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Short communication

Plasma concentration for optimal sedation and total body clearance of propofol in patients after esophagectomy

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Abstract
The present study investigated plasma propofol concentration for optimal sedation and total body clearance in patients who required sedation for mechanical ventilation after esophagectomy. Seven patients after esophagectomy were enrolled in this study. Plasma propofol concentrations were measured with high performance liquid chromatography. Total body clearance was calculated from the steady-state concentration. The infusion rate of propofol for achieving the sedation score of level 3 (drowsy, responds to verbal stimulation) was $1.74 \pm 0.82\,mg\,kg^{-1}\,h^{-1}$ (mean ± SD, $n = 7$) when the plasma propofol concentration and the total body clearance were $0.85 \pm 0.24\,\mu g\,ml^{-1}$ and $1.83 \pm 0.54\,l\,min^{-1}$ (mean ± SD, $n = 7$), respectively.

Key words Propofol · Esophagectomy · Concentration

Introduction

Propofol (2,6-diisopropylphenol) has been widely used for anesthesia during surgical procedures and for sedation of postsurgical patients in the intensive care unit (ICU) [1–4]. Propofol has many advantages such as rapid onset, easy titration, and quick recovery after withdrawal; however, it is often difficult to predict the required blood level because the propofol concentration changes differently depending on clinical situation, procedure, and level of stimulation. Therefore, it would be useful to have some guidelines for each clinical situation regarding the appropriate target levels of propofol for sedation so as to minimize side effects while maximizing drug efficacy. This study was designed to determine propofol concentration to achieve sedation at level 3 (drowsy, responds to verbal stimulation) [5] and total body clearance in patients who required sedation for mechanical ventilation after esophagectomy.

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Patients and study protocol

After obtaining local ethical committee approval and written informed consent, we studied seven patients after esophagectomy (ASA I or II) requiring sedation for mechanical ventilation in the ICU (Table 1). Patients suffering from severe hepatic disease, renal dysfunction (defined as having creatinine clearance <20 ml or as having hemodialysis), or significant hemodynamic instability were excluded from the study. After insertion of an epidural catheter (T9–T10) and administration of 3 ml 1% lidocaine as a test dose, the administration of morphine ($4\,mg\,day^{-1}$) and 0.2% ropivacaine ($48\,ml\,day^{-1}$) was started for postoperative analgesia via the epidural catheter. Anesthesia was induced using vecuronium 0.1 mg/kg and propofol 2 mg/kg and was maintained with 66% nitrous oxide, 1%–2% sevoflurane in oxygen.

Subjects were allowed to emerge from general anesthesia before the administration of propofol. Patients were sedated with a continuous infusion of propofol of approximately $1–3\,mg\,kg^{-1}\,h^{-1}$ to provide a level 3 on the sedation score [5] (level 1: fully awake; level 2: drowsy; level 3: drowsy, responds to verbal stimulation; level 4: responsive to physical stimulation only; level 5: unrousable). The level of sedation was recorded every 15 min and the rates of infusion were recorded. If the level of sedation became deeper or lighter than the desired level, then the infusion rate of propofol was changed until the desired level was maintained. Because the propofol concentration appeared to reach more than 85% of steady state 2 h after continuous infusion [6], steady state for propofol was assumed to be reached when the infusion rate had not changed for at least 4 h.

Table 1. Patient characteristics

Patient	Sex	Age (years)	Weight (kg)	Alb (mg/dl)
1	M	54	60	2.4
2	M	49	67	2.7
3	M	51	52	2.6
4	M	55	60	2.8
5	M	48	61	2.4
6	M	62	53	2.3
7	M	61	51	2.3
Mean		54.3	57.7	2.5
SD		5.5	5.9	0.20

Alb, plasma albumin concentration after operation

Table 2. Total body clearance after esophagectomy

Patient no.	Infusion rate ($mg\,kg^{-1}h^{-1}$)	Css ($\mu g\,ml^{-1}$)	Cltot ($l\,min^{-1}$)
1	1.48	0.65	2.05
2	1.02	0.5	1.67
3	2.94	1.2	2.08
4	2.18	0.8	2.5
5	1.23	1.08	1.23
6	2.55	0.9	2.22
7	0.8	0.8	1.04
Mean	1.74	0.85	1.83
SD	0.82	0.24	0.54

Css, steady-state concentration of propofol; Cltot, total body clearance of propofol

No other sedative or analgesic agents apart from propofol were given.

Propofol assay

Plasma propofol concentration was measured using high-performance liquid chromatography (HPLC) as described by Teshima et al. [7]. Total body clearance of propofol (Cltot) was calculated as propofol infusion rate divided by steady state propofol concentration (Css).

Results

As shown in Table 2, the infusion rate of propofol for achieving the sedation score of 3 was $1.74 \pm 0.82\,mg\,kg^{-1}h^{-1}$ (mean ± SD, $n = 7$). Plasma propofol concentration at steady state (Css) and total body clearance (Cltot) was $0.85 \pm 0.24\,\mu g\,ml^{-1}$ and $1.83 \pm 0.54\,l\,min^{-1}$ (mean ± SD, $n = 7$), respectively.

Discussion

Sedation with propofol reduces anxiety levels during procedures under local blockade and mechanical ventilation. However, it is often difficult to predict the required blood level because of wide interpatient variability. It would therefore be useful to develop dosing regimens regarding the target levels of propofol for optimal sedation for each clinical situation.

Oei-Lim et al. reported that a predicted concentration was $2.7\,\mu g\,ml^{-1}$ and actual blood concentration was $1.8\,\mu g\,ml^{-1}$ for sedation at level 3 [8] in dental patients. Janzen et al. examined the range of target concentration for each level of sedation in unpremedicated patients undergoing muscle biopsy under femoral nerve block [9]. They reported that the ED_{50} target propofol concentrations for sedation at level 2 (drowsy), 3 (drowsy, responds to verbal stimulation), 4 (responsive to physical stimulation only) were $1.0\,\mu g\,ml^{-1}$, $1.6\,\mu g\,ml^{-1}$, and $2.1\,\mu g\,ml^{-1}$, respectively. We showed that the blood level of propofol for sedation level 3 is $0.85 \pm 0.24\,\mu g\,ml^{-1}$ in patients after esophagectomy. These values were certainly lower than those reported, although our patients would have greater stress sources such as wound pain, artificial ventilation, and lung physiotherapy. This finding can be explained by the following two reasons. First, the residual effects of general anesthetic agents and the effect of epidural morphine and ropivacaine had additive effects with propofol and therefore the concentration was lower, although subjects were allowed to emerge from general anesthesia before the administration of propofol. Second, there might be a significant increase of unbound propofol. We previously reported an increase of unbound propofol in response to a decrease of plasma albumin concentration [10]. Although the concentration of unbound propofol was not measured in this study, we found that blood albumin level was reduced to $2.5 \pm 0.20\,mg\,dl^{-1}$. One reason why sedation level 3 could be maintained at low concentrations of propofol may be an increase in the nonbinding type of propofol.

Total body clearance is the most important pharmacokinetic parameter, especially at steady state. Altered pharmacokinetic behavior of propofol leads to a significant disproportion between predicted and measured propofol concentrations. There is a possibility that the actual propofol concentration exceeds the predicted concentration in the steady state, and it result in oversedation if the total body clearance is reduced. There have been some reports that total clearance of propofol was markedly low in ICU patients. For example, Frenkel et al. [11] reported that total body clearance of propofol was reduced in ICU patients ($1.00 \pm 0.15\,l\,min^{-1}$; APACHE II score 19.0 ± 4.0), and concluded that this change might be caused by changes in

organ perfusion resulting in reduced liver blood flow. In this context, Buckley [12] pointed out the possibility of reduction in total body clearance in accordance with the increase of APACHE II score. We examined total body clearance by the pseudo-steady-state concentration. The contributions of rapid distribution (1–3 min), slow distribution (30–50 min), and terminal elimination half-life (4–6 h) to the changes of concentration are 94.6%, 4.9%, and 0.57%, respectively [13]. There is a slight contribution of terminal half-life to an increase in concentration of propofol, but this is probably clinically irrelevant. We found that total body clearance of propofol in patients after esophagectomy was $1.76 \pm 0.391 \text{min}^{-1}$. This value was almost the same as those reported in patients receiving general anesthesia [6, 14, 15]. Propofol sedation by target-controlled infusion for patients at the postsurgical acute stage may be useful without significant hemodynamic instability.

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