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Comparison of Vasodilation Potency between Sufentanil and Fentanyl on the Isolated Aorta of the Rat

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Abstract

Sufentanil and fentanyl have a weak vasodilative effect and their vasodilation is endothelium-independent and partially through an α-adorenoceptor blocking effect. The aim of the present study was to evaluate the vasodilation potency of sufentanil and fentanyl utilizing pA2, which represents the negative logarithm of an antagonist that causes a doubling of the concentrarion of an agonist to compensate for the action of the antagonist. We measured phenylephrine-induced isometric tension of rat aortic rings without endothelium suspended in organ chambers. Incubation with sufentanil, fentanyl, or phentolamine dose-dependently shifted the concentration-contraction relationships of phenylephrine to the right and sufentanil, fentanyl, or phentolamine (greater then 5×10^{-6}, 1×10^{-7}, or 5×10^{-8} mol·l^{-1}, respectively) significantly increased the estimated concentration of phenylephrinetoinduceahalf-maximalcontraction (EC50). The pA2 values of sufentanil, fentanyl, and phentolamine, obtained from the relationships between the antagonist concentrations and EC50 ratios with to without antagonists, were 4.92, 6.10, and 7.04, respectively. Therefore, the inhibitory effects of sufentanil on phenylephrine-induced vasoconstriction are 1/15 as potent as fentanyl.

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Introduction

Generally, the efficacy of a drug may not be determined by its potency in one area alone. For instance, the anesthetic efficacy of sufentanil, a derivative of fentanyl, is five to ten times as potent as fentanyl[1~3], but that sufentanil has less of a respiratory depressive effect than fentanyl does. This implies a clinical safety advantage in the use of sufentanil[4].

Both sufentanil and fentanyl have a weak vasodilative effect[5,6]. A part of the mechanism is an α-adrenoceptor blocking effect[5,6], but to our knowledge, there have been few reports comparing their vasodilation efficacy. The purpose of the present study was the comparison of the vasodilation potency between sufentanil and fentanyl using the pA2 value[7]. The pA2 represents the negative logarithm of an antagonist-concentration that causes a doubling of the concentration of an agonist to compensate for the action of the antagonist.

Materials and methods

The study was approved by the animal ethics committee of The Royal Melbourne Hospital. Seventeen Sprague-Dawley male rats (280~390g) were killed by stunning and cervical dislocation. The thoracic descending aortae were removed and cleaned of

adventitial connective tissue. The vessels were then cut into transverse rings 3 mm long. Endothelial cells were removed mechanically because fentanyl and sufentanil dilate vessels endothelium-independently[5,8]. The rings were mounted on stainless steel hooks in organ baths containing 15 ml of physiological saline solution (PSS) at 37°C containing, in mol·l^{-1} : NaCl, 118 ; KCl, 4.8 ; $MgSO_4$, 1.2 ; $NaHCO_3$, 1.2 ; NaH_2PO_4, 24 ; $CaCl_2$, 2.5 ; glucose, 11. This buffer solution was aerated with 95% O_2 and 5% CO_2. The rings were equilibrated for about an hour, and then stretched to a final resting tension of 1g.

KCl (80 mmol·l^{-1}) was added first to cause the rings to contract. Additionally, the rings were contracted with the α-adrenoceptor agonist, phenylephrine (1×10^{-7} mol·l^{-1}) to produce about 80% of maximum contraction and then acetylcholine (1×10^{-5}mol·l^{-1}) was added to test the absence of endothelium. The subsequent contraction induced by phenylephrine was expressed as a percentage of this contraction to KCl.

The rings were washed three times with PSS and equilibrated for more than 50 minutes. When the base-line had become stable, some rings were selected randomly and incubated with sufentanil (5×10^{-6}, 2×10^{-5}, or 5×10^{-5} mol·l^{-1}) or fentanyl (1×10^{-7}, 1×10^{-6}, or 1×10^{-5} mol·l^{-1}). Twenty minutes later, phenylephrine (from 1×10^{-9} to 3×10^{-5} mol·l^{-1}) was administered cumulatively into the organ bath to obtain concentrarion-contraction relationships. Other rings were incubated with an α-adrenoceptor antagonist, phentolamine (5×10^{-8}, 3×10^{-7}, or 1×10^{-6} mol·l^{-1}) and concentrarion-contraction relationships of phenylephrine were obtained. Rings used in time control were not incubated with any drugs.

The estimated concentration of phenylephrine producing 50% of the maximum contraction (EC_{50}) by cumulatively administration was computed using a least-squares method for curve fitting to a sigmoid model[9]. Mean pA_2 values of sufentanil, fentanyl, and phentolamine were evaluated to compare their antagonism on phenylephrine-induced contraction[7]. Briefly, the pA_2 value was obtained from the relationship between negative logarithm concentrations of the antagonists (sufentanil, fentanyl, or phentolamine) and the EC_{50} ratios of the agonist (phenylephrine) in the absence against in the presence of the antagonists. A straight line could be computed from the negative logarithm of EC_{50} ratios plotted against the negative logarithm of an antagonist concentration using the least-squares method. When the crossover point of the straight line and a line, $y=\log_{10}2$ is calculated, the logarithm concentration of the antagonist is the pA_2 value.

All results were expressed as mean values and standard errors of the means (SEM). For statistical analysis, two-way analysis of variance was performed to compare concentration-contraction relationships. Student's t-test was used to compare EC_{50}s. Differences were considered statistically significant at $P<0.05$.

Results

KCl (80 mmol·l^{-1}) produced contractions of 1.95 ± 0.14 g, with no significant difference between the groups. Acetylcholine (1×10^{-5} mol·l^{-1}) had no significant effect (101.2 ± 1.1%) on contractions induced by phenylephrine (1×10^{-7} mol·l^{-1}). Incubation with sufentanil dose-dependently shifted the concentration-contraction relationships of phenyphrine significantly to the right (Fig. 1). The EC_{50} of phenylephrine alone was $0.92\pm0.22\times10^{-7}$ mol·l^{-1} (Table). Incubation with 5×10^{-6} mol·l^{-1} of sufentanil did not change the EC_{50} but 2×10^{-5} or 5×10^{-5} mol·l^{-1} significantly increased the EC_{50} (1.26 ± 0.22 or $4.06\pm2.07\times10^{-7}$ mol·l^{-1}, respectively). Fentanyl also significantly shifted the concentration-contraction relationships of phenylephrine to the right (Fig. 2). The EC_{50} was not changed by 1×10^{-7} mol·l^{-1} of fentanyl, however significantly increased by 1×10^{-6} or 1×10^{-5} mol·l^{-1} (1.17 ± 0.81 or $2.69\pm0.62\times10^{-7}$ mol·l^{-1}, respectively). Incubation with phentolamine 3×10^{-8}, 5×10^{-8} or 1×10^{-7} mol·l^{-1} significantly shifted the concentration-contraction relationships to the right (Fig. 3) and dose-dependently increased the EC_{50} (Table). Fig. 4 shows the relationship between concentrations of antagonists (sufentanil, fentanyl, and phentolamine) and EC_{50} ratios of the agonist (phenylephrine) in the absence against in the presence of the

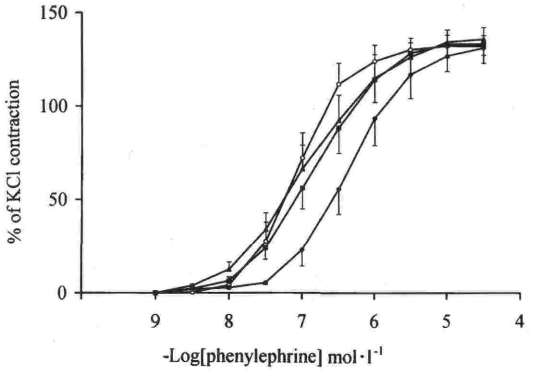

Fig. 1 Effects of sufentanil on concentration-contraction relationships of phenylephrine. Rat aortic rings without endothelium was incubated with sufentanil 5×10^{-10} (solid triangles), 2×10^{-5} (solid squares), or 5×10^{-5} mol·l^{-1}(solid circles) 20 minutes, but rings in time control (open circles) were not incubated with sufentanil. Phenylephrine was then administered cumulatively and contraction was expressed as percentage of the maximum response to a standard challenge with KCl 80 mmol·l^{-1}. Data are mean±SEM (n=6).

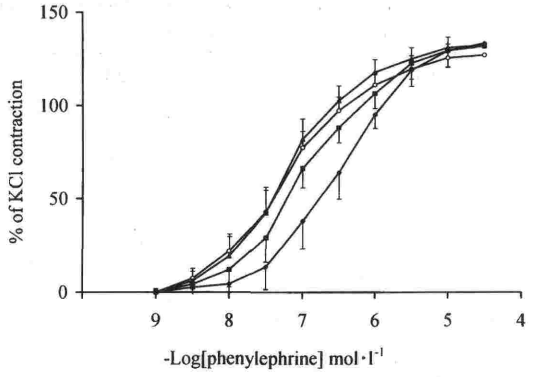

Fig. 2 Effects of fentanyl on concentration-contraction relationships of phenylephrine. Rat aortic rings without endothelium were incubated with fentanyl 1×10^{-7} (solid triangles), 1×10^{-6} (solid squares), or 1×10^{-5} mol·l^{-1} (solid circles) 20 minutes, but rings in time control (open circles) were not incubated with fentanyl. Phenylephrine was then administered cumulatively and contraction was expressed as percentage of the maximum response to a standard challenge with KCl 80 mmol·l^{-1}. Data are mean±SEM (n=6).

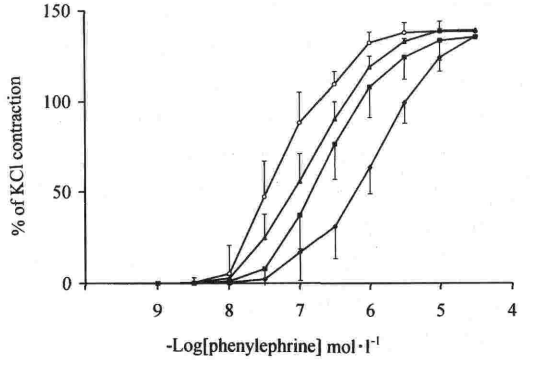

Fig. 3 Effects of phentolamine on concentration-contraction relationships of phenylephrine. Rat aortic rings without endothelium were incubated with phentolamine 5×10^{-8} (solid triangles), 3×10^{-7} (solid squares), or 1×10^{-6} mol·l^{-1} (solid cirecles) 20 minutes, but rings in time control (open circles) were not incubated with phentolamine. Phenylephrine was then administered cumulatively and contraction was expressed as percentage of the maximum response to a standard challenge with KCl 80 mmol·l^{-1}. Data are mean±SEM (n=5).

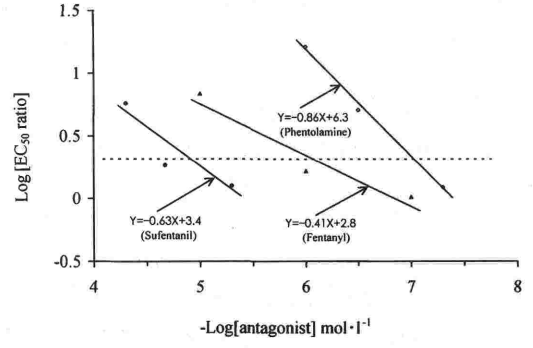

Fig. 4 Relationships between the negative logarithm concentration of antagonists (sufentanil, fentanyl, and phentolamine) and the dose (EC_{50}) ratios of the agonist (phenylephrine) in the absence against in the presence of the antagonist. The dotted line is $y=\log_{10}2$.

antagonist. Using the least-squares method, plots of the negative logarithm of EC_{50} rations against the concentration of sufentanil, fentanyl, and phentolamine gave a straight line for each agent with slopes of -0.63, -0.41, and -0.86, respectively. The dotted line in Fig. 4 shows $y=0.301$ ($\log_{10}2$). The pA_2 values of sufentanil, fentanyl, and phentolamine obtained from the x-values of their crossover points in Fig. 4, were 4.92, 6.10, and 7.04, respectively. Therefore, as the

Table. The estimated concentration of phenylephrine inducing half-maximum contraction (EC_{50}) obtained after incubation with sufentanil, fentanyl or phentolamine.

Sufentanil (n = 6)	Control	5×10^{-6} M	2×10^{-5} M	5×10^{-5} M
	0.92±0.22	1.01±0.38	1.26±0.22*	4.06±2.07**
Fentanyl (n = 6)	Control	1×10^{-7} M	1×10^{-6} M	1×10^{-5} M
	0.60±0.20	0.49±0.19	1.17±0.81*	2.69±0.62**
Phentolamine (n = 5)	Control	5×10^{-8} M	3×10^{-7} M	1×10^{-6} M
	0.79±0.32	1.87±0.47*	2.46±0.56**	12.7±3.93**

All values are mean ± SEM ($\times10^{-7}$ mol·l^{-1}). *; $P<0.05$, ** ; $P<0.01$ versus each control.

pA2 difference between fentanyl and phentolamine was 0.94, the inhibitory effect of fentanyl was 1/9 ($=10^{-0.94}$) as potent as phentolamine. The inhibitory effect of sufentanil was 1/15 ($=10^{4.92-6.10}$) as potent as fentanyl.

Discussion

This study demonstrated that sufentanil and fentanyl inhibit the contraction response of the rat aorta induced by phenylephrine, and that the inhibitory effect of sufentanil is 1/15 as potent as fentanyl. The anesthetic effects of sufentanil are five to ten times as potent as fentanyl[1~3]. Therefore, vasodilation effect of sufentanil is very weak, compared with that of fentanyl at equianesthetic potency. Bailey et al[4] reported that sufentanil induced less respiratory depression than fentanyl did. These differences between two drugs may be due to defferences of two drugs in affinities and binding potencies to plural receptors, namely α_1A, α_1B, μ_1, or μ_2. Because sufentanil has very weak vasodilative and respiratory-depressive effects and is a more potent anesthetic than fentanyl, sufentanil should prove beneficial in clinical applications.

Since sufentanil and fentanyl are known to induce hypotension especially when used in high dose for cardiac surgery[10,11], the mechanism of this hypotension is our interest. Sufentanil and fentanyl have no histamine release which is a common cause of morphine-induced hypotension[12]. Toda and Hatano[6] have reported that fentanyl inhibits norepinephrine-induced contraction by the mechanism of α_1 adrenoceptor blocking and that fentanyl does not alter the dose-response curves of histamine and serotonine, consistent with Lee et al. who has reported that fentanyl does not depress the vasoconstriction by histamine or KCL[13]. We have reported that sufentanil has also an α_1 adrenoceptor blocking effect[5] and that the inhibitory effect of sufentanil and fentanyl is endothelium-independent[5,8]. In this study, therefore, the inhibitory potency of sufentanil and fentanyl against the phenylephrine-induced contraction was compared on isolated rat aortic rings denuded of endothelium using the pA2. The pA2 value is determined pharmacologically as the negative logarithm of EC_{50} ratios of the agonists (phenylephrine) in the absence against in the presence of the antagonist, and means the negative logarithm of the dissociation constant of an antagonist. Therefore, the pA2 is independent of agonists inducing contraction, species, or organs. We used the rat aorta in this study because of its easy access.

Vascular smooth muscle from various species differ in response to opiates. Morphine contracts the cerebral artery[14], and dilates small mesenteric artery in the rat[15]. On the cerebral artery of the cat morphine induces contraction[16] or relaxation[17]. These phenomena may be due to the presence of different types of opiate receptors on the smooth vascular muscle[18]. And this may be the reason why slopes of sufentanil and fentanyl are not approximate 1 in this experiment.

Fentanyl and sufentanil increase human middle cerebral artery flow velocity as detected by transcranial Doppler ultrasonography[19]. Although fentanyl and sufentanil have indirect vasodilation effects through the autonomic nervous system[20], a part of the mechanism may be due to the direct vasodilation effect

of fentanyl and sufentanil[5,8] as demonstrated in this study. Maximum serum concentration of fentanyl may be as great as 9.2×10^{-7} mol·l^{-1} one minute after injection of fentanyl 1 mg·m^{-2} in patients[21] and that of sufentanil is approximately 2.4×10^{-6} mol·l^{-1} during clinical use[22]. Hypotension during anesthesia with high dose of sufentanil or fentanyl may be partially through the α_1 adrenoceptor blocking effect on human vascular smooth muscle. On the other hand, the binding fractions of sufentanil and fentanyl to serum protein have been reported to be 92.5 and 84.4%, respectively[23]. Therefore, the direct inhibitory effect of sufentanil on vasoconstriction in vivo may be lower than 1/15 of fentanyl, obtained in this study, because the active unbinding form of sufentanil becomes smaller than that of fentanyl.

In conclusion, sufentanil and fentanyl have an endothelium-independent vascular smooth muscle relaxation effect and the inhibitory effects of sufentanil on phenylephrine-induced vasoconstriction are 1/15 as potent as that of fentanyl. Because sufentanil is a more potent anesthetic than fentanyl, the direct vasodilation effect of sufentanil on vascular smooth muscle is less than fentanyl in equianesthetic potency, suggesting a less incidence of hypotension in clinical use.

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