05$). In M1 and M2 rats white and red blood cell and platelet counts were reduced, but ALT and AST activity was increased. In M1 and M2 rats the cerebral content of Gly and GABA increased but Glu and Asp were reduced. Conclusion: The sedative efficacy of propofol anesthesia is enhanced in rats with hepatic cirrhosis, perhaps due to reduced hepatic functional reserve, enhancement of inhibitory neurotransmitters and reduction of excitatory neurotransmitters.

Keywords: Hepatic cirrhosis, propofol, anesthesia recovery period, sedation, neurotransmitters, hepatic function

Introduction

Propofol is an intravenous anesthetic widely used in the clinic for the induction and maintenance of general anesthesia and sedation due to its fast onset, few side-effects and lack of accumulation after sustained infusion [1]. It has been previously reported that hepatic cirrhosis can influence the clinical response to propofol anesthesia [2]. The recovery of patients with hepatic cirrhosis was found to be significantly delayed and the sedative effect was found to be more potent in comparison to healthy patients [2]. However, the mechanisms responsible for the enhanced efficacy of propofol in this population are yet to be determined.

We sought to establish a rat model in which to investigate the influence of hepatic cirrhosis on the efficacy of propofol. Carbon tetrachloride (CCl$_4$) has previously been employed to induce cirrhosis in animal models [3]. CCl$_4$ is activated into CCl$_3$ through mitochondrial CYP450 in the liver, and disrupts the functional integrity of hepatocyte membranes causing hepatocyte apoptosis or defects of lipoprotein synthesis and accumulation of triglyceride and fatty acids. Long-term administration of low dose CCl$_4$ induces repeated cycles of liver damage-repair, eventually producing the hallmarks of cirrhosis [4]. Phenobarbital sodium can be administered in advance to enhance the activity of CYP450 and augment sensitivity of liver cells to CCl$_4$ [5].

We pursued this method to establish hepatic cirrhosis in rats, and then assessed the efficacy of propofol in these animals.

In a rat model of hepatic cirrhosis, disease was characterized by a reduction in hepatic reserve. The dose of propofol required to induce sedation was significantly lower in rats with cirrhosis than in control animals, and animals with cirrhosis required longer recovering from propofol-induced sedation.
Hepatic cirrhosis; Neurotransmitters

Materials and methods

Animals

One hundred healthy male Sprague-Dawley rats 180~220 g (aged 10~12 weeks) were provided by the experimental animal center of Ningxia medical university (China). Animals were housed at 20-25°C and 50 ± 5% humidity with ad libitum access to food and water and 12:12 h light/dark cycle. All procedures and animal experiments were approved by the Animal Care and Use Committee of Ningxia Medical University.

Hepatic cirrhosis rat model

Animals were divided into three groups, the control group (group C, n = 20), mild cirrhosis group (group M1, n = 35) and severe cirrhosis group (group M2, n = 45). Cirrhosis was induced in Group M1 and M2 by oral phenobarbital sodium for one week followed by subcutaneous injection of carbon tetrachloride (CCl$_4$, 99.5% purity; NO.20100907, Fuchen Chemical Reagent Factory, Tianjin, China) and oral ethanol solution, by a protocol modified from that employed by Li et al. [6], as illustrated in Table 1.

Rats in Group M1 and M2 were provided with drinking water containing 0.35% (W/V) Phenobarbital sodium (NO. 20060006, Xinya Pharmacy, Shanghai, China) for one week (induction period), after which drinking water was exchanged for 10% ethanol solution, prepared by mixing 2500 ml 40 degree edible white wine (Ningxia West King Liquor, Yinchuan, Ningxia, China) with 7500 ml distilled water and 15 g of the sweetener glycyrrhizin (flavor JH-162, Jinghao Biotechnology, Zhuhai, China). CCl$_4$ was mixed with edible neutral colza oil (Luhua Group, Yantai, Shandong, China) to yield a concentration of 40% and injected subcutaneously once at 0.5 ml/100 g. After three days the dose was decreased to 0.3 ml/100 g, which was then administered every three days until the end of the fifth week. From the beginning of the sixth week, 50% CCl$_4$ solution was administered at 0.4 ml/100 g every three days, and 20% ethanol solution containing sweetener was provided as drinking water until the end of the ninth week (M1) or twelfth week (M2).

Control group rats received saline injections on the same schedule as CCl$_4$-injected rats, and drinking water without ethanol contains sweetener.

Propofol sedative 50% effective dose ($ED_{50}$)

After successful establishment of cirrhosis (detailed below), a single doses of propofol (NO. GM391, 1% W/V, Diprivan, AstraZeneca S.p.A, Italy) was administered via a 24 G intravenous catheter in the tail vein over 10 seconds. The $ED_{50}$ and 95% confidence interval for each group was established using an up-down sequential method, with the adjacent common ratio of 0.85 until the same concentration was established six times. The standard for sedative effect of propofol was the time to loss of righting reflex of the front legs, as established by Fu [7].

Propofol anesthesia recovery time

To investigate recovery time, twice the mean $ED_{50}$ of Propofol was administered via a 24 G intravenous catheter in the tail vein over 10 seconds. Rats were immediately placed supine. Time of loss of righting reflex of the front legs and recovery of the righting reflex were recorded.

Confirmation of cirrhosis by histopathology

Table 1. Establishment of a rat model of hepatic cirrhosis

<table>
<thead>
<tr>
<th>Timeline</th>
<th>Drinking Water</th>
<th>Subcutaneous Injection</th>
</tr>
</thead>
<tbody>
<tr>
<td>From Week One</td>
<td>0.35% Phenobarbital sodium solution</td>
<td>40% CCl$_4$ solution on the 17$^{th}$ day. From the 20$^{th}$ day 40% CCl$_4$ solution including 0.3 ml/100 g SC was administered once every three days</td>
</tr>
<tr>
<td>From Week Two</td>
<td>10% ethanol solution containing sweetener</td>
<td>50% CCl$_4$ solution 0.4 ml/100 g SC was administered once every three days</td>
</tr>
<tr>
<td>From Week Six</td>
<td>20% ethanol solution containing sweetener</td>
<td></td>
</tr>
</tbody>
</table>

The chest was opened and rats were euthanized by withdrawal of 10 ml blood from the heart. Livers were removed and the right lobe of each liver was embedded in paraffin for sectioning. Five mm sections were stained with hematoxylin and eosin and scored.
Hepatic cirrhosis; Neurotransmitters

Stage 0 was defined as no fibrosis; stage I as some fibrosis in portal areas with or without fibrous septa; stage II as fibrosis in most portal areas with or without septa; stage III as fibrosis in most portal areas with occasional portal-portal bridging; stage IV as fibrosis in most portal areas with marked portal-portal bridging and portal-central bridging; stage V as marked bridging (portal-portal and/or portal-central) with occasional nodules; and stage VI as frank cirrhosis [8].

Figure 1. Effects of propofol anesthesia at ED₅₀ dose on histopathology of the livers in rat model of hepatic cirrhosis. Histopathology was assessed by hematoxylin and eosin staining (Magnification: ×10). A, D: Control animals; B, E: M1 animals; C, F: M2 animals. D: Section from control rat liver after 9 weeks showing normal hepatic architecture. Black arrow indicates central vein. E: Section from rat liver after 9 weeks of CCl₄ treatment. F: Section from M2 group rat liver after 12 weeks of CCl₄ treatment. Black arrows indicate pseudolobules, red arrows indicate formation of fibrous septa, yellow arrows indicate ballooning, and white arrows indicate focal necrosis.

Measurement of hematological index

Blood ammonia and prealbumin (PA)

A blood ammonia determination kit (Jiancheng biotechnology limited company, Nanjing, China) and ultraviolet spectrophotometer (DMS-200, Varian, USA) were employed to measure the ammonia content of a 0.5 ml sample of plasma, calculated as follows. Ammonia content (µmol/L) = (tested OD₆₃₀ value - blank OD value)/(standard OD₆₃₀ - blank OD₆₃₀) × initial substrate concentration (350 µmol/L) × dilution factor.
The serum prealbumin (PA) content was measured from a 50 μl sample with Au400 fully automatic biochemical analyzer (Olympus, Japan) according to the PA test kit (Zhongsheng Beikong Biotechnology Co., Ltd., Beijing, China).

**Table 2. Sample number and body weight before and after successful establishment of rat model of cirrhosis**

<table>
<thead>
<tr>
<th>Group</th>
<th>Number before modeling</th>
<th>Weight (g)</th>
<th>Number after successful modeling</th>
<th>Weight after successful modeling (g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>20</td>
<td>199 ± 15</td>
<td>20</td>
<td>332 ± 28</td>
</tr>
<tr>
<td>M1</td>
<td>35</td>
<td>202 ± 13</td>
<td>25</td>
<td>220 ± 25**</td>
</tr>
<tr>
<td>M2</td>
<td>45</td>
<td>200 ± 16</td>
<td>27</td>
<td>152 ± 19**</td>
</tr>
</tbody>
</table>

*Note: the data are shown as mean ± standard deviation (SD). **P < 0.01 vs. normal control group; *P < 0.05 vs. M1 group. M1: mild cirrhosis group; M2: severe cirrhosis group.*

The amino acid neurotransmitter content of rats brain tissue

Rat brains were removed immediately after euthanasia, chilled on a cold plate and hemi-brain tissue was washed in ice-cold normal saline, dried on filter paper and homogenized with 5 ml ice-cold 10% sulfosalicylic. The homogenate was centrifuged at 4°C and 10000 r/min for 15 min (AvantiTMJ-301 USA), and then 0.5 ml of the supernatant was filtered by syringe-driven filter, to obtain about 50 μl filtrate. The glutamic acid (Glu), aspartic acid (Asp), gamma-aminobutyric acid (GABA), glycine (Gly) content of a 20 μl sample was assessed on the L-8800 type fully automatic biochemical analyzer (Hitachi, Japan) [9] at a flow velocity of 0.4 ml/min.

**Table 3. ED$_{50}$ of Propofol anesthesia in rat model of hepatic cirrhosis**

<table>
<thead>
<tr>
<th>Group</th>
<th>ED$_{50}$ (mg/kg)</th>
<th>95% confidence interval (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control (n = 20)</td>
<td>6.2 ± 1.1</td>
<td>5.8~6.7</td>
</tr>
<tr>
<td>M1 (n = 25)</td>
<td>5.8 ± 1.2**</td>
<td>5.5~6.3</td>
</tr>
<tr>
<td>M2 (n = 27)</td>
<td>4.8 ± 1.1**</td>
<td>4.5~5.2</td>
</tr>
</tbody>
</table>

*Note: the data are shown as mean ± SD. **P < 0.01 vs. normal control group; *P < 0.05 vs. M1 group.*

**Table 4. Time of loss and recovery of righting reflex of Propofol anesthesia in rat model of hepatic cirrhosis**

<table>
<thead>
<tr>
<th>Group</th>
<th>Time of loss of righting reflex (s)</th>
<th>Time of recovery of righting reflex (s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control (n = 20)</td>
<td>4.0 ± 1.2</td>
<td>275.0 ± 90.3</td>
</tr>
<tr>
<td>M1 (n = 25)</td>
<td>4.4 ± 1.1</td>
<td>370.0 ± 108.2**</td>
</tr>
<tr>
<td>M2 (n = 27)</td>
<td>4.7 ± 1.2</td>
<td>501.6 ± 100.1**</td>
</tr>
</tbody>
</table>

*Note: the data are shown as mean ± SD. **P < 0.01 vs. normal control group; *P < 0.05 vs. M1 group.*

The serum prealbumin (PA) content was measured from a 50 μl sample with Au400 fully automatic biochemical analyzer (Olympus, Japan) according to the PA test kit (Zhongsheng Beikong Biotechnology Co., Ltd., Beijing, China).

**Statistical analysis**

SPSS 13.0 (SPSS, Inc., Chicago, IL) software was used for statistical analysis. All data are presented as mean ± standard deviation (SD). Single-factor analysis of variance (ANOVA) was used to compare groups, with $P < 0.05$ considered significant.

**Results**

**Successful establishment of a rat model of hepatic cirrhosis**

During establishment of the rat model of hepatic cirrhosis, rats in group M1 and M2 were sluggish with dry hair, slow reactions, and reduced appetite. Animals in the model groups began to die at the beginning of the fifth week, and five of the 35 rats in group M1, and 14 of the 45 rats in M2, died before the end of the ninth or twelfth week, respectively.

Hepatic cirrhosis was confirmed by examination of the liver and histopathology. In control rats, the surface of the liver was smooth, the texture was soft and the color was red brown (Figure 1A). The hepatic lobule and hepatocyte structures were retained and the central veins were clearly seen under light microscope (Figure 1D). Hepatic cirrhosis was observed in rats from group M1 and group M2. The liver surface was rough with obvious granular nodules, the texture was hard and the color was gray brown (Figure 1B and 1C). Pseudolobules accompanied by hepatocyte regenerative nodules were visible, the central veins were absent or deviation and some new small bile duct and pseudo-bile ducts were visible in some samples (Figure 1E and 1F). Focal necrosis was also observed in the livers of some rats in the group M2 (Figure 1F).

After pathological examination, the modeling success rates were 71.4 % (25/35) and 60.0%
Table 5. Effects of propofol anesthesia (ED_{50}) on WBC, RBC, PLT counts and Hb levels in rat model of hepatic cirrhosis

<table>
<thead>
<tr>
<th>Group</th>
<th>WBC (10^9/L)</th>
<th>RBC (10^{12}/L)</th>
<th>PLT (10^9/L)</th>
<th>Hb (g/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control (n = 20)</td>
<td>7.5 ± 0.7</td>
<td>6.5 ± 1.2</td>
<td>846 ± 100</td>
<td>132 ± 12</td>
</tr>
<tr>
<td>M1 (n = 25)</td>
<td>3.8 ± 0.5**</td>
<td>4.0 ± 1.3**</td>
<td>555 ± 86**</td>
<td>96 ± 10**</td>
</tr>
<tr>
<td>M2 (n = 27)</td>
<td>2.4 ± 0.6**</td>
<td>3.0 ± 1.1**</td>
<td>495 ± 88**</td>
<td>83 ± 10**</td>
</tr>
</tbody>
</table>

Note: the data are shown as mean ± SD. **P < 0.01 vs. normal control group; *P < 0.05 vs. M1 group. WBC: white blood cells; RBC: red blood cells; PLT: platelet; Hb: hemoglobin.

Table 6. Effects of propofol anesthesia (ED_{50}) on Serum TP and Alb levels and ALT and AST activity in rat model of hepatic cirrhosis

<table>
<thead>
<tr>
<th>Group</th>
<th>TP (g/L)</th>
<th>Alb (g/L)</th>
<th>ALT (IU/L)</th>
<th>AST (IU/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control (n = 20)</td>
<td>70 ± 10</td>
<td>35 ± 5</td>
<td>52 ± 12</td>
<td>161 ± 29</td>
</tr>
<tr>
<td>M1 (n = 25)</td>
<td>55 ± 8**</td>
<td>20 ± 5**</td>
<td>72 ± 11**</td>
<td>179 ± 34**</td>
</tr>
<tr>
<td>M2 (n = 27)</td>
<td>40 ± 9**</td>
<td>13 ± 3**</td>
<td>65 ± 14**</td>
<td>168 ± 31**</td>
</tr>
</tbody>
</table>

Note: the data are shown as mean ± SD. **P < 0.01 vs. normal control group; *P < 0.05 vs. M1 group. TP: total protein; Alb: albumin; ALT: alanine aminotransferase; AST: aspartate aminotransferase.

(27/45) in group M1 and group M2, respectively (Table 2). Furthermore, rats in group M1 and M2 weighed significantly less (220 ± 25 g and 152 ± 19 g, respectively) than control rats (332 ± 28 g, P < 0.01) (Table 2).

**ED_{50} and propofol anesthesia recovery time in rat model of hepatic cirrhosis**

Rats were administered propofol and the ED_{50} was calculated according to the time to loss of righting reflex of the front legs. The propofol ED_{50} was significantly lower in rats with mild and severe cirrhosis (5.8 ± 1.2 mg/kg and 4.8 ± 1.1 mg/kg, respectively) than in control rats (6.2 ± 1.1 mg/kg, P < 0.05) (Table 3). The ED_{50} was also significantly lower in rats with severe cirrhosis than rats with mild cirrhosis (P < 0.05) (Table 3).

Following administration of twice the mean ED_{50} of Propofol, the time to loss of righting reflex did not differ significantly between control rats and those with cirrhosis (P > 0.05), but the time to recovery of righting reflex was significantly longer in rats with mild and severe cirrhosis (370.0 ± 108.2 s and 501.6 ± 100.1 s, respectively) than in control rats (275.0 ± 90.3, P < 0.05) (Table 4). The time to recovery of righting reflex was also significantly longer in rats with severe cirrhosis than rats with mild cirrhosis (P < 0.05) (Table 4).

Effects of propofol anesthesia ED_{50} on blood ammonia and PA and amino acid neurotransmitter of the brain in rat model of hepatic cirrhosis

Following administration of the ED_{50} of propofol, the concentration of PA was significantly lower in rats with mild and severe cirrhosis (93.4 ± 17.7 mg/L and 52.3 ± 14.5 mg/L, respectively) than in control rats (110.7 ± 15.2 mg/L) (P < 0.05, Figure 2A). The concentration of PA was also significantly lower in rats with severe cirrhosis than in rats with mild cirrhosis (P < 0.05, Table 6).
Following administration of the ED$_{50}$ of propofol, the content of inhibitory neurotransmitters, GABA and Gly, in the brain was significantly higher in rats with mild (1.92 ± 0.15 ng/g and 5.15 ± 0.42 ng/g, respectively) and severe cirrhosis (2.22 ± 0.12 ng/g and 5.56 ± 0.50 ng/g, respectively), than in control rats (1.19 ± 0.13 ng/g and 4.59 ± 0.52 ng/g, respectively) ($P < 0.05$, Figure 3), the content of GABA and Gly in the brain was significantly lower in rats with severe cirrhosis than in rats with mild cirrhosis ($P < 0.05$, Figure 3).

Following administration of the ED$_{50}$ of propofol, the content of excitatory neurotransmitters, Glu and Asp, in the brain was significantly lower in rats with mild (11.18 ± 1.42 ng/g and 11.34 ± 0.81 ng/g, respectively) and severe cirrhosis (1.92 ± 0.15 ng/g and 5.15 ± 0.42 ng/g, respectively) than in control rats (15.52 ± 1.73 ng/g and 12.72 ± 1.14 ng/g, respectively) ($P < 0.05$, Figure 3), the content of Glu and Asp in the brain was significantly lower in rats with severe cirrhosis than in rats with mild cirrhosis ($P < 0.05$, Figure 3).

**Discussion**

The sedative efficacy of propofol anesthesia is reduced in patients with hepatic cirrhosis [1]. We sought to establish a rat model in which to investigate this observation. Following administration of phenobarbital sodium, carbon tetrachloride and ethanol solution [6], we confirmed successful establishment of mild and severe cirrhosis in rats by histopathological observation. Furthermore, body weight decreased in rats with mild or severe cirrhosis, circulating cell counts, TP, alb and PA levels were depressed and blood ammonia levels and ALT and AST activity were elevated.

The ED$_{50}$ of propofol was reduced in animals with mild or severe cirrhosis in comparison to control animals, and animals with hepatic cirrhosis took longer to recover from propofol anesthesia.
Hepatic cirrhosis; Neurotransmitters

administration, as previously observed in clinical cases of cirrhosis [1]. We also confirmed that the $ED_{50}$ of propofol was reduced with increasing cirrhosis severity.

Serum PA is a reactive protein synthesized in the liver and released into peripheral blood during the acute phase [10]. Serum PA level is positively correlated with the Child-Pugh score, and therefore, PA is commonly used to measure hepatic reserve function [10]. Circulating levels of PA were reduced in cirrhotic rats, most significantly in rats with more severe cirrhosis after propofol administration. Over 90% of administered propofol is glucuronidated and hydroxylated in liver, and the hydroxylation catalyzed by cytochrome enzymes accounts for 40% of the total propofol metabolism [11, 12]. With the progression of liver cirrhosis, the time taken to recover from propofol anesthesia is prolonged, likely as a result of decreased hepatic function, serum ammonia and brain neurotransmitter concentrations.

Propofol binds extensively to plasma proteins. About 98% Propofol is bound to hemoglobin in vivo and only 1-3% is free [13, 14]. Free drug concentration is also likely to be significantly affected by the availability of plasma proteins and the duration of action is likely to be significantly influenced by liver function. Successful establishment of the cirrhosis model was accompanied by depressed WBC, RBC and PLT counts, and Hb, TP and Alb levels were in both mild and severe cirrhosis. Meanwhile, ALT and AST activity was increased in mild and severe cirrhosis. We speculate that during cirrhosis of the liver the reduced circulating plasma protein concentration causes an increase in circulating free drug and hence, a reduced $ED_{50}$. With reduced functional reserve, these animals also clear propofol less quickly.

In addition we observed elevated blood ammonia levels in animals with cirrhosis. Elevated blood ammonia can promote GABA accumulation [15-18]. Since propofol elicits sedative effectiveness by binding to the GABA receptor [19], the ammonia content of blood is likely to impact propofol efficacy. When liver cirrhosis causes liver damage and increases the serum ammonia concentration to 0.15-0.75 nmol/L, it can stimulate the GABAergic neurons to secrete GABA, thereby enhancing the inhibitory effect of GABA in the central nervous system [15]. The prolonged recovery time could result from the increased level of inhibitory neurotransmitters and decreased level of excitatory neurotransmitters in the brains of rats with cirrhosis.

With increased blood ammonia, GABA transaminase activity decreases, which leads to accumulation of GABA in the plasma [18-20]. During cirrhosis, the brain tissue absorption of ammonia increases, and high ammonia concentrations can inhibit uptake of GABA and Gly by the presynaptic membrane, promote the release of GABA and Gly, and increase the utilization of GABA in the synaptic cleft GABA A receptor [14, 21, 22]. Propofol can enhance the responsiveness of the GABA receptor, increasing GABA concentration and prolonging propofol sedation [23]. With the increase in blood ammonia accompanying cirrhosis, Glu in the brain is combined with ammonia to produce Gin, increasing consumption of Glu and reducing the availability of Glu in the brain, as we observed in the rat model [17, 24]. The conduction of excitatory neurotransmitters in the CNS, particularly Glu, can be depressed by propofol, and propofol sedation was prolonged when the concentration of Glu dropped [7]. Asp has a similar physiological effect to Glu, but excitatory transmitters may be less important than inhibitory transmitters to the mechanism of anesthesia, which remains to be determined.

In conclusion, the sedative effect of propofol can be enhanced in rats with hepatic cirrhosis, and recovery from propofol-induced anesthesia is also prolonged. These observations are likely a result of the lower hepatic functional reserve, increased blood ammonia, increased inhibitory amino acid neurotransmitter availability, and decreased excitatory neurotransmitter availability in animals with hepatic cirrhosis.

Disclosure of conflict of interest

None.

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Hepatic cirrhosis; Neurotransmitters


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