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Pharmacokinetics of Pentazocine in Dogs under Halothane Anesthesia

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The pharmacokinetics of pentazocine were studied in dogs under halothane anesthesia. Pentazocine was spectrofluorometically measured in plasma and cerebrospinal fluid (CFS) of dogs receiving 2.5, 5.0, 10.0 mg/kg doses intramuscularly. The concentration-time curves of pentazocine were describable in terms of a 2-compartment model, and the pharmacokinetic parameters were calculated accordingly.

The half-life of the β-phase (elimination phase) was independent of the dose, while the area under the curves (AUC) were proportional to the dose levels.

Pharmacokinetic parameters of pentazocine in unanesthetized dogs were also calculated and compared with those in anesthetized dogs. The half-life was approximately the same in both groups. It is concluded that halothane anesthesia does not significantly modify the half-life of pentazocine.

Keywords——pentazocine; halothane anesthesia; concentration-time curves; 2-compartment model; half-life value; AUC

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Pentazocine is a potent analgesic which causes little addition in man[2] and is administered to alleviate clinical pain. Although many investigators have examined the analgesic efficacy after single administration of pentazocine.[3–6] There are few reports on the pharmacokinetics of this drug under general anesthesia. In this study the effects of halothane on some pharmacokinetic parameters of pentazocine have been studied, since halothane is most frequently employed in clinical anesthesia.

Experimental

Material and Methods——Twenty-eight unpremedicated dogs of either sex (weight range, 5—21 kg) were anesthetized with halothane (2-bromo-2-chloro-1,1,1-trifluoroethane, Fluothane®, Takeda Chemical Industries Co.) and oxygen. After tracheal intubation, respiration was maintained spontaneously. Pentazocine (1,2,3,4,5,6-hexahydro-2,6-methano-6,11-dimethyl-3-(3-methyl-2-butenyl)-3-benzazocin-8-ol, Pentagin

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injection 30®, Sankyo Co.) was administered into the thigh muscle of the dogs. Animals were divided into 4 groups, each consisting of 7 dogs. Dogs in the first 3 groups received 2.5, 5.0, 10.0 mg/kg pentazocine under halothane anesthesia. The inspired concentration of halothane was 4% for induction. After that, the concentration was kept at approximately 0.89%, equivalent to 1.0 minimum alvelar anesthetic concentration (MAC). End-expired halothane concentration was determined by gas chromatography. Dogs in the last group were given pentazocine without halothane anesthesia.

Pentazocine in biological fluids were extracted by the method of Berkowitz and Way.[7,8] Blood samples (5 ml) were collected through a catheter from the femoral artery and were centrifuged at 3000 rpm for 10 min. After centrifugation, 2 ml of plasma, the same volume of redistilled water, 400 mg of an equal mixture of $NaHCO_3$–Na_2CO_3 (to bring the pH to 8—9, Wako Pure Chemical Co.), and 7 ml of benzene (Dotite Luminasol®, Dojin Lab.) were placed in Teflon-capped glass centrifuge tubes. The tubes were shaken for 10 min. A 5 ml aliquot of benzene was transferred to a 20 ml glass centrifuge tube containing 2 ml of 0.2 N HCl, shaken for 10 min, then centrifuged at 3000 rpm for 10 min. The upper layer was discarded, and the acid phase was assayed with a Hitachi 204 spectrophotofluorometer (Ex. 285 nm, Em. 305 nm, uncorrected). Pentazocine standard solution added to Plasmanate® (heated human plasma protein containing 144 mg protein/ml, Green Cross Corp.) as well as blank plasma samples were also taken through the procedure. The results with Plasmanate were used to provide a calibration curve for the concentration of pentazocine in plasma. Pentazocine concentration in CFS was also measured. CFS was collected from the cervical vertebrae of dogs, and the drug concentration in CFS was assayed in the same way as in plasma. Concentration-time curves for pentazocine have been reported to be describable in terms of a 2-compartment model.[9,10] Although the intramuscular route of administration was used, the data could be successfully treated in the same way as in intravascular administration because of the rapid absorption of the drug from the injection site (muscle). Thus plasma levels, Cp, can be written as follows

$$Cp = Ae^{-\alpha t} + Be^{-\beta t} \quad (1)$$

where A, B, α, and β are constants. The concentration-time curves were plotted on semilogarithmic gragh paper, and B and β were calculated from the elimination phase. Values of A and α were calculated as residuals from Cp and the β-phase and the half-life was calculated as $t_{1/2}=(1n\ 2)/\beta$, $AUC_{0\to\infty}$ is the sum of $AUC_{0\to\text{final sampling time}}$ and $AUC_{\text{final sampling time}\to\infty}(=(\text{Cfinal sampling time})/\beta)$.

Results

Figure 1 shows the plasma level curves for pentazocine in dogs receiving 2.5, 5.0, 10.0 mg/kg of pentazocine *i.m.* At all dose levels, pentazocine exhibited a peak within 10 min and was falling at the sampling time (5 min). Most of the data (24 items out of 28) could

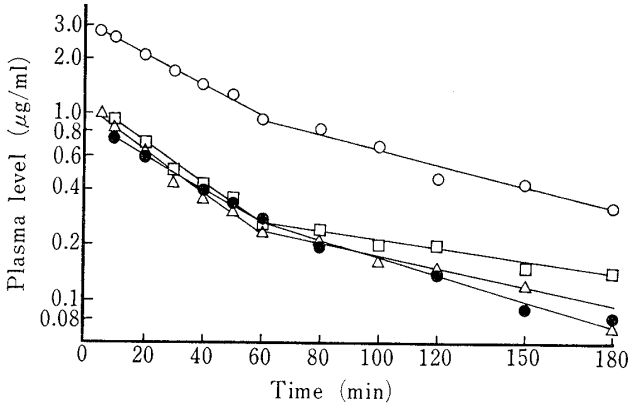

Fig. 1. Plasma Levels of Pentazocine in Dogs following *i.m.* Administration

(○) 10 mg/kg
(□) 5 mg/kg } under halothane anesthesia.
(△) 2.5 mg/kg
(●) 2.5 mg/kg in unanesthetized Dog.

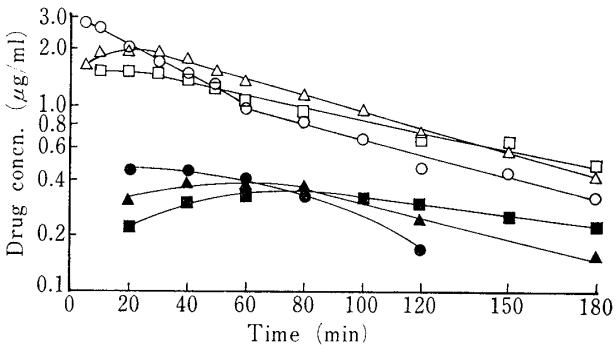

Fig. 2. Pentazocine Concentrations in Plasma and CSF in 3 Dogs following *i.m.* Administration of 10 mg/kg

{open symbols: drug concentration in plasma.
closed symbols: drug concentration in CSF.
Identical forms of symbol represent the same dog.

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Table I. Pharmacokinetic Parameters (Mean±S.D.) for Pentazocine in Dogs (n=numbers of dogs)

Dose mg/kg	n	A μg/ml	α hr^{-1}	B μg/ml	β hr^{-1}	t 1/2 hr	AUC μg·hr/ml
2.5[a]	7	0.851±0.537	3.864±2.180	0.366±0.067	0.637±0.149	1.137±0.241	0.718±0.138
2.5	5	0.830±0.699	3.972±1.826	0.520±0.196	0.614±0.154	1.167±0.260	0.967±0.206
5.0	6	0.407±0.337	2.692±0.888	0.774±0.292	0.678±0.272	1.167±0.486	1.709±0.554
10.0	6	1.348±2.251	2.351±1.160	2.056±0.334	0.572±0.060	1.236±0.149	3.607±0.285

a) Unanesthetized dogs.

be treated in terms of a 2- compartment model. The pharmacokinetic parameters obtained are shown in Table I. The observed half-life values of the 4 groups were similar, *i.e.*, they did not depend on the administered doses within the present dose range. However the values of the AUC of anesthetized groups were evidently correlated with the doses.

Pentazocine concentration in CSF were also assayed, because the drug concentration in CSF is thought to reflect the drug concentration in the brain. Figure 2 shows the concentration-time curves of pentazocine in plasma and CSF in three dogs. The concentrations in CSF were lower than those in plasma, and there did not appear to be correlation, *i.e.*, the concentration peak time in CSF did not correspond with that in plasma. There was considerable variation in the CSF drug level among dogs. The half-life was approximately the same in anesthetized and unanesthetized dogs. However, on comparing the B and AUC values of both groups, the values in anesthetized dogs were slightly larger than those in un anesthetized dogs.

Discussion

White *et al.*[11] have found that $t_{1/2}$ of ketamine hydrochloride, a short-duration intravenous anesthetic, was prolonged by halothane. In the present experiment, however, it was found that halothane anesthesia did not affect the half-life of pentazocine. Halothane administration thus may not lower the ED_{50} of pentazocine clinically.[12] Increase in dose had little effect on $t_1/_2$ within the present dose range.

There were slight differences in the values of B and AUC between anesthetized and unanesthetized dogs. Dogs in the anesthetized group showed larger B and AUC values. Since AUC can be calculated as

$$\text{AUC} = \frac{\text{A}}{\alpha} + \frac{\text{B}}{\beta} \tag{2}$$

a larger value of B gives a larger AUC. The apparent volume of distribution, Vd, is given by

$$\text{Vd, area} = \frac{\text{Dose}}{\text{AUC}\cdot\beta} \tag{3}$$

Dogs in the anesthetized group that showed greater AUC thus had smaller Vd, area. Thus, halothane anesthesia might affect Vd, area. Smaller Vd under anesthesia might be due to the decrease in blood flow rate. The alteration of cardiac output produced by anesthesia may lead to a reduction of blood flow rate in the liver and kidney.[11,13] A fall in total blood flow in the rabbit on halothane administration has been reported.[14] Furthermore, reduction in

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blood flow has been suggested to be propotional to the decrease in cardiac output in Rhesus monkeys.[15] In dogs, many investigators have reported that the cardiac circulatory function is significantly depressed by halothane inhalation.[16] However, the value of Vd may also be influenced by other factors, and further experiments are required.

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Determination of Δ^1-Pyrroline as 2,3-Trimethylene-4-quinazolone

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2,3-Trimethylene-1,2-dihydroquinazolinium hydroxide, a reaction product of Δ^1-pyrroline and *o*-aminobenzaldehyde, was quantitatively converted to 2,3-trimethylene-4-quinazolone by chromic acid oxidation in dilute sulfuric acid. The reaction was successfully applied for determining as little as 10 nmol of Δ^1-pyrroline in deproteinized supernatant of rat liver by gas chromatography using a flame ionization detector.

Keywords——Δ^1-pyrroline; polyamine; γ-aminobutyraldehyde; 2,3-trimethylene-4-quinazolone; chromic acid oxidation; gas chromatography

In connection with the catabolism of naturally occurring diamines and polyamines, we have been interested in γ-aminobutyraldehyde, which cyclizes spontaneously to give Δ^1-pyrroline (I). The compound is produced by the action of either diamine oxidase on putrescine or spermidine oxidase on spermidine, although the latter activity has been found only in some bacteria.[2] The former activity is of interest in mammalian systems in view of the existence of an alternative pathway to γ-aminobutyric acid[3] and 2-pyrrolidone.[4,5] There is another report that I is the major natural co-substrate for thiaminase I.[6]

Before investigating the biological significance of I, we sought to establish a sensitive and reliable method for the determination of I in biological materials, since the only method available at present is based on a specific color reaction with *o*-aminobenzaldehyde (II), which has been applied to the determination of diamine oxidase activity[7] and to a specific enzymatic assay for spermidine.[2] The present paper describes the quantitative conversion of I to 2,3-trimethylene-4-quinazolone (V) as a procedure for the determination of I.

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