Journal of Zhejiang University SCIENCE
ISSN 1009-3095
http://www.zju.edu.cn/jzus
E-mail: jzus@zju.edu.cn

Cerebrospinal fluid and plasma propofol concentration during total intravenous anaesthesia of patients undergoing elective intracranial tumor removal*

LUO Wei (罗 巍)[1], LI Yu-hong (李玉红)[†‡2], YANG Jian-jun (杨建军)[3], TIAN Jie (田 婕)[3], XU Jian-guo (徐建国)[3]

([1]*Department of Neurology, Second Affiliated Hospital, School of Medicine, Zhejiang University, Hangzhou 310009, China*)
([2]*Department of Anesthesiology, First Affiliated Hospital, School of Medicine, Zhejiang University, Hangzhou 310003, China*)
([3]*Department of Anesthesiology, Nanjing Jinling Hospital, Nanjing 210002, China*)
[†]E-mail: yuh_li2002@hotmail.com

Received Jane 16, 2005; revision accepted May 12, 2005

Abstract: Objective: The aim of this paper is to compare the propofol concentration in plasma and cerebrospinal fluid (CSF) in patients scheduled for intracranial tumor removal and anaesthetized using propofol as part of a total intravenous anaesthesia technique. Methods: Twenty-seven patients (ASA I-II) scheduled for elective intracranial tumor removal were studied. Anesthesia was induced with 2 mg/kg propofol for 5 min and infused at 10 mg/(kg·h) for 5 min and then stopped. CSF and arterial blood were collected simultaneously before infusion of propofol and at different time points after infusion of propofol according to bispectral index (BIS) values. Concentrations of propofol in plasma and CSF were measured by HPLC with fluorescence detection. The correlation coefficient and regression equation between plasma and CSF concentration of propofol were worked out by linear simple regression. Results: The propofol CSF concentration that we measured was 1.46% of the plasma concentration. The coefficient of relation between plasma and CSF concentration was 76.7%. Conclusions: The propofol CSF concentration was positively correlated with and much lower than the plasma concentration. Discrepancies may result from high plasma protein binding of propofol, intracranial pathology and sampling volume.

Key words: Propofol, Cerebrospinal fluid, Total intravenous anaesthesia
doi:10.1631/jzus.2005.B0865 **Document code:** A **CLC number:** R4

INTRODUCTION

The specific morphologic properties of choroidal epithelium and the existence of a cerebrospinal fluid (CSF) pathway for drug distribution to the central nervous system (CNS) suggest that the choroid plexus-CSF route may be more significant than previously thought for drug delivery to the brain (Ghersi-Egea and Strazielle, 2001). There is limited information about the CSF pharmacokinetics of propofol in humans (Engdahl *et al.*, 1998; Dawidowicz *et al*., 2001a).

Propofol's main site of action is CNS. The invasive techniques required to study the distribution of propofol in the brain have limited such studies to animal models (Shyr *et al*., 1995; De *et al*., 2000; Dutta and Ebling, 1998; Dutta *et al*., 1998). The concentration of propofol in and surrounding the cells of the human brain during clinical anaesthesia is unknown. The propofol concentration in human CSF had been measured (Engdahl *et al.*, 1998; Dawidowicz *et al*., 2001b) infrequently because of limited

‡ Corresponding author
* Project supported by Startup Foundation for Introducing Talent of Zhejiang University, China

accessibility to the CSF. Knowledge of propofol concentration in human CSF is useful for delineating the molecular and cellular mechanisms of propofol anaesthesia.

According to the theory of classical pharmacokinetics, CSF as a kind of tissue fluid can be considered the effect site of a drug when we explore the pharmacokinetics and pharmacodynamics of a drug.

The aim of this study is to investigate the propofol concentration in plasma and in CSF in patients scheduled for intracranial tumor removal and anaesthetized using propofol as part of a total intravenous anaesthesia technique. The study results will provide useful information for further study of the pharmacokinetics and pharmacodynamics of propofol.

SUBJECTS AND METHODS

After obtaining approval from the hospital's Human Investigation Committee and informed consent from the patients, 27 patients (ASA I-II) without symptoms of increased intracranial pressure (ICP), scheduled for elective removal of intracranial tumor, were studied. Patients were excluded from the study if they had serious impairment of respiratory, cardiovascular, hepatic, renal, or endocrine function; or if they were receiving medication likely to influence the course of anesthesia.

Patients did not receive any premedication. In the operating room, one IV (intravenous) cannula was inserted into a large forearm vein for infusion of propofol only and another in the contralateral arm for infusion of fluid, fentanyl and vecuronium. A radial artery catheter was inserted for both arterial blood sampling and continuous measurement of arterial blood pressure. As a part of the surgical procedure, an external Drainage System (Codman, Johnson and Johnson Medical Ltd, UK) for drainage was inserted into the subarachnoid cisterns. In addition the BIS (Bispectral index), ECG, heart rate, end-tidal carbon dioxide partial pressure (P_{ET,CO_2}) and oxyhemoglobin saturation (P_{S,O_2}) were monitored continuously throughout the study.

Before induction of anesthesia, patients received crystalloid solution (Ringer's solution) 20 ml/kg body weight. With the patients breathing 100% oxygen, anesthesia was induced by a manually controlled infusion (Graseby 3500 pump, Graseby Medical, Watford, UK) with a bolus dose of propofol (Diprivan or Diprivan; Zeneca Pharmaceuticals, Macclesfield, UK) at 2 mg/kg for 5 min followed by a constant continuous infusion of propofol at the rate of 10 mg/(kg·h) that was maintained for 5 min and then stopped.

Arterial blood and CSF samples for propofol examination (5 ml and 2.5 ml respectively) were obtained simultaneously before infusion of propofol and during continuous infusion of propofol according to the BIS values. Only CSF samples without red blood cells were saved for further analysis. All plasma samples were collected in heparinized tubes and centrifuged within 30 min, transferred to polypropylene tubes and frozen at −20 °C until assay. Propofol concentrations in plasma and CSF were measured by high-pressure liquid chromatography with fluorescence detection (Plummer, 1987).

Data are expressed as mean±*SD*. The coefficient of correlation and regression equation between plasma and CSF concentration of propofol were worked out by linear regression. All data analyses were performed in Microsoft Excel 2000.

RESULTS

Demographic characteristics of the patients are listed in Table 1. The study group was comprised of 14 males and 13 females, with mean age of 48 (range 17~74) years, weight of 66 (range 47~98) kg.

Table 1 Demographic data on study patients (*n*=27)

Demographic characteristics	All patients
Number of individuals	27 patients
Number of CSF samples	162
Number of plasma samples	162
Sampling site	Arterial and subarachnoid
Age (years)*	17~74 (48±16)
Body weight (kg)*	47~98 (66±12)
Gender (M:F)	14:13
Type of surgery	Neurosurgery

* Data are expressed as range (mean values±*SD*)

The concentration of propofol was measured within 1 month. The linear range of propofol in CSF

was 5~200 ng/ml (r=0.9994). The limit of detection was 2 ng/ml. The linear range of propofol in plasma was 16~10000 ng/ml (r=0.9995). The lower limit of detection was approximately 5 ng/ml propofol in plasma. The coefficient of variation of the HPLC method did not exceed 10% in the concentration range encountered in this study.

Arterial blood and CSF propofol concentrations are shown in Fig.1. Mean propofol concentration during the time of the study was 2.69 (*SD* 1.23) μg/ml and that in CSF was 39.20 (*SD* 14.27) ng/ml. The ratio of propofol in CSF to that in plasma was 1.46% during the study.

Regression analysis revealed that the coefficient of correlation between plasma and CSF concentration was 0.77 (y=68.28x, y stands for plasma concentration, while x for CSF concentration).

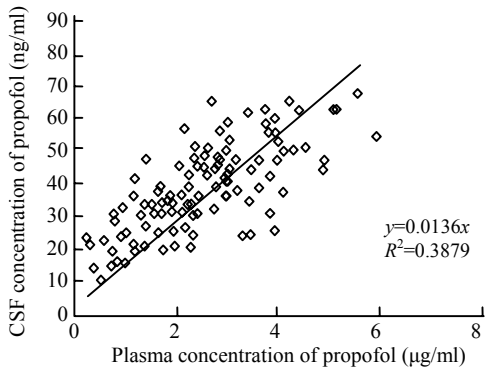

Fig.1 All measured propofol concentrations against calculated concentrations, with the regression line (solid line)

DISCUSSION

We have demonstrated that CSF concentration of propofol was 1.46% of plasma concentration, which is in fair agreement with the values from the following three papers (Engdahl *et al*., 1998; Dawidowicz *et al*., 2001a; 2003a). Engdahl *et al*.(1998) showed that within 30 min of anaesthesia, equilibrium between the propofol concentration in plasma and in CSF was reached, and that propofol concentration in CSF was 50- to 100-fold lower than that in plasma. Dawidowicz *et al*.(2001a) discusses the relationship between propofol concentration in plasma and in CSF during long-lasting anaesthesia maintenance. Dawidowicz *et al*.(2003a) shows that different type of neurosurgical procedure can result in significant difference in CSF propofol concentration (P<0.005).

The linear relationship between propofol concentration in CSF and in plasma indicates that the trend of change of concentration in CSF was consistent with that in plasma during the time of the study (Fig.1).

Among many determinants of propofol uptake into CSF is the cerebral blood flow, which determines the rate at which a drug is delivered to the effect site or biophase and there is a general assumption that the rate of uptake into the CSF and brain of highly lipophilic drugs such as propofol is flow-limited. It is possible therefore; that a reduction in cerebral perfusion pressure and cerebral blood flow induced by an anaesthetic agent may limit its own biophase distribution. It is believed that for lipid-soluble IV anaesthetics, the rate of their uptake by brain is determinated primarily by blood perfusion (Dutta and Ebling, 1998). Cerebral blood flow, however, may be reduced by 50% during propofol anaesthesia (Ludbrook and Upton, 1997). During the study, we therefore maintained the hemodynamics variables and end-tidal CO_2 of each patient stable to eliminate the effects of this phenomenon. Nevertheless, some of the patients can be expected to have regional disturbances of cerebral blood flow secondary to their intracranial pathology and this could explain, in part, the interpatient variation in CSF concentrations of propofol.

The great discrepancy in the propofol concentration in CSF and in plasma may be attributed to differences in intracranial pathology. In a variety of pathological conditions, vascular permeability of the blood-brain barrier could be observed (Gumerlock, 1996). It is well known that the passage of drugs from the blood to CSF is increased after rapture of an intracranial aneurysm.

As is known from literature, propofol in blood is strongly bound to plasma proteins (Zamacona *et al*., 1997; Dawidowicz *et al*., 2001a) and to cellular blood elements (Dawidowicz *et al*., 2001a; Mazoit and Samii, 1999). Only 1%~3% of propofol in blood exists in the unbound form (Gin, 1993; Vuyk *et al*., 1992). It was deemed that only the free or unbound fraction of the drug enters across the choroid plexus and exits in CSF. Therefore there is about 60-fold difference in the concentration of propofol in CSF and

in plasma (Engdahl *et al*., 1998; Dawidowicz *et al*., 2001b; Dawidowicz *et al*., 2003a). In contrast to the above founding, the results presented by Dawidowicz *et al*.(2003b) showed that free propofol concentration in blood was lower than the total drug concentration in CSF. Moreover, the unbound CSF propofol percentage in blood is significantly greater than that in blood and is about 30%.

The normal rate of CSF production has been estimated to be 0.5 ml/min. During the study we sampled a greater volume of CSF than that produced and this could have affected the concentration in CSF.

In summary, the concentrations of propofol in CSF that we demonstrated were consistent with its physicochemical properties. The observed discrepancies between the concentration in CSF and in blood could have resulted from the high protein binding of propofol, intracranial pathology, sampling rate and other unknown reason at present.

References

Dawidowicz, A.L., Fijalkowska, A., Nestorowicz, A., 2001a. The influence of blood sample storage time on the propofol concentration in plasma and solid blood elements. *Biomed. Chromatogr.*, **15**:408-412.

Dawidowicz, A.L., Nestorowicz, A., Fijalkowska, A., 2001b. Propofol concentration in cerebrospinal fluid during TIVA. *Minerva. Anestesiol.*, **67**(Suppl):244-245.

Dawidowicz, A.L., Fijalkowska, A., Nestorowicz, A., 2003a. Cerebrospinal fluid and blood propofol concentration during total intravenous anaesthesia for neurosurgery. *Br. J. Anaesth.*, **90**(1):84-86.

Dawidowicz, A.L., Kalitynski, R., Fijalkowska, A., 2003b. Free and bound propofol concentrations in human cerebrospinal fluid. *Br. J. Clin. Pharmacol.*, **56**:545-550.

De, P.L., De, G., Testa, C., 2000. Disposition of propofol between red blood cell, plasma and cerebrospinal fluid in rabbits. *Eur. J. Anaesthesiol.*, **17**:18-22.

Dutta, S., Ebling, W.F., 1998. Formulation-dependent brain and lung distribution kinetics of propofol in rats. *Anaesthesiology*, **89**:678-685.

Dutta, S., Matsumoto, A., Muramatsu, A., 1998. Steady-state propofol brain: Plasma and brain. Blood partition coefficient and the effect-site equilibrium paradox. *Br. J. Anaesth.*, **81**:422-424.

Engdahl, O., Abrahams, M., Bjornsson, A., 1998. Cerebrospinal fluid concentration of propofol during anaesthesia in humans. *Br. J. Anaesth.*, **81**:957-959.

Ghersi-Egea, J.F., Strazielle, N., 2001. Brain metabolism, and multidrug resistance at the choroid plexus. *Microsc. Res. Tech.*, **52**:83-88.

Gin, T., 1993. Pharmacodynamics of propofol and free drug concentrations. *Anesthesiology*, **78**:604.

Gumerlock, M.K., 1996. Blood-Brain Barrier and Cerebral Edema. *In*: Tindall, G.T., Cooper, P.R., Barrow, D.L. (Eds.), The Practice of Nuerosurgery. Williams & Wilkins, Baltimore, p.4-12.

Ludbrook, G.L., Upton, R.N., 1997. A physiology model of induction of anaesthesia with propofol in sheep. II. Model analysis and implications for dose requirements. *Br. J. Anaesth.*, **79**:505-513.

Mazoit, J.X., Samii, K., 1999. Binding of propofol to blood components: Implications for pharmacokinetics and for pharmacodynamics. *Br. J. Clin. Pharmacol.*, **47**:35-42.

Plummer, G.F., 1987. Improved method for the determination of propofol in blood by high-performance liquid chromatography with fluorescence detection. *J. Chromatogr.*, **421**:171-176.

Shyr, M.H., Tsai, T.H., Tan, P.P.C., 1995. Concentration and regional distribution of propofol in brain and spinal cord during propofol anesthesia in the rat. *Neurosci. Lett.*, **184**:212-215.

Vuyk, J., Engbers, F.H.M., Lemmens, H.J.M., 1992. Pharmacodynamics of propofol in female patients. *Anesthesiology*, **77**:3-9.

Zamacona, M.K., Suarez, E., Aguilera, L., 1997. Serum protein binding of propofol in critically ill patients. *Acta Anaesthesiol Scand.*, **41**:1267-1272.