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The Influence of the Severity of Chronic Virus-Related Liver Disease on Propofol Requirements during Propofol-Remifentanil Anesthesia

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Purpose: The purpose of this study was to investigate the influence of chronic virus-related liver disease severity on propofol requirements. **Materials and Methods:** In this study, 48 male patients with chronic hepatitis B infection were divided into three groups according to Child-Turcotte-Pugh classification of liver function (groups A, B, and C with mild, moderate and severe liver disease, respectively). After intubation, propofol concentration was adjusted by ±0.3 µg/mL increments to maintain bispectral index in the range of 40-60. Target propofol concentrations at anesthesia initiation, pre-intubation and pre-incision were recorded. **Results:** The initial concentration used in group C was significantly lower than that used in group A or B ($p<0.05$), whereas no difference was observed between groups A and B. At pre-intubation, the actual required concentration of propofol increased significantly (3.2 µg/mL) in group A ($p<0.05$), which lead to significant differences between the groups ($p<0.05$). At pre-incision, the requirements for propofol decreased significantly in both groups A and B (3.0 µg/mL and 2.7 µg/mL, respectively) compared with those at pre-intubation ($p<0.05$), and were significantly different for all three groups ($p<0.05$), with group C demonstrating the lowest requirement (2.2 µg/mL). The required concentrations of propofol at pre-incision were similar to those at induction. **Conclusion:** In this study, propofol requirements administered by target-controlled infusion to maintain similar depths of hypnosis were shown to depend on the severity of chronic virus-related liver dysfunction. In other words, patients with the most severe liver dysfunction required the least amount of propofol.

Key Words: Propofol, liver disease, electroencephalography

INTRODUCTION

The metabolism of many anesthetics takes place in the liver. However, liver function can be compromised in liver disease by substantial decreases in the number of functioning hepatocytes and altered hepatic blood supply. Moreover, chronic liver disease severity has been shown to substantially affect patient outcomes.[1] Furthermore, accumulation of anesthetics metabolized by the liver may occur, resulting in

over-anesthetization in patients with severe liver dysfunction during surgery.

Propofol, a short-acting intravenous anesthetic primarily metabolized by the liver, has been extensively used and evaluated in most clinical conditions.[2-7] However, to our knowledge, the pharmacokinetics and pharmacodynamics of propofol in cirrhotic patients, especially in those with severe liver dysfunction, have not been well studied to date, making its use in these patients ungrounded. Accordingly, even patients that undergo liver transplantation only receive a low dose (or target concentration) of propofol as a supplement to anesthesia.[8,9] Recently, however, the use of propofol has been increasing in patients with cirrhosis.[10,11] In addition, in recent clinical practice, we noted that patients with virus-related liver cirrhosis seemed to require a lower propofol target concentration compared to those with normal liver function. Thus, in this regard, the effect of liver disease severity on propofol requirement seems an interesting and important clinical issue deserving of further studied. In this study, we hypothesized that propofol requirement in patients with chronic virus-related liver disease would decrease with increasing liver disease severity. Accordingly, the purpose of this study was to investigate the influence of chronic virus-related liver disease severity on propofol requirements. The study included patients with post-hepatitis cirrhosis, the most common etiology of liver dysfunction in China.

MATERIALS AND METHODS

The present study was approved by our Ethics Committee and written informed consent was obtained from all 48 male patients scheduled for liver transplantation for cirrhosis or hepatocellular carcinoma with chronic hepatitis B virus infection. None of the patients had hepatic encephalopathy at the time of the study. The patients were divided into three groups according to the severity of their liver disease as assessed by the Child-Turcotte-Pugh (CTP) classification.[12] Group A comprised patients with mild liver disease (n=16), group B with moderate liver disease (n=16) and group C with severe liver dysfunction (n=16). All patients were unpremedicated. The time of interest for the study lasted from the start of propofol infusion to the beginning of the operation.

Upon each patient's arrival at the operating room, two peripheral vein accesses were obtained for administration of fluids and drugs, respectively. Right radial arterial line was established for blood pressure monitoring, and stan-dard physiological monitors including electrocardiography and pulse oximetry were placed. A bispectral index (BIS) "Quatro" sensor strip was placed on the patient's left forehead according to the manufacturer's instructions for the Aspect A-2000 XP Bispectral monitor (Aspect Medical Systems, Newton, MA, USA; software version 3.31). The BIS value reported here refers to the 1-min average of recordings displayed on the screen and was adopted to adjust the propofol target concentration after intubation. Artifacts due to poor signal quality were excluded.

Anesthesia was induced with effect-site target-controlled infusion (TCI) of propofol (Marsh pharmacokinetic model with a plasma effect-site equilibration rate constant K_{e0} of 1.21 1/min)[13,14] and remifentanil (Minto pharmacokinetic model with a K_{e0} of 0.516 1/min[15]) using a microcomputer-controlled pump (Veryark Technology CO. LTD., Guangxi, China). The infusion information was transferred synchronously into a personnel computer at an interval of 1 min. The initial target effect-site concentration of propofol was determined according to the literature[7] and our preliminary clinical observation based on the liver function status of each patient and was administered over 3 min. The modified observer's assessment of alertness/sedation scale (OAA/S)[16] was administered and loss of consciousness (LOC) was defined as an OAA/S of <2. If LOC was not obtained with the initial target concentration, the propofol concentration was increased by 0.3 μg/mL every 3 min. Every 3 min later or at the time of BIS ≤65, the consciousness of the patient was re-assessed to confirm that unconsciousness was achieved. Then cisatracurium 0.15 mg/kg and atropine 0.5 mg were administered and effect-site target-controlled infusion of remifentanil 3.2 ng/mL was initiated. The patient was intubated 5 min later and then mechanically ventilated with oxygen/air (FiO2 0.5) to ensure $P_{et}CO_2$ at 38-43 mm Hg. Anesthesia was maintained with propofol-remifentanil total intravenous anesthesia technique. After intubation, remifentanil target concentration was kept constant and a continuous infusion of cisatracurium 0.1 mg/kg/h was administered as a muscle relaxant throughout the study interval. BIS values (1-min average recordings displayed in the BIS monitor screen) were maintained at the range of 40-60 during the study in order to sustain hypnosis at a similar depth for each patient. When BIS was beyond the range of 40-60, artifacts due to high electromyography activity and poor signal quality were first examined. After excluding the artifacts, propofol target effect-site concentration was altered in steps of ±0.3 ug/mL with

an interval of 3 min to maintain BIS at the predefined range of 40-60. After intubation, a 2-lumen central venous catheter (or pulmonary artery catheter, if necessary) was inserted via the right internal jugular vein to monitor center venous pressure (and pulmonary artery pressure) continuously. If hypotension [defined as a systolic arterial blood pressure <85 mm Hg or mean arterial blood pressure (MBP) <55 mm Hg] occurred during the period from post-intubation to pre-incision, it was treated by ephedrine without volume expansion. The infusion rate of sodium lactate Ringer's solution during the study period was less than 2 mL/kg/h.

In order to compare the stability of hypnosis among the groups, we assessed variations in BIS for each patient during the period from post-intubation to before skin incision by calculating the constancy error (CE), according to the method of Veselis, et al.,[17] as:

CE=(BIS-mean)/(mean)×100,

where mean is the mean BIS value recorded during the period from post-intubation to before skin incision for each patient. Subsequently, the median absolute constancy error (MDACE) for the ith subject was also calculated as:

$MDACE_i$=median ($|CE_{ij}|$, j=1,…,N),

where N is the number of BIS recorded during the period from post-intubation to before skin incision.

Statistical analysis

Data are presented as mean (SD) or median (10-90% percentile). Tests for normality of distribution and homogenei-

ty were made for measurement data. Values obtained from the three groups were compared using parametric and non-parametric statistical tests where appropriate. Patient characteristics; preoperative albumin concentrations (ALB); propofol effect-site target concentrations at induction, pre-intubation and pre-incision; BIS values at pre-induction (BIS-baseline) and intubation (BIS-intubation) were analyzed using one-way analysis of variance with a post hoc Student-Newman-Keuls test. Preoperative values (bilirubin concentration, prothrombin time and international normalized ratio, and amounts of ascites) and mean BIS values during the period from post-intubation to pre-incision (mean BIS) as well as corresponding MDACE values of BIS were analyzed using Kruskal-Wallis test with Bonferroni's correction to account for multiple testing. Comparisons of propofol target concentrations within the groups were analyzed using repeated measurement analysis of variance. Frequency data were analyzed with Fisher's exact test. $p<0.05$ was considered statistically significant.

RESULTS

Demographic characteristics and preoperative data for the three groups are shown in Table 1. There were no statistically significant differences between the groups in age, weight and height. Although all patients in the study had the history of chronic hepatitis B virus infection, the causes that presented

Table 1. Patient Characteristics for Each Groups

	Group A (n=16)	Group B (n=16)	Group C (n=16)
CTP classification	A	B	C
Age (yrs)*	46.4 (8.0)	49.3 (6.9)	42.9 (10.6)
Weight (kg)*	65.9 (6.7)	63.1 (8.9)	64.8 (9.7)
Height (cm)*	169.6 (5.7)	169.7 (4.1)	170.5 (4.9)
Diagnosis (number of patients)[†]	HCC (14) Cirrhosis (2)	HCC (9) Cirrhosis (7)	HCC (5) Cirrhosis (11)
Albumin (g/liter)*	40.0 (5.4)	35.3 (3.9)[§]	33.6 (3.2)[§]
Bilirubin (μmol/liter)[‡]	25.0 (18.0-37.0)	41.6 (22.9-84.0)[§]	533.0 (99.5-824.0)[§,‖]
Prothrombin time (s)[‡]	13.0 (11.6-15.3)	15.2 (12.2-18.8)[§]	26.3 (17.9-60.0)[§,‖]
INR[‡]	1.13 (1.01-1.33)	1.32 (1.08-1.64)[§]	2.29 (1.56-5.22)[§,‖]
Ascites (mL)[‡]	0 (0-100)	300 (0-2600)[§]	800 (100-3000)[§]
MELD score	9.8 (1.5)	13.4 (2.2)[§]	29.4 (7.5)[§,‖]

CTP classification, Child-Turcotte-Pugh classification; HCC, hepatocellular carcinoma; INR, international normalized ratio; MELD, model for end-stage liver disease.
*Data are means (SD).
[†]All patients suffered from chronic hepatitis B virus infection.
[‡]Data are medians (10-90% percentile).
Group B or C vs. group A, [§]$p<0.05$.
Group C vs. group B, [‖]$p<0.05$.

the need for liver transplantation were different among the groups. Accordingly, almost all patients in group A suffered from hepatocellular carcinoma, whereas group C predominately comprised severe cirrhotic patients. Model for end-stage liver disease scores were significantly higher in group C than in groups B and A, whereas group B scores were significantly greater than those of group A, coinciding with CTP classification of liver function. Preoperative values for liver function parameters including albumin, bilirubin, prothrombin time and international normalized ratio, as well as the amounts of ascites, increased with more severe liver dysfunction, although albumin levels and the amounts of ascites demonstrated no significant differences between groups B and C.

There were no differences in baseline BIS values between the three groups. The initial effect-site target concentration of propofol used in induction of anesthesia was 3.0 μg/mL in group A, 2.8 μg/mL in group B, and 2.2 μg/mL in group C, respectively. The initial concentration used in group C was significantly lower than that used in group A or B ($p<0.05$), whereas no difference was found between group A and B. There were no differences in BIS values at pre-intubation between the groups, but the actual required effect-site concentration of propofol at pre-intubation increased significantly in group A (3.2 μg/mL) ($p<0.05$), which was significantly different in comparison to the other two groups ($p<0.05$). After intubation, mean BIS and its MDACE values during the study period were kept at similar levels for all three groups. The required effect-site concentration of propofol decreased significantly at pre-incision for both groups A and B (3.0 μg/mL and 2.7 μg/mL, respectively) compared with those at pre-intubation ($p<0.05$), and was signif-

icantly different between the groups ($p<0.05$), with group C having the lowest requirement (2.2 μg/mL). The required concentrations of propofol at pre-incision were similar to those at induction (Table 2). There were no differences in time intervals from induction to intubation and from post-intubation to pre-incision between the groups.

Induction of anesthesia was smooth in all patients. No clinical significant changes in heart rate and blood pressure were observed during the peri-intubation period. During the period from post-intubation to pre-incision, mean blood pressure and heart rate were well maintained at relatively stable levels in the majority of the patients. There was no difference in the incidence of hypotension between the groups. Three patients in group A, four in group B and four in group C required ephedrine therapy to maintain stable hemodynamics; moreover, no hypertension was observed in these patients thereafter.

DISCUSSION

In this study, we investigated whether propofol requirements in patients with chronic liver disease are influenced by liver dysfunction severity. We found that under propofol-remifentanil total intravenous anesthesia, propofol requirements decreased with increasing degrees of liver dysfunction severity, when depths of anesthesia were maintained at sufficient and similar levels, as monitored by BIS.

Previously studies have investigated the effect of propofol on sub-clinical hepatic encephalopathy in patients with compensated liver cirrhosis.[11,18] These studies found that propofol sedation during upper gastrointestinal endoscopy

Table 2. Propofol Requirements and BIS Values for the Three Groups

	Group A (n=16)	Group B (n=16)	Group C (n=16)
C_{target} at induction (μg/mL)	3.0 (0.3)	2.8 (0.3)	2.2 (0.3)[∥,¶]
C_{target} at pre-intubation (μg/mL)	3.2 (0.3)[‡]	2.9 (0.3)[∥]	2.3 (0.3)[∥,¶]
C_{target} before incision (μg/mL)	3.0 (0.3)[§]	2.7 (0.5)[∥,§]	2.2 (0.4)[∥,¶]
Baseline BIS	93 (4.6)	95 (2.0)	91 (7.3)
BIS at pre-intubation	55 (7.9)	56 (7.5)	51 (8.4)
Mean BIS*	48 (4.2)	50 (8.1)	48 (6.0)
BIS-MDACE[†]	7.5 (4.2-11.6)	7.0 (3.3-10.0)	6.2 (2.4-8.3)

C_{target}, effect-site target propofol concentration; MDACE, median absolute constancy error; BIS, bispectral index.
*The mean value of BIS after excluding the artifacts during the period from post-intubation to pre-incision.
[†]Data are medians (10-90% percentile).
Compared with C_{target} at induction, [‡]$p<0.05$.
Comparison between C_{target} at pre-intubation and C_{target} before insicion, [§]$p<0.05$.
Group B or C vs. group A, [∥]$p<0.05$.
Group C vs. group B, [¶]$p<0.05$.

did not cause acute deterioration of sub-clinical hepatic encephalopathy.[11,18] However, in patients with liver cirrhosis, hepatic function reserve is quite limited, and a cirrhotic liver is less tolerant to hemodynamic changes and surgical stress.[1] Therefore, anesthetic agents should be titrated with caution in cirrhotic patients to minimize the adverse effects of drugs and to stabilize hemodymanics. Recently, Wang, et al.[19] demonstrated that the worse the liver function, the least end-tidal concentration of isoflurane was required to achieve a preset target of BIS at 45-55. Although propofol is presently being used as a predominant hypnotic in clinical anesthesia practice, its pharmacological character in cirrhotic patients, especially in those patients with decompensated cirrhosis, is still not well known. In a study from 1990 by Servin, et al.,[2] the pharmacokinetics of propofol was examined in 10 patients with uncomplicated liver cirrhosis. The results showed that no significant changes were found in the pharmacokinetics of propofol in cirrhotic patients when compared to those with normal liver function; however, the recovery of consciousness was delayed in cirrhotic patients. In their study, they used the same propofol infusion regimen in both cirrhotic and healthy patients; the average dose of propofol in patients with cirrhosis (7.0 mg/kg/h) was only higher slightly than those with normal liver function (6.5 mg/kg/h).[2] The real cause for delayed recovery from unconsciousness in cirrhotic patients was undiscerned from their study. Although the hypnotic effect of propofol was not measured, increased brain sensitivity to propofol in patients with cirrhosis, as seen in the elderly,[3] was likely responsible for the longer time to recovery of consciousness. In addition, their results need to be further validated because only a small population was involved in their study. More recently, Li, et al.[20] demonstrated that end-stage liver disease was associated with significantly prolonged time to recovery after propofol infusion in rats. Their results were consistent with our clinical observations in this study in that patients with the most severe liver dysfunction exhibited the lowest propofol requirements.

According to the literature[2,7] and in our preliminary clinical experience, we initially used similar effect-site concentrations of propofol at induction of anesthesia in patients with mild and moderate cirrhosis, but lower effect-site concentrations in patients with severe cirrhosis. However, the initial effect-site concentrations in patients with mild cirrhosis underestimated the required values at pre-intubation. The required effect-site concentration at pre-intubation in patients with mild cirrhosis was similar to the results reported

by Xu, et al.,[7] who reported a C_{95} for effect-site concentration of 3.2 μg/mL, with 95% confidence intervals of 3.1-3.3 μg/mL, for a healthy Chinese population. After intubation, the amount of propofol required in each group to maintain BIS in the range of 40-60 decreased, and before incision, was closed to the initial concentration administered at induction of anesthesia. The potentiating effect of remifentanil likely accounts in part for the decreased propofol concentration.[21,22]

Comparison of propofol requirements between patients with different degrees of liver dysfunction necessitated that depths of hypnosis be maintained at a similar level. BIS monitoring works well in this regard, and has been extensively accepted as a convenient and versatile tool for which to deliver hypnotic agents and to reduce drug consumption, therefore allowing for faster recovery.[23,24] In this study, BIS values at pre-intubation were similar between the groups, and was also satisfactory maintained at relative constant levels, as shown by the small, comparable MDACE values recoded during the study, suggesting that the depths of hypnosis were almost identical.

In addition, elimination of remifentanil is known to be independent of liver function. Previous studies showed that the metabolism of remifentanil was unchanged in patients with severe, chronic liver disease[25] or even in the anhepatic phase of liver transplantation;[26] however, EC_{50} values in patients with liver disease were less than those in patients without liver disease, when remifentanil was used, suggesting the need for less of a dose to provide analgesia in patients with liver disease.[25] Moreover, although the optimal propofol concentration is thought to be much lower when it was combined with remifentanil, compared with that when combined with fentanyl, sufentanil, or alfentanil, by computer simulation, based on both pharmacokinetic and pharmacodynamic interaction data,[27] Wang, et al.[28] found that low and moderate remifentanil infusion rates did not alter the target-controlled infusion propofol concentrations necessary to maintain anesthesia, as assessed by BIS monitoring. Thus, in this study we used a fixed effect-site target concentration of remifentanil 3.2 ng/mL in all patients to minimize the influence of remifentanil on propofol, so that the differences in requirements of propofol would not be misrepresented by possible potentiating effects of remifentanil.

Furthermore, remifentanil can produce useful obtundation of motor and autonomic responses to nociceptive stimuli. Remifentanil has been shown to attenuate hemodynamic responses to laryngoscopy and orotracheal intubation, yet

the occurrence of bradycardia and hypotension must be anticipated, especially for patients in whom a high infusion regimen was used. Moreover, when co-administered with a high target concentration of propofol, profound hypotension may arise. In this study, there were almost no clinical significant signs of hypotension, and the incidence of hypotension among the groups was comparable utilizing our dosing regimen. The suitable depth of hypnosis guided by BIS and the low target concentration of remifentanil might have contributed to this. Of course, the optimal target concentration of remifentanil for use in inhibiting cardiovascular responses to tracheal intubation in patients with cirrhosis needs further investigation.

Large differences were previously found in the predicted propofol concentrations at LOC using the TCI approach.[29] Different pharmacokinetics model with an unfit K_{e0} value,[14,29-31] as well as different definitions used for LOC in the study protocol, explain the differences that occurred in these previous studies. Actually, the measured plasma propofol concentrations for inducing loss of eyelash reflex and loss of consciousness in these studies were similar, even though different pharmacokinetics models were used.[32] Moreover, most of patients with decompensated liver disease exhibited varying degrees of ascites; the influence of ascites on the propofol requirements are difficult to be predict. Such patients likely involved an increased volume of distribution and required a higher initial target concentration of propofol; however, on the other hand, body weight in the patients with ascites was overestimated, which might offset the influence of increased volume of distribution on propofol requirement. Unfortunately, as a limitation of this study, we did not measure plasma propofol concentrations, and furthermore, we could not discern whether differences in propofol requirements in patients with different degrees of liver dysfunction are caused by interindividual variability or by changes in pharmacokinetics, pharmacodynamics, or both. Other limitations of this study include the small number of patients in each group and the recruitment of only patients with chronic virus-related liver disease. Whether other etiologies such as alcoholic cirrhosis or fatty cirrhosis have the same impact on propofol requirements remains uncertain. However, in this preliminary observation, we set out to evaluate the clinical requirements of propofol in chronic virus-related, cirrhotic patients using the most direct method available to clinicians. Notwithstanding, the pharmacokinetics and pharmacodynamics of propofol in cirrhotic patients, especially in those with severe liver dysfunction,

warrant further investigation.

In conclusion, we performed a preliminary observation of the influence of chronic virus-related liver disease severity on propofol requirement during propofol-remifentanil anesthesia. Our results showed that propofol requirements administered by TCI to maintain similar depths of hypnosis depend on the severity of chronic virus-related liver dysfunction. Patients with the most severe liver dysfunction necessitated the lowest propofol requirements. Further studies determining the pharmacokinetic and pharmacodynamic parameters of propofol in these cirrhotic patients are warranted.

ACKNOWLEDGEMENTS

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