Pharmacodynamic analysis of target-controlled infusion of propofol in patients with hepatic insufficiency

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Abstract. The effect of liver dysfunction on target-controlled infusion (TCI) of propofol remains poorly documented. The pharmacodynamic performance of propofol TCI was evaluated in a cohort of Chinese patients with hepatic insufficiency. Fifty-three patients with hepatic insufficiency were enrolled in the current prospective, observational study. Anesthesia was induced with propofol via TCI to a plasma concentration of 3 μg/ml. Following loss of consciousness (LOC), fentanyl and cisatracurium were administered. Pharmacodynamic parameters were recorded during TCI, including time to LOC, bispectral index (BIS), heart rate (HR) and blood pressure. Patients were divided into two groups based on model of end stage liver disease (MELD) score: Those with a MELD score of ≤9 and those with a MELD score of ≥10. BIS, mean arterial pressure and HR were demonstrated to vary according to time, but were not affected by liver dysfunction. Hypotension was prominent in patients with a MELD score of ≥10 30 min after induction. The proportion of bradycardia and hypotension at the other time points was not significantly different between MELD scores of ≤9 and ≥10. Notably, no bradycardia was observed in MELD of ≥10. Thus, bradycardia and hypotension was observed in patients with hepatic insufficiency over time, although patients with different severities of hepatic insufficiency did not present with different depths of anesthesia. TCI of propofol to 3 μg/ml may be not suitable for patients with hepatic insufficiency, particularly those with severe liver dysfunction. Predictive concentrations (Cp) of TCI propofol requires further investigation and adjustment in patients with hepatic insufficiency (trial registration no. ChiCTR-OCH-12002255).

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Introduction

Target-controlled infusion (TCI) is an intravenous administration system, which provides desired target plasma concentrations of therapeutic agents and aims to maintain an appropriate depth of anesthesia (1-5). TCI has become increasingly popular in clinical practice, due to its ability to maintain more consistent plasma concentrations with fewer fluctuations (6), the smooth process of induction (7) and easily adjustable depth of anesthesia (8), as well as more predictable recovery time (9). The Marsh pharmacokinetic parameters (10) that are incorporated into the Diprifusor TCI system were derived from a relatively small number of healthy individuals without organs dysfunction (11). These parameters have been proven to provide a stable blood-therapeutic agent concentration for propofol induction and maintenance of anesthesia in patients without organ dysfunction (10,12-14).

Propofol is widely administered in clinical practice for induction and maintenance of anesthesia due to its rapid onset of action, large volume of distribution and high-clearance rate (15-17). The pharmacokinetics of propofol are dependent on the liver in multiple ways. Previous studies demonstrated that propofol could be viewed as an acceptable choice for patients with liver dysfunction, as it was proven to be safe in patients with moderate cirrhosis undergoing gastrointestinal endoscopy (18,19), and displayed a protective, antioxidant-like effect on liver damage and dysfunction, as well as ischemic reperfusion injury in liver transplant recipients (20,21). However, the free fraction of the therapeutic agent in circulation depends on the liver's synthetic ability to produce albumin (22) and its clearance is also dependent on hepatic metabolism (23). Therefore, the actual propofol concentrations that are administrated via Diprifusor TCI, where the parameters are derived from healthy individuals, may be higher than expected due to decreased hepatic function and should not be overlooked in patients with hepatic insufficiency.

Thus, the metabolism of propofol is predominantly reliant on the liver; therefore, the reliability of TCI of propofol in patients with hepatic insufficiency remains largely unknown. Whether TCI of propofol to 3 μg/ml, which is recommended

to patients without severe liver dysfunction, is suitable for patients with liver dysfunction during induction and intubation remains unclear. Thus, the purpose of the current study was to assess the performance of induction, via hemodynamics and the depth of anesthesia during TCI of propofol to 3 μg/ml, in patients with varying degrees of liver dysfunction.

Materials and methods

Ethical approval. Ethical approval for the current study was provided by the Ethics committee of the Third Affiliated Hospital, Sun Yat-sen University (Guangzhou, China). Written informed consent was obtained from all patients prior to commencing the investigations (Trial registration no. ChiCTR-OCH-12002255).

Selection and description of participants. Fifty-three (45 males and 7 females) consecutive patients (aged, 18-65 years), with cirrhosis or hepatic carcinoma, who were scheduled for elective liver transplantation, partial hepatectomy or splenectomy from the Third Affiliated Hospital, Sun Yat-sen University (Guangzhou, China), between June 2014 and June 2015 were recruited for this prospective observational study. Exclusion criteria included a history of serious impairment in respiratory, cardiovascular, renal and central nervous systems, and long-term use of mental or neurological drugs.

Administration of anesthesia. No premedication was provided. Heart rate (HR), peripheral arterial oxygen saturation (SpO_2), invasive arterial pressure and central venous pressure were continuously monitored (IntelliVue MP60; Philips Medizin Systeme Boeblingen GmbH, Boeblingen, Baden-Wurttemberg, Germany).

Prior to induction, patients were intravenously administered with Plasma-Lyte A in order to maintain a steady state from induction to the time just prior to commencing surgery. General anesthesia was induced with TCI propofol [Diprivan (200 mg/20 ml); Corden Pharma S.P.A., Caponago, Milano, Italy] set at a plasma target concentration of 3 μg/ml. Following loss of consciousness (LOC), tracheal intubation was facilitated with 0.2 mg/kg cisatracurium [Cisatracurium Besilate (10 mg); Jiangsu Hengrui Medicine Co., Ltd., Lianyungang, China] and 4.0 μg/kg fentanyl [Fentanyl Citrate (0.1 mg/2 ml); Yichang Humanwell Pharmaceutical Co., Ltd., Yichang, China]. Lungs were mechanically ventilated with 50% oxygen to maintain the partial pressure of carbon dioxide between 30-35 mmHg. The propofol infusion was discontinued 30 min after its administration and surgery was then performed. Thereafter, anesthesia was maintained with sevoflurane [Sevofrane (250 ml); Maruishi Pharmaceutical Co., Ltd., Chuoku, Osaka, Japan] inhalation. A bolus dose of cisatracurium (5 mg) and fentanyl (50 μg) was administered when necessary. All data were collected just before starting surgeries.

On occasion, bolus doses of either 50 μg phenylephrine [Phenylephrine Hydrochloride (10 mg/1 ml); Shanghai Harvest Pharmaceutical Co., Ltd., Shanghai, China] or 5 mg urapidil [Urapidil Hydrochloride (25 mg/5 ml); Takeda GmbH, Konstanz, Freiburg, Germany] were administered to maintain the mean arterial pressure (MAP) within a physiological range. Hypotension was defined as a 30% decrease in MAP and was treated with an intravenous bolus of phenylephrine (24,25). Atropine was administered at doses of 0.25 mg to maintain HR ≥50 bpm and doses were repeated as necessary.

Data collection. HR, MAP and bispectral index (BIS) were monitored and recorded at the following measurement time points: Before the study (baseline), and 1, 2, 5, 10, 20 and 30 min after drug administration. In addition, time to LOC (defined as the interval between the start of TCI and loss of responsiveness to a verbal command to open the eyes, which was assessed every 5 sec) and propofol consumption until LOC were recorded.

The primary outcomes of the study were fluctuation of intraoperative hemodynamics, defined by changes of HR, MAP, and the occurrence of hypotension and bradycardia during induction, and changes of BIS. Additional outcomes were time to LOC and the administration of vasoactive drugs.

Statistical analysis. Data were expressed as means ± standard deviation, median (25th percentile, 75th percentile), n (%), or n/total number (%), and analyzed using SPSS version 12.0 software package (SPSS, Inc., Chicago, IL, USA). General information was analyzed with either one-way analysis of variance (ANOVA) or Fisher's exact test. The time to LOC, dosage of propofol until LOC, dosage of phenylephrine and atropine were analyzed using the Wilcoxon signed-rank test. MAP, HR and BIS were analyzed with using measures ANOVA. The ratios of hypotension and bradycardia were analyzed with Fisher's exact test. $P<0.05$ was considered to indicate a statistically significant difference.

Results

Grouping and characteristics of patients. Fifty-three patients exhibiting hepatic insufficiency were enrolled in the current study. A previous study revealed that patients with a model of end stage liver disease (MELD) score <9 experienced a mortality rate of 1.9% at 3 months, whereas those with a MELD score >10, were associated with a mortality rate that was increased by more than three times, and increased exponentially as the MELD score increased (26). Accordingly, the patients were divided into two groups based on MELD score (min., -1, max., 33) as follows: 32 patients were enrolled in the group with a MELD score of ≤9 and 21 were enrolled in the group with a MELD score of ≥10. Patient characteristics were comparable between the two groups, except for MELD score (Table I). Furthermore, the types of disease and surgery are presented in Table I.

Time to LOC and BIS changes subsequent to TCI with equal concentrations of propofol. Liver dysfunction affected neither the time nor the dosage of propofol until LOC (Table I). In addition, repeated measures ANOVA indicated that BIS was impacted by time, but not by liver dysfunction (Fig. 1).

Changes of MAP and HR subsequent to TCI with equal concentrations of propofol. During TCI, the MAP and HR of all patients significantly decreased subsequent to induction

Table I. Characteristics of the patients.

Characteristics	MELD, ≤9 [n=32 (60.38%)]	MELD, ≥10 [n=21 (39.62%)]
Age (years)	46.44±7.26	50.50±8.64
Gender (male/female)	27/5	19/2
Body mass index	21.75±2.80	22.19±3.19
MELD score	5.19±2.74	16.71±8.09
Median (25th percentile, 75th percentile)	5.5 (4.0, 7.8)	11.0 (11.0, 23.5)
Types of disease		
Cirrhosis	19 (59.38%)	12 (57.14%)
Hepatic carcinoma	13 (40.63%)	9 (42.86%)
Types of surgery		
Liver transplantation	5 (15.63%)	17 (80.95%)
Partial hepatectomy	19 (59.68%)	4 (19.05%)
Splenectomy	8 (25.00%)	0 (0.00%)
Time to LOC (sec)	77 (62, 142)	84 (58, 129)
Dosage of propofol until LOC (mg/kg)	0.90 (0.85, 1.10)	0.91 (0.81, 1.06)

The MELD score was calculated from the objective values of preoperative serum bilirubin, serum creatinine, and INR as follows: MELD score = 3.8 x ln (bilirubin mg/dl) + 11.2 x ln (INR) + 9.6 x ln (creatinine mg/dl) + 6.4. Data are expressed as means ± standard deviation, or n (%), or median (25th percentile, 75th percentile). All variables were comparable in the two groups (P>0.05). MELD, model of end stage liver disease; LOC, loss of consciousness; INR, international normalized ratio.

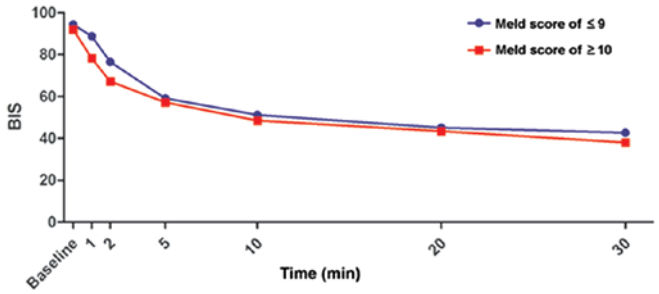

Figure 1. Changes in the BIS of the two groups during target-controlled infusion of propofol (plasma concentration, 3 μg/ml). According to the mean value of each group at each time point, the trends of BIS significantly decreased following anesthesia induction (P<0.05). Repeated measures analysis of variance indicated that BIS was impacted by time, but there were no significant differences between the two groups at each time point. BIS, bispectral index; MELD, model of end stage liver disease.

of anesthesia (P<0.05; Fig. 2A and B). MAP or HR were not significantly different between the two MELD score groups (P>0.05).

Hypotension occurred 5 min after TCI of propofol in the two groups, although not in all of the patients. Furthermore, the proportion of hypotension was not significantly different between patients in the two groups, except for at 30 min (Table II).

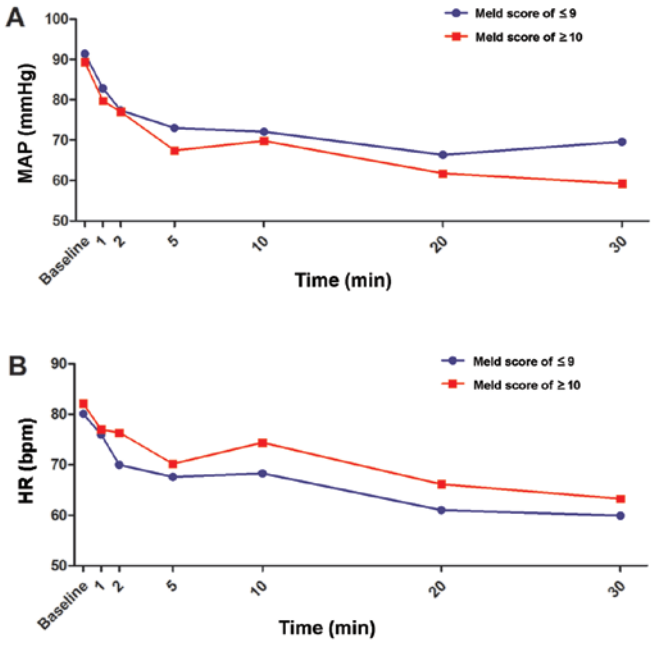

Figure 2. Changes in (A) MAP and (B) HR in the two groups during TCI of propofol. The trends of MAP and HR are presented as the mean value of each group at each time point. During TCI, the MAP and HR of all groups significantly decreased following anesthesia induction (P<0.05). Neither MAP nor HR were significantly different between the two MELD score groups. MAP, mean arterial pressure; HR, heart rate; TCI, target-controlled infusion.

The proportion of bradycardia was not significantly different between the two groups (P>0.05); however, it should be emphasized that there was no bradycardia observed in patients with MELD scores of ≥10 (Table III). In addition, no differences were observed concerning the quantity of phenylephrine or atropine administered (Table IV).

Discussion

This prospective observational study assessed the differences of pharmacodynamics of TCI of 3 μg/ml propofol during induction and intubation in patients with varying degrees of liver dysfunction. The results of the current study demonstrated that the proportion of bradycardia and depth of anesthesia was not significantly different between the different MELD score groups. However, bradycardia and hypotension were observed, and the patients with severe liver dysfunction were more likely to develop into hypotension over time. These results provided novel evidence and a possible research direction for TCI of propofol in patients with hepatic insufficiency.

The TCI system is a frequently used device in daily clinical practice. Marsh parameters incorporated into the Diprifusor TCI system have been derived from subjects with normal liver function (27). In previous studies (28,29), propofol predictive concentrations (Cp) set at 3 μg/ml provided effective conditions for intubation, stabilized hemodynamics and appropriate depth of anesthesia, whether the patients were adults or children, with mild or moderate liver disease (30). In line with these studies, the present study demonstrated that with the same induction program of TCI of propofol, the patients with different degrees of hepatic dysfunction experienced the same trend of depth of anesthesia. However,

Table II. Proportion of hypotension.[a]

Time (min)	MELD, ≤9	MELD, ≥10	P-value
1	0/32 (0)	0/21 (0)	-
2	0/32 (0)	0/21 (0)	-
5	11/32 (34.38)	9/21 (42.86)	0.573
10	5/32 (15.63)	6/21 (28.57)	0.310
20	12/32 (37.50)	13/21 (61.90)	0.099
30	11/32 (34.38)	14/21 (66.67)	0.027

[a]Values are expressed as n/total number (%). Hypotension was defined as a decrease in MAP of >30% from baseline. MELD, model of end stage liver disease.

Table III. Proportion of bradycardia.[a]

Time (min)	MELD, ≤9	MELD, ≥10	P-value
1	0/32 (0)	0/21 (0)	-
2	1/32 (3.13)	0/21 (0)	1.000
5	2/32 (6.25)	0/21 (0)	0.512
10	1/32 (3.13)	0/21 (0)	1.000
20	2/32 (6.25)	0/21 (0)	0.512
30	3/32 (9.38)	0/21 (0)	0.269

[a]Values are expressed as n/total number (%). Bradycardia was defined as heart rate <50 bpm.

a recent study indicated that, to maintain similar depths of anesthesia, the propofol requirements administered by TCI were dependent on the severity of liver dysfunction (30). It was suggested that greater central nervous sensitivity to intravenous anesthetics was affected in certain ways by liver dysfunction, such as by progressive cognitive dysfunction or slowing of brain activity (31). Hepatic dysfunction has already been demonstrated to enhance sensitivity to sedative agents (32). Therefore, it was suggested that the exact dose of propofol, administered by TCI for appropriate depth of anesthesia in patients with severe impaired liver function, requires further investigation.

Table IV. Quantity of vasoactive therapeutic agents.[a]

Therapeutic agent	MELD, ≤9	MELD, ≥10	P-value
Phenylephrine (μg)	0.0 (0.0, 0.0)	0.0 (0.0, 37.5)	0.134
	17.19±51.76	28.57±56.06	0.399
Atropine (mg)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.095
	0.04±0.13	0.00	1.000

[a]Data expressed as medians (25th percentile, 75th percentile), or means ± standard deviation.

MELD has been used as an objective scale of disease severity for management of patients with end-stage liver disease, and validated as a predictor of long-term survival or short-term mortality for patients with decompensated cirrhosis (33,34). Thus, the present study classified patients according to MELD score. Furthermore, the MELD score includes renal function, which may be more suitable for assessing pharmacokinetics and pharmacodynamics of propofol in patients with hepatic insufficiency that is often accompanied by renal insufficiency. It has been widely recognized that the actual concentration of propofol in patients with severe liver dysfunction is higher (35,36). The increased concentration of propofol did not lead to significant changes in the depth of anesthesia in the present study. However, the incidence of cardiovascular events tended to differ between the two groups, particularly hypotension. In the present study, the proportion of hypotension was significantly prominent in the MELD score of ≥10 group when compared with the MELD score of ≤9 group at 30 min, but not at the other time points. Propofol exhibits suppressive cardiac effects, and the magnitude of hypotension depends on the drug concentration in plasma (37). A higher actual plasma concentration of propofol in more severe hepatic dysfunction was shown to suppress cardiac function more significantly (38). In the present study, the association of liver function with blood pressure (BP) became more significant over time, although the proportion of hypotension did not vary between the different severities of liver dysfunction during the first 20 min. With regard to HRs, the proportion of bradycardia was not significantly different between patients in the two groups. It was, however, noteworthy that no bradycardia was observed in the MELD score of ≥10 group. This was consistent with a previous study, which showed that propofol was often accompanied by a significant decrease in arterial BP and HR, while bradycardia and hypotension were not commonly associated (39). The lack of association between bradycardia and hypotension may be attributed to the cardiac depressor reflex, although the exact mechanism remains unclear.

China is one of the most highly endemic areas of the hepatitis virus infection, with an incidence of HBV infection of >8% (40,41). Patients that are infected with the hepatitis virus may develop liver dysfunction to varying degrees. This may result in abnormal levels of serum albumin, bilirubin and coagulation, which affects the pharmacokinetics and pharmacodynamics of certain therapeutic agents. In the present study, the incidence of cardiovascular events in patients with liver dysfunction may potentially have resulted from a higher

measured concentration than Cp of propofol. Although the liver dysfunction was moderate it should be acknowledged. The target concentration requires further investigation and adjustment, although a previous study reported that the pharmacokinetics and protein binding of propofol were not markedly affected by cirrhosis (42). Thus, the difference in pharmacokinetics of TCI of propofol in patients with liver dysfunction may explain the difference of pharmacodynamics; however, this requires further investigation in our future research.

There were certain limitations of the present study. First, the actual measured plasma concentration and pharmacokinetics were not analyzed at the same time, predominantly due to a limited observation time and lack of manpower. Secondly, the study observation time period in this current investigation was too short, limited to the period between anesthesia induction and surgery initiation. Third, the small number of patients may have reduced the power of the present results, which require clarification in a larger population.

In conclusion, the current study revealed that TCI of propofol to 3 μg/ml in patients with liver dysfunction did not result in a varying depth of anesthesia, while bradycardia and hypotension was observed in patients over time. It was suggested that TCI of propofol Cp requires investigation and adjustment in patients with hepatic insufficiency. A lower target concentration may be more suitable for this type of patients; however, further verification in future studies is required.

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