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Affinity of Propofol to Human Serum Albumin and Cardiovascular Effects

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ABSTRACT

Propofol is used in general anesthesia and sedation. İt is an lipofilic agent and metabolize to inactive form in liver then excreted in the urine. In body it is turnover changes by human serum albumin amount. >97% of propofol is bound to serum albumin. So that hypoalbunemia changes propofol effects. Free form of propopol can pass all membrans such as the blood-brain barrier and the cellular membrane of the cardiac endothelium. Propofol may cause significant myocardial depression, decrease blood pressure and cause life threatining arytmias. Changes in the ratio of free and bound forms of propofol and albumin depending on the dose and duration of administration, the effects of this ratio on cardiac profile are discussed in this study. According to the findings, it was determined that the albumin affinity of propofol decreased in all dose groups in time. Since free HSA and free propofol ratio will increase, this situation is thought to affect the cardiac profile negatively.

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Propofolün İnsan Serum Albuminine Affinitesi ve Kardiyovasküler Etkileri

MAKALE BİLGİSİ

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ÖZ

Propofol genel anestezi ve sedasyonda kullanılır. Bir lipofilik ajandır ve karaciğerde aktif olmayan forma dönüştürülür, sonra idrarla atılır. Vücuttaki etkileri çözünür albüminle değişir. Propofolün %97'den fazlası serum albümine bağlanır. Böylece hipoalbunemi propofol etkilerini değiştirir. Serbest propopol formu, kan-beyin bariyeri ve kardiyak endotelin hücresel zarı gibi tüm zarları geçebilir. Propofol, önemli miyokard depresyonuna neden olabilir, kan basıncını düşürebilir ve hayatı tehdit eden aritmilere sebep olabilir. Uygulama dozu ve süresine bağlı olarak serbest ve bağlı propofol ve albümin formlarındaki değişiklikler, bu oranın kardiyak profil üzerindeki etkileri bu çalışmada tartışılmıştır. Bulgulara göre, propofole albümin afinitesinin tüm doz gruplarında zamana bağlı olarak azaldığı tespit edildi. Serbest albumin ve serbest propofol oranı artacağından, bu durumun kalp profilini olumsuz yönde etkileyebileceği düşünülmektedir.

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Introduction

Propofol (2.6-diisopropylphenol) is an lipofilic, shortacting hypnotic agent used in general anesthesia and sedation (Kayhan, 2004). Propopol provides rapid loss of consciousness (one arm-to-brain circulation time) and rapid awakening (2-8 min). Because of this characteristic, it is preferred in small surgical procedures in daily cases. Inactive metabolites in the liver is destroyed and excreted in the urine (Morgan et al., 2008).

Human serum albumin (HSA) is the most common plasma protein in the blood plasma (40-50 mg/mL). HSA plays an important role in the transport of drugs, metabolites, and fatty acids in the body. The pharmacokinetic and pharmacodynamic effects of drugs linked to albumin affect by binding (Carter and Ho, 1994). General anesthetics especially propofol bind to HSA after administration (Altmayer et al., 1995), important changes in the drug's pharmacokinetics and pharmacodynamics.

In humans, >97% of propofol is bound to serum albümin (Mazoit and Samii, 1999; Schywalsky et al., 2005). In *invitro* (Mazoit and Samii, 1999) and *invivo* (Zamacona et al., 1997) investigations hypoalbuminemia increased the free fraction of propofol. In *invivo* investigation in patients with hypoalbuminea observed that higher free fraction of propofol than in patients with normal serum albumin concentrations and also they observed linear correlation between the percentage of free drug and the serum albumin concentration (Zamacona et al., 1997). Free drug alone is able to cross the blood-brain barrier and the cellular membrane of the cardiac endothelium (Tozer, 1981). Only the free form of the drug is metabolically and pharmacological active. Severe hypoalbuminemia has increased the percentage of free propofol, causing lots of adverse effect to systems such as cardiovascular system.

Propofol is an intravenous anesthetic that causes significant myocardial depression. Myocardial depression results in a decrease in the musculature of the heart muscle, a dramatic decrease in blood pressure. The most effective way to keep this decline under control is to apply the drug as slowly as possible, to apply it at the minimum dose that can be administered, and to treat the patient's hypovolemia prior to administration. Hypovolemic patients become more sensitive to all drugs. The dose should be reduced. In addition, elderly patients are more sensitive to myocardial depressant drugs and actually all drugs. Dose requirements are reduced and the rate of administration should be reduced.

Its administration can be associated with serious cardiovascular side-effects that include decrease in arterial blood pressure and cardiac output. In rare cases, propofol causes life-threatening propofol infusion syndrome characterized by bradycardia, severe arrhythmias, rhabdomyolysis of the myocardium and skeletal muscles, heart failure, renal insufficiency, hepatomegaly and metabolic acidosis (Krajčová et al., 2015). Propofol has many direct effects on cardiomyocytes which cause a decrease in cardiac contractility. These effects are affected by calcium channel metabolism such as modulation of Na-Ca exchange activity, decrease in sarcoplasmic reticulum calcium input-output and changed sensitivity of myofilaments to calcium ions (Wickley et al., 2006; Wickley et al., 2007; Sprung et al., 2001). In some observations propopol has not any effects on cardiomyocytes (Riou et al., 1992).

The effects of propofol occur in the plasma by its free form. Free fraction of propofol can be increased by various drugs that could bind to the same site on albumin, conformational alterations of molecular albumin or changes in plasma protein concentration change free propofol dose in plasma (Dawidowicz et al., 2008). The plasma concentration of propofol should be between 5-50 μmol/L. Over 30μmol/L, can be considered to be high (Soehle et al., 2015). Mostly propofol in the body bound to the albumin, the free form should be 1-5% of the total concentration (Mazoit and Samii, 1999).

Pharmacokinetic and pharmacodynamic effects of propofol vary according to albumin level. Changes in the ratio of free and bound forms of propofol and albumin depending on the dose and duration of administration, the effects of this ratio on cardiac profile are discussed in this study.

Materials and Methods

Preparation of Stock Solution

- Propofol (pure substance, ICI Pharma, Plankstadt, Germany) and protein (HSA) (Human-Albumin Kabi 20%, Pharmacia Upjohn, Erlangen, Germany) were dissolved in 0.02 mol/L (20 mmol/L) phosphate buffer solution (pH: 7.4) (Shityakov et al., 2017).
- Final concentration of protein (HSA) solution: 42.5 mg/mL and Propofol concentration: 2.5 mg/mL (Shityakov et al., 2017).
- Propofol and HSA solutions were prepared as 25, 50 and 100 μL
- A series of Propofol-HSA solutions were prepared by mixing different concentration protein solution (25, 50 and 100 μL) with different concentration of Propofol solutions (25, 50 and 100 μL).
- The total final volume of the solutions in all tubes were fixed as 1mL. And then the protein (HSA) amounts of solutions in all tubes were determined according to the colorimetric method of Lowry et al. with some modifications (Lowry et al., 1951).

Measurements of UV Absorption

The protein (HSA) amounts of the solutions in all tubes were measured according to the method of Lowry et al. step by step below (Lowry et al., 1951):

- Spectrophotometer was reset with the blind sample.
- All samples absorbance were determined in 695 nm UV spectrophotometer.
- Firstly, absorbance of Propofol and HSA were read.
- Propofol and HSA were mixed with 25, 50 and 100 μL concentrations each mixing sample.
- After that, all mixing samples were waited 0^{th}, 15^{th} min, 30^{th} min, 60^{th} min and 120^{th} min in darkness.

Results and Discussion

Based on the data we obtained, free and bound albumin levels and Propofol and HSA affinity ratios were determined based on the time and dose relationship and the results are shown in Table 1. According to the findings, it was determined that HSA affinity of propofol decreased in all dose groups in time.

Analyses were consisted with 3 replicates (Experiments were made as 3 parallel)

Decrease of HSA with time is due to the binding of propofol. After 30th min, absorbance of HSA increased again because of decreasing affinity of propofol to HSA. This result is in accordance with the study done by Shistyakov S. et al (Shityakov et al., 2017). As Mazoit and Samii pointed out, propofol as a high-clearance compound is not expected to show any changes of clearance with changing protein binding (Mazoit and Samii, 1999). Because of this nonrestrictive clearance, plasma half-life will increase with decreasing binding, resulting in a prolonged awakening time. In internal care unite patients it is fact that they usually have hypoalbunemia this should not be overlooked. With special regard to pharmacodynamics, the greater the degree of protein binding the less drug can cross compartment barriers, in particular cell membranes (Wood, 1986). We all know free propopol is active in whole body, if free and bound form of drug changes its effect increases. The reported increasing demand of propofol to hold a defined effect could therefore also be an effect of increased serum albumin concentration instead of acute tolerance to propofol (Ihmsen et al., 2002, Albrecht et al., 1999).

Propofol and HSA interaction in *invivo* conditions showed similar results with the our *invitro* studies.

Relationship between propofol and albumin changes drug effect in body. Increase in free propofol may decrease in arterial blood pressure and cardiac output, bradycardia, severe arrhythmias, rhabdomyolysis of the myocardium and skeletal muscles, heart failure, renal insufficiency, hepatomegaly and metabolic acidosis. As a result of i*nvivo* and *invitro* studies, the rates of albumin propofol interaction show similar findings and this result has a significant effect on the cardiovascular system.

In our study we only investigated concentrations 25 µL and 100 µL. we didn't do any low titration such as 5, 10, 15, 20 µL. and we didn't study time interval lower. For example 1, 5, 10, 15 min.

Table 1 Changes in HSA levels in 0th , 12th, 15th, 30th, 60th and 120th min with Protein UV-vis measurements in the all groups.

Groups	Time				
	0th	15th min	30th min	60th min	120thmin
HSA (25 µL)	1.291	1.291	1.291	1.291	1.291
Pro (25 µL)	0.097	0.097	0.097	0.097	0.097
Free HSA in mixing HSA(25 µL) + Pro(25 µL)	1.256±0.016	0.775±0.022	0.283±0.016	1.065±0.025	1.07±0.027
The HSA that binding Propofol	0.035	0.516	1.008	0.226	0.221
Affinity of Propofol %	2.71	39.97	78.08	17.51	17.12
HSA (50 µL)	1.632	1.632	1.632	1.632	1.632
Pro (50 µL)	0.154	0.154	0.154	0.154	0.154
Free HSA in mixing HSA(50 µL) + Pro(50 µL)	1.17±0.053	1.211±0.030	0.63±0.057	1.538±0.051	1.605±0.022
The HSA that binding Propofol	0.462	0.421	1.002	0.094	0.027
Affinity of Propofol %	28.31	25.80	61.40	5.76	1.65
HSA (100 µL)	2.188	2.188	2.188	2.188	2.188
Pro (100 µL)	0.395	0.395	0.395	0.395	0.395
HSA in mixing HSA(100 µL)+Pro(100 µL)	2.144±0.053	2.141±0.026	1.024±0.030	2.088±0.026	2.079±0.063
The HSA that binding Propofol	0.044	0.047	1.164	0.1	0.109
Affinity of Propofol %	2.01	2.15	53.20	4.57	4.98

Conclusions

According to data we can say that Propofol and HSA absorbance data were determined higher after 30 minutes because of the affinity of propofol decreased after 30 min and free albumin was increased in ambiance according to after 30 min groups for each concentration. As a result, we thought that binding of propofol to HSA was increased by time. But after 30 min, it was decreased. Since free HSA and free propofol ratio will increase, this situation is thought to affect the cardiac profile negatively.

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