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Hemodynamic Interaction of Verapamil with Lidocaine during large doses of Fentanyl-Nitrous Oxide anesthesia in dogs

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Introduction

Large doses of fentanyl(50-100mcg/kg) are commonly employed to maintain hemodynamic stability and the suppress stress hormone response during cardiac surgery.[1-3] Acute administration of lidocaine may be indicated peioperative before the immediate control of premature ventricular contracture and ventricular irritability. In addition, lidocaine may also be indicated for regional anesthesia in patients treated with verapamil. The effect of lidocaine may cause an impairement of cardiac performance[4-6]. Furthermore, patients with cardiovascular disease frequently may require therapy with verapamil intraoperatively for the immediate control of supraventricular tachycardias[7] and myocardial ischemia[8].

Although calcium channel blockers inhibit the transmembrane movement of calcium[9] and local anesthetics inhibit the transmembrane movement of sodium[10], both groups of drugs affect intracellular calcium homeostasis in cardiac and vascular smooth muscle cells[11]. Vasodilation can be elicited by verapamil[12] or lidocaine[13], and both drugs decrease myocardial contractility[9,14].

In addition, both drugs are highly bound to plasma protein and have high clearance.[15-17]. Rosenblatt et al. reported verapamil potentiates toxicity of local anesthetics in rats[18]. The clinical verapamil preparation is a racemic mixture with both calcium and sodium channel blocking properties, and has been shown to have local anesthetic properties at high level[19].

Verapamil and lidocaine have been used in succession and in combination as attempts to treat serious ventricular arrythmias[12-23]. While addictive hemodynamic depression has been described, vera pamil with lidocaine has been administered during inhalation anesthesia in animals[24,25]. But, the interactions of verapamil with the effect of lidocaine during large doses of fentanyl have been little explored.

The purpose of this study was to investigate the hemodynamic effect on three levels of additional verapamil to lidocaine during fentanyl and nitrous oxide anesthesia in dogs.

Materials and Methods

The experimental protocol was approved by the institutional Animal Research Comittee. Ten Korean mongrel dogs(weight 12-15kg) were anesthetized with sodium thiopental(20mg/kg), intubated, and ventilated to normocapnia with a mixture of 50% nitrous oxide and oxygen. Nitrous oxide was used to ensure an adequate depth of anesthesia. Fentanyl, 50mcg/kg and vecronium, 0.1mg/kg, were given, followed by an continuous infusion of 0.5 mcg/kg/min. and ventilation was controlled to maintain $P_a CO_2$ between 35 and 45 torr.

Arterial blood gas tensions and pH were mea sured with an Instrumentation Laboratories model. Sodium bicarbonate was administered intravenously as needed to correct arterial base deficit. Temperature was maintained between 37−38℃ with a

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warming blanket and a heat lamp.

A peripheral vein was cannulated for fluid and drug administration. A femoral artery was cannulated for obtaining blood samples and for measurement of mean arterial blood pressure(MAP). Heparin 3000U/kg intravenously was administered to prevent blood coagulation. A ballon-tipped, 6 F flow-directed catheter was positioned in a pulmonary artery via a right femoral vein for measurement of right atrial(central venous pressure) and pulmonary artery wedge pressures(PAWP), and for determination of thermodilution cardiac outputs in triplicate(Hewlet-Packard cardiac output computer, model 788534C, U.S.A). Heart rate(HR), femoral arterial and RA pressures were continously recorded on Hewlett Packard model. The electrocardiogram(ECG) was intermittently recorded at fast paper speed(100mm/s) for measurement of P-R intervals. Cardiac index(CI) and systemic and pulmonary vascular resistance indices(SVRI and PVRI), and left and right ventricular stroke work indices were calculated using standard formulae. Baseline cardiovascular hemodynamic measurements were taken after 30 min of stable hemodynamic parameters.

The bolus and infusion rates for lidocaine were 2mg/kg over 1 min, followed by 200mcg/kg/min during overall periods of protocol(Fig. 1). After 30min of lidocaine infusion, an intravenous bolus of verapamil 0.2mg/kg was given over 1 min, followed by a continuous infusion at 3mcg/kg/min(V_1), 6mcg/kg/min(V_2), and 9mcg/kg/min(V_3). Each infusion period lasted 30 min. Hemodynamic measurements were obtained at 5, 15 and 30 min during each infusion period. Calcium chloride, 20mg/kg, were given after the final infusion period(V_3) and the measurements were repeated at 1 min(Fig. 1).

Arterial blood was taken for measurement of

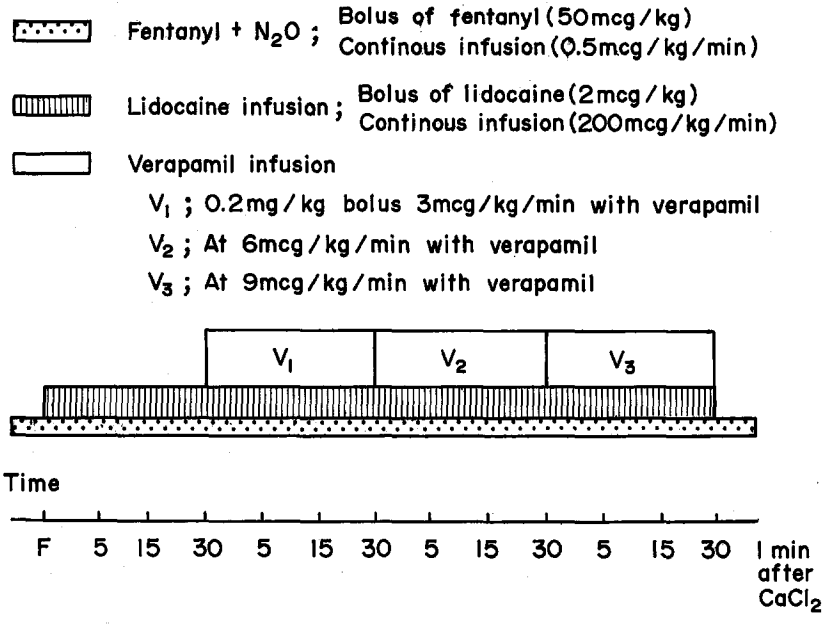

Fig 1. Experimental protocol.

blood gas tension at the end of each infusion period. Values obtained each administration period were compared to control by repeated measures of analysis of variance. Paired T test were used to compare hemodynaimic values at V_3 the those obtained after calcium administration. $P<0.05$ was considered significant for all variable studied.

Results

In our present hemodynamic data, Lidocaine, 2 mg/kg was given, followed by an infusion of 20 mcg/kg/min. The change observed with the lidocaine infusion along is the the MAP, CI and LVSWI was reduced but the CVP, PAWP, HR and SVRI was slightly increased. Upon adding verapamil, 0. 2mg/kg, followed by an infusion of 3mcg/kg/min of continuous lidocaine infusion, HR and CI were increased. Thereafter at 6－9mcg/kg/min of verapamil infusion, CI, MAP and LVWSI were decreased progressively(Tab. 1).

Changes of the MAP and HR against continuous infusion with various doses of lidocaine and vera pamil, Lidocaine along reduced the MAP. But increased the HR slightly. HR progressively decreased. After a calcium chloride bolus injection, the HR was suddenly decreased and there frequently appeared 2:1 block.

The MAP progressively decreased(Fig. 2.). The CVP and PAWP progressively increased (Fig. 3). With lidocaine infusion alone, the CI decreased. CI increased with the lidocaine adding V_1 infusion. After V_1 infusion, the CI continued to decrease(Fig. 4). Five minutes after adding verapamil, 0.2mg/kg followed by and infusion of continuous lidocaine, the SVRI significantly decreased. The PVRI showed little change compared with fentanyl anesthesia(Fig. 5). The LVSWI progressively reduced. But RVSWI was not significantly changed(Fig. 6). Treatment of the depressed blood pressure and cardiac index with calcium chloride were not restored until baseline measurement values due to 2° heart block with 2:1 conduction occurred in 7 dogs.

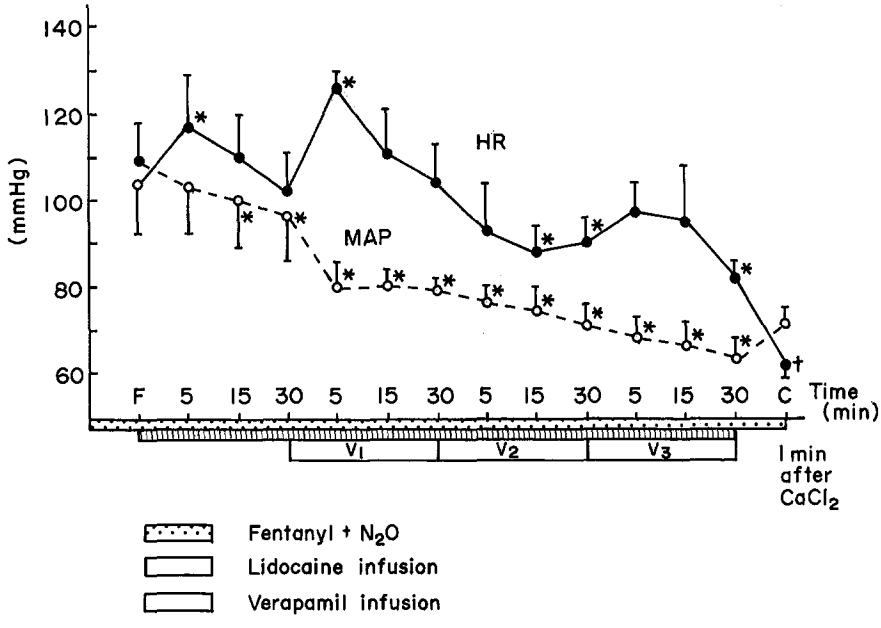

Fig. 2. Changes of MAP and HR values against continous infusion with various dosages of lidocaine and verapamil, Mean±SEM. * = $p<0.05$ compared with control.
+ = $p<0.05$ compared with V_3 at 30min.

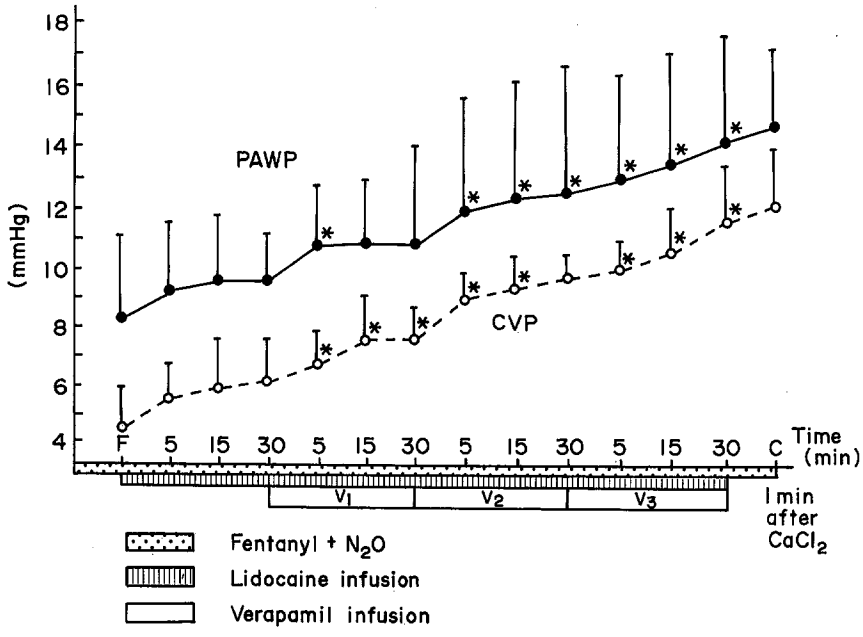

Fig. 3. Changes of PAWP and CVP values against continous infusion with various dosages of lidocaine and verapamil, Mean±SE. * =p<0.05 compared with control.

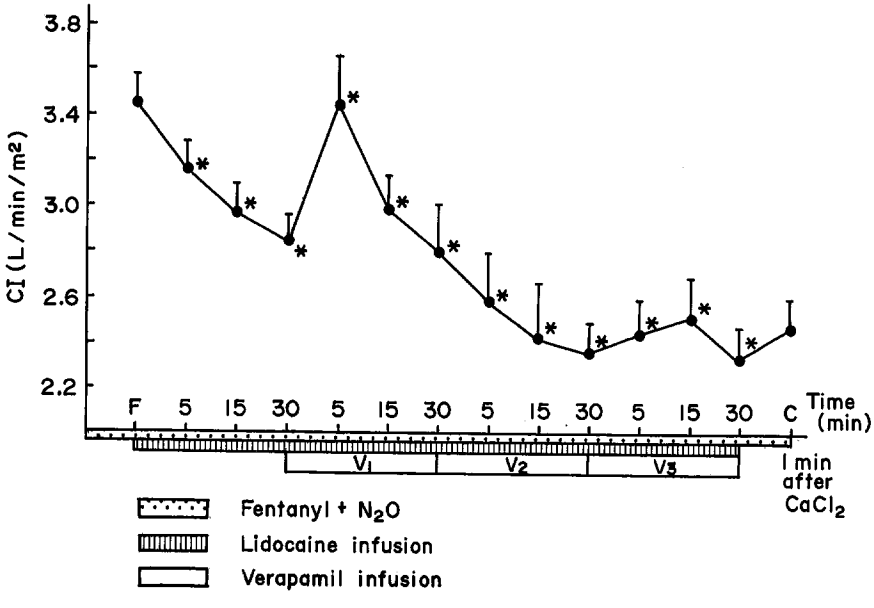

Fig. 4. Changes of CI valuses against continous infusion with various dosages of lidocaine and verapamil, Mean±SEM. * =p<0.05 compared with control.

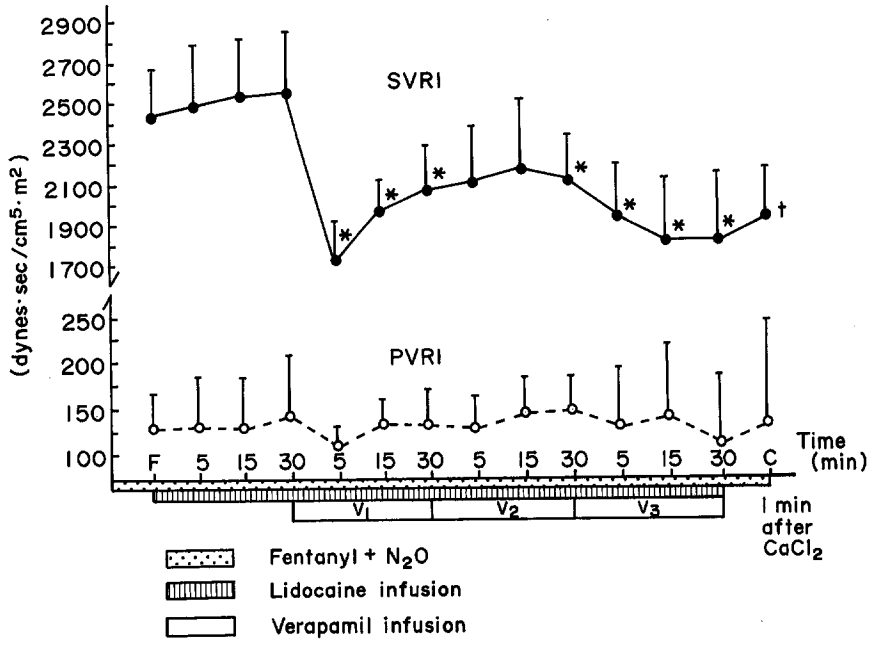

Fig. 5. Changes of PVRI and SVRI values against continous infusion with various dosages of lidocaine and verapamil, Mean±SEM. * =p<0.05 compared with control.
+ =p<0.05 compared with V_3 30min.

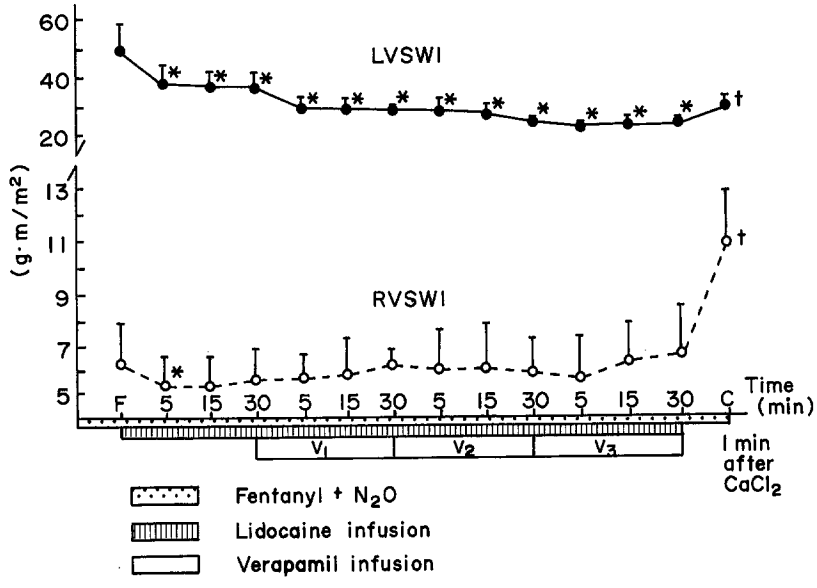

Fig. 6. Changes of RVSWI and LVSWI values against continous infusion with various dosages of lidocaine and verapamil, mean, Mean±SEM.
* =p<0.05 compared with control.
+ =p<0.05 comapred with V_3 30min.

Table 1. Hemodynamic values

	time (min)	F	L	V1	V2	V3	C
HR (bpm)	5	104±12	117±12*	126±4	93±11	97±7	62±
	15		110±10	111±10	88±6*	95±13	
	30		102±9	104±9	90±6*	82±4*	
MAP (mmHg)	5	109±9*	103±11	80±6+	76±4*	68±5*	71±4
	15		100±11*	80±4*	74±6*	66±6*	
	30		96±10*	79±3*	71±5*	63±5*	
CI (L/min/m²)	5	3.45±0.13	3.16±0.13*	3.44±0.23	2.58±0.22*	2.44±0.16*	2.47±0.14
	15		2.97±0.13	2.98±0.16*	2.43±0.24*	2.51±0.19*	
	30		2.84±0.12*	2.80±0.21*	2.36±0.14*	2.33±0.15*	
PAWP (mmHg)	5	8.3±2.8	9.2±2.3	10.7±2.0*	11.8±3.8*	12.8±3.5*	14.5±.6
	15		9.5±2.2	10.7±2.2	12.2±3.9*	13.3±3.7*	
	30		9.5±1.6	10.7±3.3	12.3±4.4*	14.0±3.6*	
SVRI (dyne x sec/ cm⁵m²)	5	2435±247	2483±309	1724±193*	2093±279	1919±267*	1918±246
	15		2533±281	1958±150*	2155±350	1802±309*	
	30		2545±306	2059±225*	2092±231*	1808±35*	
LVSWI (g x m/m2)	5	49.7±9.0	38.2±6.2*	29.8±3.2*	28.8±4.5*	23.3±1.8*	38.5±2.9
	15		37.0±5.3*	29.4±3.5*	27.8±3.2*	24.1±2.8*	
	30		36.6±5.7*	28.9±1.5+	25.2±1.6*	24.5±1.8*	

Mean SEM.* = $p<0.05$ compared with control. + = $p<0.05$ compared with V_3 at 30min.

Discussion

It has previously been estabilished that during inhalation anesthesia with lidocaine, verapamil produces further myocardial depression as a result of pharmacokinetic and pharmacodynamic interaction. At levels approaching toxicity or in anesthetized with subjects, however, lidocaine may be associated with impaired cardiac performance. The lidocaine levels achieved with the low dose of lidocaine are at the lower end of the therapeutic antiarrhythmic range(1.5−6mc/ml) in man[26], and equivalent to plasma levels achieved during local and regional anesthesia[27-30] or from doses of lidocaine sufficient to suppress cardiovascular responses to tracheal intubation[31].

Plasma lidocaine levels of approximately 3.5mcg/ml were sufficient to suppress ischemic induced arrhythmias in the dog[32].

The high lidocaine levels are at or just above the upper advisable therapeutic antiarrhythmic level in man. Similar levels have been reached in man during bolus administration of lidocaine for cough suppresion during tracheal intubation[33]

Patients with cardiovascular disease frequently present for anesthesia and surgery while under therapy with a calcium channel blocking drug. Futhermore, they may require with calcium channel blocking drug intraoperatively. Since verapamil and lidocaine may be indicated intraoperatively in patients with depressed cardiac fuction, it is important to know the interactions between lidocaine, verapamil, fentanyl and nitrous oxide.

High dose fentanyl has been shown to produce adequate anesthesia and remarkable cardiovascular stability[34,35]. Therefore, it has been advocated as the anesthetic agent of choice in patients with se-

rious heart disease requiring general or cardiac surgery. Griffin et a[36] investigated the effect of a contiunous infusion of different concentrations of verapamil during high dose fentanyl nitous oxide anesthesia in dogs. He has been suggested that caution may be advised if the addition of lidocaine by whatever route is indicated in patients who have recently recieved intravenous verapamil or diltiazem in the setting of isoflurane anesthesia.

In the present study, the predominant hemodynamic effects lidocaine adding verapamil were significant reductions in SVRI and MAP. With increasing doses of verapamil, changes in SVRI and MAP were enhanced(Fig. 2, 5). The increase in heart rate observed during the infusion of lidocaine along and lidocaine adding verapamil, 3mcg/kg/min, 5min, may have been related to a reflex response to the peripheral vasodilation and myocardial depression induced by verapamil and lidocaine. Cardiac index was progresively decreased at lidocaine infusion alone, which may be explained by a myocardial depression and transient increased at lidocaine adding verapamil, 3mcg/kg/min at 5min, which may be related by the reduced afterload caused by pronounced vasodilation, or a reflex increased in heart rate. The combination of these effects may have cancealed the direct negative inotropic effects produced by lidocaine adding the increasing verapamil doses levels. An increase in CVP implies an increase in venous return. An increase in venous tone is probably due to a direct stimulation of smooth muscle. PAWP was progressively increased, which may be explained by the effects of cardiovacular interactions between the lidocaine and verapamil. MAP was not occurred below 50 mmHg in overall animals.

Calcium chloride was given to reverse the hemodynamic changes produced by lidocaine adding verapamil. Although LVSWI and MAP were slightly increased, Heart rate was suddenly decreased, which may be explained by baroreceptor reflex. cardiac conduction block(2:1) occurred in seven of the ten animals. The administration of calcuim chloride did not reverse the hemodynaimic effects of lidocaine adding verapamil.

With regard to the 200mcg/kg/min infusion rates of lidocaine used in the V_3 adding lidocaine period of the present experimental protocol, plasma lidocaine concentration was ranged from 7.55±0.79 to 8.23±1.18ng/ml. There is evidence that hepatically metabolized drug, such as lidocaine, can be expected to accumulate in the present of hepatic dysfuction or hepatic underperfusion. According to increase doses of verapamil, plasma lidocaine concentration slightly was increased because of the lidocaine and verapamil(V_3) leaded to worsening cardiac fuction. The severe cardiovascular depression in lidocaine and verapamil(V_3) infusion period may relate to evidence that sodium channel blockade itself can lead to impairment of intracelluar calcium homeostasis. Sodium channel blocking drugs, such as lidocaine, may also contribute to depressed myocardial contractility by altering calcium release from the sarcoplasmic reticulum.

Summary

This study demonstrates that the infusion of increasing concentrations of verapamil with lidocaine during fentanyl-nitrous oxide anesthesia had less depression of the hemodynamic consequence compare with during inhalation anesthetics, such as isoflurane. But, clinical implications of present study show that caution may be advised if the addition of verapamil is indicated in patients who have recently received intravenous lidocaine in the setting of fentanyl-nitrous oxide anesthesia.

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=국문초록=

과량의 Fentanyl-Nitrous Oxide 마취중 Lidocaine과 Verapamil의 혈역학적 상호작용

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김진모 · 이정구 · 김재숙 · 전재규

과량의 Fentanyl-Nitrous Oxide 마취중 Lidocaine을 지속적 점적 정주된 상태에서 Verapamil의 혈역학적 상호작용을 관찰하기 위하여 10마리의 한국산 잡견을 이용하여 실험준비가 완료된 30분후 안정상태의 혈역학치를 대조군(F)으로 lidocaine 200mcg/kg/min를 실험 완료시까지 점적 정주하였고 Verapamil 3mcg/kg/min를 V_1, 6mcg/kg/min를 V_2, 9mcg/kg/min를 V_3로 하여 30분 동안 점적 정주하여 5, 15, 30분의 혈역학치를 측정하고 Verapamil의 효과를 역전하기 위하여 $CaCl_2$ 20mg/kg를 정주후 혈역학변화를 측정하였다.

Lidocaine 200mcg/kg/min 지속적 점적정주시 lidocaine의 혈주농도는 7.85±0.97ng/ml이고 평균동맥압, 심장지수 및 좌심실 박출 작업지수는 약간 감소되고 중심정맥압, 폐동맥쐐기압, 심박수 및 전신혈관 저항지수는 경미하게 증가하였다.

V_1 5분에 전신 혈관저항 지수와 평균동맥압은 의의있게 감소되고 이로 인하여 심장지수도 의의있게 증가하였다.

좌심실 박출작업 지수와 평균동맥압은 V_1 5분 부터 의의있게 감소되었고 점차적으로 감소하는 양상을 보였다.

심장지수는 lidocaine 점적정주시 감소하고 V_1 5분에 의의있게 증가하고 이후 점차적으로 감소하는 경향이다.

중심정맥압과 폐동맥쐐기압은 점차적으로 증가하는 양상을 보였다.

우심실 박출작업지수와 폐혈관 저항지수는 별 변화가 없었다.

요약하면 lidocaine이 정주되는 상태의 환자에 칼슘통로차단제인 verapamil을 사용하여야 할 경우 세심한 주의가 요망된다고 사료된다.

Key Words : Cardiovascular Fentanyl, Lidocaine, Nitrous Oxide, Verapamil