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Pharmacokinetics of Succinylcholine in Man

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HOSHI, K., HASHIMOTO, Y. and MATSUKAWA, S. *Pharmacokinetics of Succinylcholine in Man.* Tohoku J. Exp. Med., 1993, **170** (4), 245-250 —— The pharmacokinetics of succinylcholine (SCh) 1 or 2 mg/kg was studied in 14 anesthetized patients. Arterial blood concentrations of SCh were measured using a high-performance liquid chromatographic assay. The arterial concentration vs. time data were analyzed by log-linear regression and fitted to an one-compartment model. The pharmacokinetic parameters were (SCh 1, $n=8$ and 2 mg/kg, $n=6$): apparent volume of distribution (16.4 ± 14.7 and 5.6 ± 6.8 ml/kg, mean$\pm$S.D.), total body clearance (40.5 ± 38.7 and 15.0 ± 14.8 liter/min), area under the plasma concentration-time curve (124.3 ± 163.2 and 695.3 ± 1008.9 min$\cdot\mu$g/ml), and elimination half-life (16.6 ± 4.8 and 11.7 ± 4.5 sec). The rapid disappearance of SCh from the blood may be due to diffusion out of the blood vessel. ———— pharmacokinetics; succinylcholine; high-performance liquid chromatography

The brief duration of action of succinylcholine (SCh) is known to be due to a rapid enzyme hydrolysis in vitro by plasma cholinesterase (ChE) (Kalow 1959). There are no in vivo pharmacokinetic data of SCh in man based on direct plasma measurements. This has largely been due to the lack of an adequate assay of SCh. Recently, pharmacokinetic parameters for SCh were reported in dogs using a gas chromatographic assay (Baldwin and Forney 1988). The results of this study demonstrated that the best model to be a two-compartment model and beta half-life for SCh 1 mg/kg was approximately 5 min.

We have developed a sensitive and specific high-performance liquid chromatographic assay for acetylcholine related compounds that can measure blood concentration of SCh. This study was therefore designed to define the pharmacokinetics of a bolus dose of SCh.

MATERIALS AND METHODS

After approval was obtained from the institutional Human Investigation Committee, we studied 14 consenting patients (7 males and 7 females), ASA Physical Status 1 or 2 undergoing general anesthesia for elective surgical procedures. Patients were aged 31-75

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years and had normal cardiac, hepatic, renal and pulmonary function. None of the patients was receiving medication, was grossly obese, or had a history of neuromuscular disease. Premedication consisted of i.m. meperidine 50 mg and atropine 0.5 mg, given 1 hr prior to the scheduled time of anesthetic induction. On arrival in the operating room, an i.v. infusion of lactated Ringer's solution was commenced and a 22-G cannula was inserted into the left radial artery for continuous measurement of blood pressure and collection of blood samples.

Anesthesia was induced with thiopental 250–500 mg and supplemental doses of thiopental were given as needed to maintain anesthesia. Ventilation was controlled manually to produce normocapnia (end-tidal pCO_2 of 30–35 mmHg) with 100% oxygen throughout the period of study. When consciousness was lost, a bolus of i.v. SCh 1 ($n=8$) or 2 mg/kg ($n=6$) was given using a randomized allocation. Arterial blood samples for the determination of the SCh concentration were collected every 30 sec for 5 min after the administration of SCh. One ml of blood samples was immediately mixed with 1 ml of 0.2 N perchloric acid to inactivate plasma ChE.

Measurement of SCh

The arterial blood SCh was measured using high-performance liquid chromatography (HPLC). The mixtures of arterial blood and 0.2 N perchloric acid, with 50 μg butyrylcholine (BCh) added as the internal standard, were centrifuged at 4,000 rpm for 20 min at 4°C, and the pH of 1 ml supernatant fluids was adjusted between 6 and 7 by titrating with 5 M $KHCO_3$. The fluids were centrifuged again cold (4°C) at 4,000 rpm for 20 min, then 0.8 ml of supernatant fluids were centrifiltrated as above with micro filter (MF-1; Bioanalytical System, Tokyo). The filtrates 50 μl were injected onto the HPLC column.

Chromatographic analysis was performed with a Bioanalytical Systems 400A HPLC device equipped with an electrochemical detector consisting of an electrolytic cell and LC-4B amplifier (both from Bioanalytical Systems, Tokyo). This assay is based on the separation of acetyl Ch and Ch by reverse-phase HPLC (Potter et al. 1983). For the electrolytic cell, the dual platinum action electrode and $Ag/AgCl_2$ electrode were used as a comparative electrode. The setting voltage was +500 mV and the sensitivity of an detector was 20 nA. Separation was carried out with a analytical column of SCh, and the fixing enzyme columns of ChE and choline oxidase (Bioanalytical Systems, Tokyo). The measurements were done in duplicate at the column temperature of 35°C. The mobile phase was 0.05 M Na-phosphate buffer solution (pH 8.4) with 1 mM EDTA and 0.7 mM Na-octyl sulfate infused at a rate of 0.8 ml/min. The lower limit of detection of SCh was 2 μg/ml.

Pharmacokinetic analysis

Linear regression analysis for the construction of the standard curve was performed, comparing the SCh concentrations (10–500 μg) to the SCh/BCh (50 μg) peak area ratios determined in 1-ml aliquots of blood from fasting normal person after adding 1 ml of 0.2 N perchloric acid in the procedure of the assay. From the chromatograph from each unknown sample, the SCh/BCh area ratio was calculated. The concentrations of SCh in arterial blood samples were then calculated using the line equation.

Concentration vs time data were fitted to an one-compartment ($\log C = \log Co - Kt/2.303$) model by log-linear least-squares regression programs for micro computer using Damping Gauss-Newton method (Yamaoka and Tanigawara 1983). The pharmacokinetic parameters of apparent volume of distribution (Vd), total body clearance (Cl), area under the plasma concentration-time curve (AUC) and elimination half-life (t1/2) were calculated for each patient according to standard formula (Gibaldi and Perrier 1982). For both of SCh 1 and 2 mg/kg doses, mean arterial blood decay lines were constructed by calculating the mean SCh concentration at each time point.

Data are reported as mean$\pm$S.D. Relationships between variables were examined by Student's t-test. $p<0.05$ was regarded as statistically significant.

Results

Table 1 indicates the demographic data for patients in SCh 1 and 2 mg/kg. Chromatogram of SCh and BCh in the standard solution shows in Fig. 1. The retention time for SCh and BCh were 9.6 and 22.1 min, respectively. These peaks could be separated to the baseline and good resolution between SCh and BCh was obtained. Over a range of the calibration curve for SCh (10-500 μg) the response of the detector was linear (Fig. 2). A linear regression analysis yielded $y=88.5x-2.8$ with a correlation coefficient of 0.9999 ($p<0.01$), where y is the injected amount of SCh (μg/ml) and x is the peak area ratio of Sch/Bch. The within-run coefficients of variation for 10 measurements was 4.5%.

The pharmacokinetic parameters determined for SCh 1 and 2 mg/kg doses are present in Table 2. The mean Cl and t1/2 values were lower in the SCh 2 mg/kg than 1 mg/kg dose, the differences were not statistically significant. The arterial blood SCh concentrations at 30 and 120 sec after injection were 79.5±108.4 and

Table 1. *Patient demographies*

	Succinylcholine	
	1 mg/kg ($n=8$)	2 mg/kg ($n=6$)
Age (year)	44±7	49±16
Gender (male/female)	4/4	3/3
Weight (kg)	58±6	60±8
Height (cm)	158±7	160±6

Values are mean±S.D. There is no significant differences in this table.

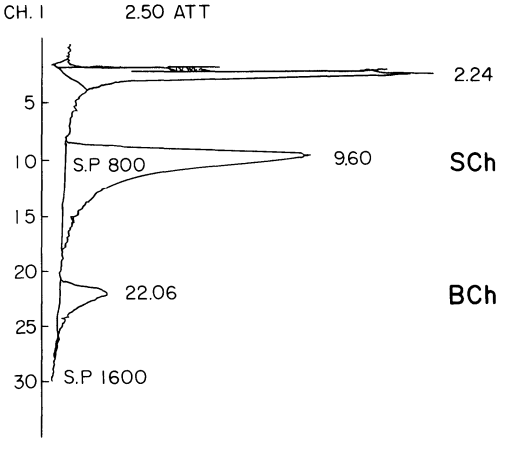

Fig. 1. Chromatogram of succinylcholine (SCh, 100 μg) and butyrylcholine (BCh, 50 μg) in the standard solution. A 50-μl of sample solution was loaded onto the column.

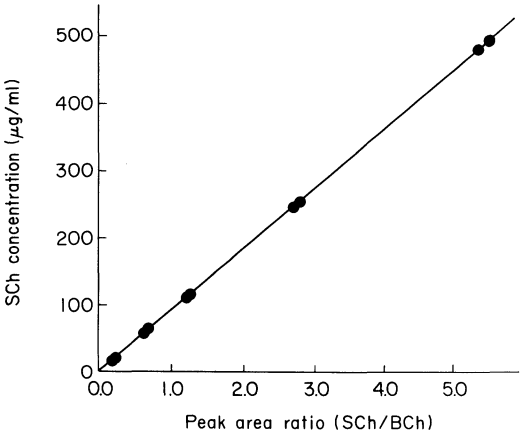

Fig. 2. Calibration curve for the high-performance liquid chromatographic method showing linear relation of arterial blood concentration of succinylcholine (SCh) to peak area ratio of SCh/butyrylcholine (BCh).

TABLE 2. *Pharmacokinetic parameters, derived by one-compartment model, analysis of arterial blood succinylcholine concentration vs time data*

	Succinylcholine	
	1 mg/kg ($n=8$)	2 mg/kg ($n=6$)
Vd (ml/kg)	16.4±14.7	5.6±6.8
Cl (1/min)	40.5±38.3	15.0±14.8
AUC (min μg/ml)	124.3±163.2	695.3±1008.9**
t1K2 (sec)	16.6±4.8	11.7±4.5

**$p<0.01$

3.3±6.7 μg/ml in the SCh 1 mg/kg, and 336.2±512.5 and 7.2±13.0 μg/ml in SCh 2 mg/kg dose, respectively (Fig. 3). SCh was not detectable in both doses after 150 sec of administration.

DISCUSSION

The results of this investigation indicated that blood concentration vs time curves for SCh 1 and 2 mg/kg were the best fit to an one-compartment model with rapid distribution to the tissues. Baldwin and Forney (1988) found in the dogs that the peak plasma concentrations of i.v. SCh 1 mg/kg were 76 μg/ml, and this value is consistent with our study in man. They also demonstrated that the best correlation was attained using two-compartment model for SCh and the beta t1/2 was 4.7 min. The reason for this discrepancy between 6 kinetic models is unknown. However, the apparent first-order kinetics for elimination of SCh 0.5-4 mg/kg i.v. in adults and in newborn has been shown by Levy (1967, 1970).

The disappearance rate of SCh from the blood includes; 1) a hydrolysis by

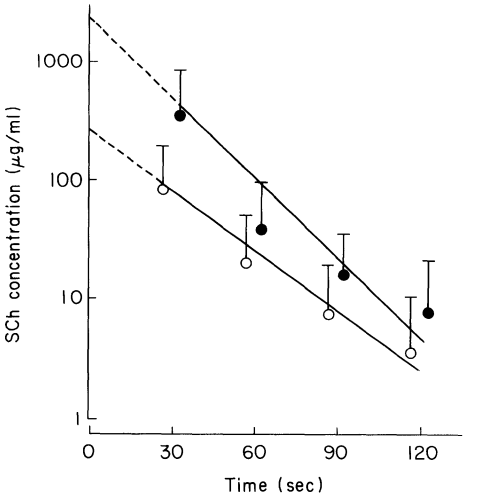

Fig. 3. Semilogarithmic plot of mean arterial blood concentration vs. time lines for succinylcholine 1 (○, $n=8$) and 2 mg/kg (●, $n=6$). Each point is the mean value at that time point. Error bars are S.D. The lines represent the best fit of an one-compartment model to each set of data. They are described by the equations $\log C = 2.50 - 0.02t$ (SCh 1 mg/kg) and $\log C = 3.45 - 0.03t$ (SCh 2 mg/kg), where C is the arterial blood concentration (μg/ml) at time t.

plasma ChE, 2) diffusion out of blood vessel to the tissues, 3) plasma protein binding, and 4) renal excretion. Dal Santo (1968) has shown by use of radioactive-labeled SCh that the last 2 factors are negligible in the 1st min after injection. It has been generally accepted in vitro that the rapid disappearance of SCh from plasma is due to hydrolysis by plasma ChE. Kalow (1963) pointed out that SCh 1 mg/kg may be hydrolyzed within 1 min by plasma of a patient with an average concentration of ChE.

Peck (1972) showed in vivo that, during constant i.v. infusion of SCh to maintain 50% reduction of twitch tension, in Resus monkey, most of SCh is hydrolyzed by the ChE in plasma before reaching the motor endplates. However, Holst-Larsen (1976) has observed in adults that 1 arm had been occluded with a tourniquet immediately before i.v. SCh 1 mg/kg and the occlusion was relieved after a period of 1-3 min. He found that the duration of neuromuscular block occurred 5-10 sec after releasing the tourniquet even after 3 min on the occluded arm. On this basis, he has suggested that the hydrolysis rate must be less in vivo than in vitro, and diffusion of SCh out of the blood occur rapidly. The other finding in dogs that SCh is rapidly eliminated even after the high dose (10-106 mg/kg) i.v. during artificial ventilation, but the decrease in plasma SCh stopped on circulatoly failure under no ventilation (Nordgren et al. 1984), indicates that the rapid disappearance of SCh from plasma is not due to enzymatic hydrolysis.

In summary, we used a high-performance liquid chromatographic assay to

determine the pharmacokinetics of SCh in anesthetized patients. The rapid distribution to tissues may play an important role in the disappearance of SCh from blood.

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