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２００２年度日中医学協会共同研究等助成事業報告書

－中国人研究者・医療技術者招聘助成－

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財団法人 日中医学協会
理事長 殿

招聘責任者氏名 石部 裕一 ㊞
所属機関名 鳥取大学医学部
職名 教授
所在地 〒683-8504 鳥取県米子市西町36-1
電話 0859-34-8128 内線

1．招聘研究者氏名 闻 大翔
所属機関 上海第二医科大学附属仁済医院 職名 医師

2．研究テーマ
①髄腔内へ投与された麻酔薬の薬物動態
②筋弛緩が肺循環へ及ぼす影響

3．日本滞在日程
1）2002年10月3日来日
2）2002年10月7日～12月24日
鳥取大学医学部麻酔・集中治療医学教室において、上記①の研究テーマに共同研究者として参加した。とくに、HPLC による髄液及び血中の麻酔薬濃度測定に専門的立場から助言を与え、研究遂行に大きく寄与した。
3）2002年12月25日～2003年1月8日―この間中国へ帰国した。
4）2003年1月9日～3月31日
上記②の研究テーマについて、研究計画を作成し主体的に実験を行った。その結果、これまで明らかにされなかった脱分極性筋弛緩薬 Atracurium、Vecuronium が低酸素刺激による肺の血管収縮を用量依存性に抑制することを観察した。この結果はさらに追加確認実験を行った上で、日本麻酔科学会、米国麻酔科学会において発表する予定である。
5）2003年4月3日帰国予定

4．研究報告書

別紙「研究報告書の作成について」の体裁に倣い、指定の用紙で作成し添付して下さい。

研究発表中または研究中の被招聘者のスナップ写真を添付して下さい。

※研究成果を発表した場合は、発表原稿・抄録集等も添付して下さい。

※研究成果発表に当っては、*日中医学協会助成金による*旨を明記して下さい。

—日中医学協会助成事業—

髄腔内へ投与された麻酔薬の薬物動態の研究

研究者氏名　足立　泰
日本研究機関　鳥取大学医学部麻酔・集中治療医学教室
指導責任者名　教授　石部　裕一
共同研究者名　閏　大翔、岡崎　直人、稲垣　喜三

Abstract:

Purpose: This study was designed to investigate the pharmacokinetic profiles of ketamine and s-ketamine after epidural administration by measuring the concentrations of two drugs both in plasma and CSF. **Methods:** 16 white Japanese rabbits were divided into 2 groups with 8 in each group which received ketamine and s-kitamine respectively. Anesthesia was induced with pentobarbital and maintained with inhalation of sevoflurane in oxygen. Two catheters inserted at L5-6 epidural space and C2-3 subarachnoid space for epidural injection and CSF samples collection respectively. The right carotid artery was catheterized for blood samples collection. Both of blood and CSF samples were collected at 1,3,5,10,15,30,60 and 120min after epidural injection of ketamine (2mg/kg) or s-ketamine (2mg/kg). Plasma and CSF concentrations were measured with high-performance liquid chromatography(HPLC). Pharmacokinetic parameters of plasma and CSF were estimated with 3-compartment model. **Result:** AUC were significantly different between ketamine and s-ketamine in plasma and ($p<0.05$). Cmax of ketamine and S-ketamine in plasma were similar but were significantly higher than that in CSF ($p<0.05$). Both Tmax of ketamine and S-ketamine in plasma were similar to that in CSF. $T_{1/2}\beta$ of S-ketamine in plasma was significantly longer than that in CSF ($p<0.05$).

Conclusion: There were significant differences of AUC, Cmax and elimination half-life between ketamine and S-ketamine in plasma and CSF, the differences are remain to be fully elucidate.

Key words: ketamine, S-ketamine, cerebrospinal-fluid (CSF) , high-performance liquid chromatography (HPLC)

Backgeound

Ketamine is not only a anesthetic but also a powerful analgesic which has been widely used in clinical anesthesia and pain clinic. Clinically-used ketamine is a racemic mixture of two isomers, S-ketamine and R-ketamine. Smith et al. suggested that ketamine is able to bind stereospecifically to opiate receptors in the brain and spinal cord. The existence of opioid receptors in the spinal cord led the possibility to administer ketamine by epidural route. After stereoselective separation, the S-ketamine is now clinical available. Although several studies of pharmacokinetics and pharmacodynamics of ketamine or S-ketamine after i.v. administration had been carried out, however, only a little had evaluated the pharmacokinetic profiles of ketamine and S-ketamine after epidural administration. This study was designed to investigate the pharmacokinetic profiles of ketamine and s-ketamine after epidural administration by measuring the concentrations of two drugs both in plasma and CSF.

Materials and Methods

This study obtained the approval of institutional ethics committee for animal experiment 16 white Japanese rabbits weighs 2.6~3.5kg were divided into 2 groups with 8 in each group which received ketamine and Sketamine respectively(K group and S-k group).

After anesthesia, tracheotomy and mechanical ventilation were performed. Anesthesia was maintained with inhalation of 2~3% sevoflurane in oxygen. Then, a catheter was inserted into the right carotid artery for collecting blood samples and for monitoring arterial pressure. Rabbits were fixed in a prone position and laminectomy was carried out at C2~3 intervertebral space and a polyethylene catheter was inserted to subarachnoid space for collecting CSF sample. And then, epidural puncture were performed at L5~6 intervertebral space and a polyethylene catheter was placed for injection keamine and Sketamine.

Ketamine or S-ketamine was administered at a dose of 2mg/kg through the epidural catheter. Blood samples (2ml) and CSF samples (0.2ml) were collected simultaneously at 1,3,5,10,15,30,60 and 120min after epidural injection of ketamine or s-ketamine. The blood samples were collected into heparinized tubes and centrifuged at 3000g for 10min without delay and the plasma samples were decanted. The CSF samples were transferred to ultra-centrifugal filter units and were ultra-centrifuged at 12000g for 40min. All plasma and CSF samples were stored at –20℃ until analysis.

Analytical Tachnique

Measurement of ketmine and S-ketamiane in plasma and CSF were performed by HPLC. Bupivacaine was selected as interval standard in this study. 0.01 ml bupivacaine (20ug/ml, as I.S) was added into 0.1ml CSF sample, mixed 5min and 10 ul was injected onto HPLC column for measurement. The plasma extraction procedure is shown as following:

1ml plasma + 0.1ml bupivacane (20ug/ml, as I.S)

↓

0.5 ml 1N NaOH (alkalization, agitatiton for 5min)

↓

5ml cyclohexane (extraction, agitation for 5min)

↓

transfer organic layer to a second tube

↓

5 ml cyclohexane (re-extraction, agitation for 5min)

↓

transfer organic layer to a third tube

↓

0.5 ml 2.5N HCl (back extraction, agtitation for 5min)

↓

discard cyclohexane solution

↓

evaporate HCl solution to dryness under gentle stream of N_2

↓

redissolve dry residue with mobile phase (100ul)

↓

inject 10ul onto HPLC column for measurement

Results

AUC were significantly different between ketamine and s-ketamine in plasma and ($p<0.05$). Cmax of ketamine and S-ketamine in plasma were similar but were significantly higher than that in CSF ($p<0.05$). Both Tmax of ketamine and S-ketamine in plasma were similar to that in CSF. $T_{1/2}\beta$ of S-ketamine in plasma was significantly longer than that in CSF ($p<0.05$).The pharmacokinetic parameters of ketamine and Sketamine in plasma and CSF were

summarized in table 1.

Table 1. Pharmacokinetic parameters of ketamine andS-ketamine in plasma and CSF

		AUC	Cmax	Tmax	$T_{1/2}\alpha$	$T_{1/2}\beta$
Ket	Plasma	77.3(37.1)*#	1.7(0.7)#	6.0(4.4)	10.9(6.8)*	147.0(133.1)*
	CSF	29.9(4.9)	0.6(0.2)	8.6(3.3)	14.2(11.6)*	133.5(110.1)
S-ket	Plasma	141.0(48.1)#	2.1(0.4)#	9.8(4.7)	31.3(27.6)#	228.1(201.5)#
	CSF	36.4(5.5)	0.6(0.1)	7.9(4.1)	7.0(3.7)	95.7(33.7)

AUC = area under the concentration-time curve (ug/ml/min),

Cmax = maximal concentration (ug/ml), Tmax = time of maximal concentration (min)

$T_{1/2}\alpha$ = distribution half-life (min), $T_{1/2}\beta$ = elimination half-life (min)

Parameters presented as mean(SD),

*P < 0.05 (ketamine vs.S-ketamine), #P < 0.05 (plasma vs. CSF)

Discussion

In this study, the time courses of ketamine and S-ketamine after epidural administration were similar to that of oral or intramuscular administration. Both Tmax of ketamine and S-ketamine in plasma or CSF were short, this demonstrated that ketamine and S-ketamine transferred rapidly to the CSF and with a high vascular eptake. This properties are account for the rapid increase in drug concentration in CSF and plasma. And significant vascular absorption reduced the concentration gradient relatively quickly. This also can be demonstrated from this study by both of the ketamine and S-ketamine had a long elimination half-life, which were 147.0 (133.1) and 228.1 (201.5) min respectively. The pharmacokinetics of the epidural route of drug administration are complicated because of several processes can influence the different steps of drug absorption, distribution and elimination, such as, dural penetration, fat deposition and system absorption. Some other factors such as physicochemical properties of drugs, pKa and degree of lipid solubility are also play a important role in the pharmacokinetics of drugs.

Pedraz JL et al. found the Cmax of CSF of ketamine was higher than that of plasma (about 2times). However, we got contrary results, in our study, both of Cmax of ketamine and S-ketamine in plasma were high than that of in CSF (about 3times). Because only a little investigations evaluated the pharmacokinetics of ketamine and S-ketamine after epidural administration, the pharmacokinetic profiles of racemic ketamine and it's two isomers, S-ketamine and R-ketamine are remained to be fully elucidated.

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—日中医学協会助成事業—

筋弛緩が肺循環へ及ぼす影響と低酸素性血管攣縮の家兎の遊離灌流肺

研究者氏名　閏　大翔
中国所属機関　上海第二医科大学附属仁済医院、主治医師
日本研究機関　鳥取大学医学部麻酔・集中治療医学教室
指導責任者名　教授　石部　裕一
共同研究者名　岡崎直人、杭　燕南

Abstract:

Purpose: This study was designed to observe the effects of three kinds of muscle relaxants on the pulmonary circulation in isolated perfused rabbit lung. Methods: 18 Japanese white rabbits were divided into 3 groups with 6 in each group which received atracurium, vecuronium and rocuronium respectively. After anesthesia, tracheostomy and sternotomy were performed. The pulmonary artery and left atrium were cannulated and isolated perfused rabbit lung preparation were established. The perfusate were consists of PSS perfusate and autologous blood. The doses of each muscle relaxant were injected to the perfusate reservoir in an accumulative manner, which from 4 times of ED_{95} to 32 times of ED_{95} of each muscle relaxant. The Ppa, Ppv , Pao, Pvo and ΔPpa after HPV were recorded. The resistance of pulmonary circulation and HPV inhibition rate (percentage) were calculated. Results: There were not significant changes of Ppa, Ppv and resistances of pulmonary circulation (Rt, Ra and Rv) after each dose of muscle relaxant. There were significant inhibition effects of all three muscle relaxant on the HPV. ($p < 0.05$). Conclusion: Atracurium, vecuronium and rocuronium did not influence the pulmonary pressure and resistances of pulmonary circulation. They had inhibition effects on HPV.

Key words: Artacurium, vecuronium, rocuronium, isolated perfused lung, resistance, hypoxia pulmonary vasoconstriction, inhibition

Background

Atracurium, vecuronium and rocuronium are intermediate duration nondepolarizing neuromuscular block agents which are most widely used muscle relaxants in clinical anesthesia. Several investigation were carried out on the influence of these muscle relaxants on the hemodynamics. However, all of these investigations were concentrated on systemic circulation. The effects of muscle relaxants on the pulmonary circulation were not clear. This study was designed to observe whether or what kind of effects these muscle relaxants have on the pulmonary circulation.

Materials and Methods

Animals and Isolated Lung Preparation

This study was approved the Tottori University Faculty of Medicine Laboratory Animal Care Committee. 18 female Japanese white rabbits (weighing 1.8-3.0kg) were divided into 3 groups with 6 in each group which received atracurium, vecuronium and rocuronium respectively. After anesthesia and anticoagulation. Tracheostomy and sternotomy were performed. The lungs were ventilated with a warm humidified gas mixture of 21%O_2, 5%CO_2, and balanced N_2. The

cannulation of pulmonary artery and left atrium were completed. The hear, lung and mediastinal structures were removed *en bloc* from the chest cavity. The isolated lungs were perfused with a peristaltic pump at a flow rate of 40 ml_kg^{-1}_min^{-1} monitored with an electromagnetic blood flowmeter. The perfusate volume was 100ml which contained approximately 60 ml PPS and 40 ml autologous blood. The hematocrit of the perfusate was adjusted to approximately 15%. The PH of the perfusate was adjusted to 7.35-7.45. Pulmonary arterial (Ppa) and venous (Ppv) pressures were monitored continuously.

Experimental protocol and measurement

After 30 min of stabilization, the doses of each muscle relaxant were injected to the perfusate reservoir in an accumulative manner, which from 4 times of ED_{95} to 32 times of ED_{95} of each muscle relaxant. The whole experiment separated into four 25-minute periods. During each period, at 3 min and 10 min after muscle relaxant was injected, the Ppa, Ppv, arterial and venous occlusion pressures (Pao and Pvo) were measured. The pulmonary vascular resistances were calculated using the following equations: 1)Rt = (Ppa – Ppv)/Q, 2)Ra = (Ppa – Pao)/Q, 3)Rv = (Pvo – Ppv)/Q, where Rt, Ra and Rv represent resistance of total pulmonary vascular, pulmonary arterial and pulmonary venous respectively. Q represent blood flow. Then, HPV was induced by switching the inhaled gas to a hypoxia gas mixture ($3\%O_2$, $5\%CO_2$, balanced N_2) for 5min. The pulmonary vascular response to HPV was expressed as the difference in Ppa (ΔPpa) before and after 5 min of hypoxia stimuli. The inhibitory effect of muscle relaxants was calculated in percentage by dividing each ΔPpa after each dose of muscle relaxant by the ΔPpamax, which was measured during the control phase before the initial dose of muscle relaxant was injected. After the 5-min HPV response test, a fresh normoxic gas mixture was inspired again to allow the Ppa to return to the baseline level. At the end of experiment, the Ppa, Ppv, Pao and Pvo were measured again to compare with the baseline level. The whole experiment protocol is graphically presented in Figure1.

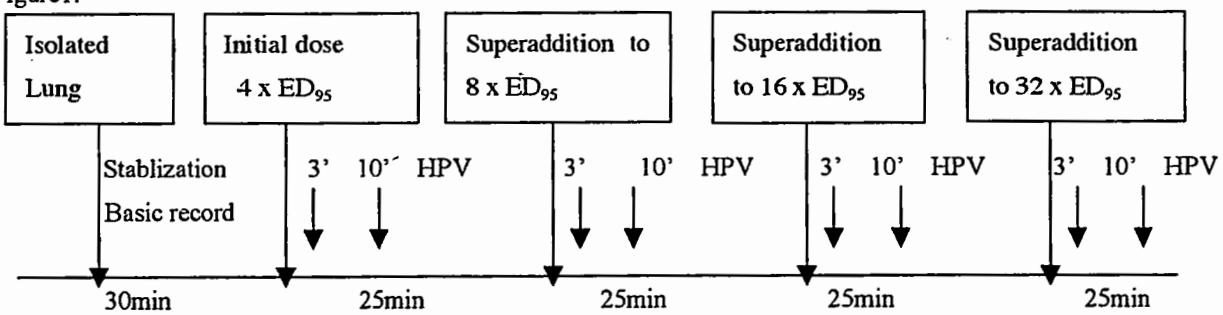

Fig. 1 experiment procudures

Statistics

All data were presented as mean ± SD. Differences within groups were analyzed by the one-way analysis of variance with repeated measures.

Results

No significant changes in Ppa, Ppv and resistance of pulmonary circulation were find after each dose of muscle relaxant in all three groups. The effects of 3 kinds of muscle relaxants on Ppa, Ppv, Rt, Ra and Rv are shown in Tab.1 to Tab.3 respectively.

Tab.1 Effects of atracurium on Ppa, Ppv and resistances(mean±SD)

Atr	Ppa	Ppv	Rt	Ra	Rv
base	12.4±1.6	5.4±0.3	69.3±10.2	39.8±8.5	24.5±4.5
1mg/ 3'	12.3±1.4	5.5±0.3	68.9±12.4	37.1±5.9	26.6±7.6
1mg/10'	12.2±1.4	5.5±0.3	67.8±11.9	37.5±5.9	24.7±8.4
2mg/3'	12.4±1.3	5.4±0.3	69.7±10	41.3±12.9	23±4.6
2mg/10'	12.3±1.2	5.4±0.3	69.2±10.1	38.3±5.9	25.1±5.7
4mg/3'	12.8±1.3	5.4±0.3	73.7±8.4	42.3±6.7	25.9±5.5
4mg/10'	12.9±1.3	5.5±0.3	74.2±8.6	42.6±7.4	25.3±5.4
8mg/3'	13.3±1.4	5.5±0.4	77.5±10.7	48.5±14.8	22.6±7.5
8mg/10'	13.3±1.4	5.5±0.3	78.3±11.4	48.7±15.1	23.5±6.7

Tab.2 Effects of vecuronium on Ppa, Ppv and resistances(mean±SD)

Vec	Ppa	Ppv	Rt	Ra	Rv
base	10.7±0.5	5.4±0.3	54.9±4.8	30.2±10.4	25.5±6.7
0.2mg/ 3'	10.8±0.5	5.4±0.2	53.7±5.2	32.4±6.6	21.5±6.2
0.2mg/10'	10.7±0.5	5.4±0.2	54.8±5.3	32.6±6.5	22.0±6.6
0.4mg/3'	10.7±0.5	5.3±0.2	55.0±5.7	32.9±7.8	21.9±7.8
0.4mg/10'	10.6±0.5	5.3±0.2	54.3±6.1	30.9±6.7	23.4±6.0
0.8mg/3'	10.8±0.5	5.3±0.3	56.4±6.2	33.4±6.8	22.8±7.0
0.8mg/10'	10.8±0.5	5.3±0.3	56.1±6.7	33.7±6.2	22.0±7.6
1.6mg/3'	11.0±0.5	5.3±0.3	58.6±6.7	36.0±6.1	22.5±7.1
1.6mg/10'	11.0±0.5	5.3±0.3	58.2±6.7	34.5±6.4	23.3±8.1

Tab.3 Effects of rocuronium on Ppa, Ppv and resistances(mean±SD)

Roc	Ppa	Ppv	Rt	Ra	Rv
base	12.8±1.3	5.5±0.4	84.1±9.0	53.8±8.9	27.9±8.1
1.2mg/ 3'	12.8±1.3	5.4±0.5	85.0±10.6	49.7±7.2	32.7±14.0
1.2mg/10'	12.9±1.4	5.5±0.5	86.1±10.2	53.0±9.5	30.6±10.0
2.4mg/3'	13.0±1.7	5.4±0.5	87.2±12.9	53.5±7.0	31.1±13.8
2.4mg/10'	13.0±1.6	5.4±0.5	86.7±12.6	55.8±8.7	28.3±13.6
4.8mg/3'	13.1±1.9	5.5±0.6	88.2±16.2	55.1±10.1	30.1±12.9
4.8/mg10'	13.4±2.1	5.3±0.5	90.1±18.3	55.0±12.7	28.2±16.4
9.6mg/3'	13.7±2.0	5.5±0.5	94.1±16.5	61.4±11.9	29.8±15.6
9.6mg/10'	13.7±2.1	5.5±0.5	94.5±17.8	59.6±13.3	32.0±14.5

Ppa = pulmonary arterial pressure(mmHg), Ppv = pulmonary venous pressure(mmHg), Rt, Ra and Rv represent resistance of total pulmonary vascular, pulmonary arterial and pulmonary venous respectively (mmHg/L/min).

The HPV response were significantly inhibited by all of three kind of muscle relaxants. The inhibition percentages after each dose of each kind of muscle relaxant were shown in table 4.

Tab.4 Dose-HPV Response of Muscle Relaxants (mean±SD)

		Base	1mg	2mg	4mg	8mg
Atr	ΔPpa(mmHg)	5.12±1.82	4.07±1.60*	3.53±1.48*	3.04±1.31*	2.66±1.26*
	Inhibition(%)		21.02±3.99#	31.79±6.61#	41.14±6.85#	48.96±7.68#
		Base	0.2mg	0.4mg	0.8mg	1.6mg
Vec	ΔPpa(mmHg)	3.87±1.67	3.02±1.40*	2.63±1.14*	2.32±1.01*	1.97±0.94*
	Inhibition (%)		22.84±3.02#	32.35±2.91#	40.22±5.79#	49.29±8.31#
		Base	1.2mg	2.4mg	4.8mg	9.6mg
Roc	ΔPpa(mmHg)	4.04±1.61	3.25±1.34*	2.94±1.23*	2.59±1.14*	2.16±1.01*
	Inhibition (%)		20.01±2.73#	27.68±3.29#	36.76±3.47#	47.52±5.37#

*P < 0.05 versus base value of ΔPpa

#p < 0.05 versus base inhibition rate

Discussion

Almost all the nondepolarizing drugs can potentially block all autonomic receptors. Interactions with cholinergic recceports, including nicotinic and muscarinic receptor, form the basis for some of the classic cardiovascular side effects

of the muscle relaxants. Many investigations were carried out on the hemodynamic changes induced by muscle relaxants and almost of these investigation were concentrated on the systemic circulation. As most one of widely used three kinds of intermediate duration nondepolarizing muscle relaxants, atracurium, a benzylisoquinolinium, may cause histamine release at high dosage and result in decreasing of mean arterial pressure and tachycardia. Vecuronium is about 20 times weaker as a vagolytic substance than pancuronium. The markedly reduced vagolytic property, together with absent ganglionic blocking and histamine release, results in noteworthy minimal cardiovascular effects of vecuronium. Rocuronium, a newer steroidal relaxant, it's safety ratio for vagal block is about 10 times less than that of vecuronium. In some studies, when rocuronium was administered at high dose, increasing in heart rate of about 20 percent may be observed. This may due to the weak vagolytic effect. Rocuronium was reported may cause pulmonary vascular resistance increasing especially in patients with pulmonary hypertension or valvular heart disease. Atracurium was reported associated with increase of pulmonary artery pressure in Fallot Tetralogy patients. In this study, there were no significant changes of Ppa, Ppv and pulmonary resistance after each dose of all of three kinds of muscle relaxant. The Ppa and pulmonary resistance slightly increased at the large dose of rocuronium compare to that of baseline, however, it was not statistically significant. The new discover in this study was that all of three kinds of muscle relaxants had significant inhibition effects on HPV-response. The mechanism of this inhibition effect is unclear. It may results from the interaction of muscle relaxants with some receptors located in pulmonary vascular or possibly other vosoactive substances are released. Further studies are necessary to elucidate the mechanism of the interesting HPV inhibition effect.

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