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Hemodynamics and Histamine Release during Induction with Sufentanil or Fentanyl

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Sufentanil citrate is a new thienyl derivative of fentanyl that has 5–10 times the analgesic potency of fentanyl. Most reports suggest that its hemodynamic effects compare favorably with those of fentanyl.[1–3] Administration of high doses of any narcotic can produce vasodilation and hypotension, but these effects are much less prominent with fentanyl than with morphine. This difference is due, in part, to the fact that fentanyl does not release histamine.[4] Sebel and Bovill[2] studied 40 patients undergoing cardiac surgery and reported that two of them experienced precipitous hypotension after receiving 15 $\mu g \cdot kg^{-1}$ sufentanil. Flushing was not described, and systemic vascular resistance was not measured.

We believe that any new drug proposed for intravenous use should be tested for histamine release in humans. The present study, therefore, was undertaken to compare histamine release and hemodynamics during induction of anesthesia with fentanyl or sufentanil.

MATERIALS AND METHODS

Twenty patients, 32–72 years of age, gave written informed consent to this institutionally approved protocol. All were classified as ASA Class III or IV and were scheduled for elective coronary artery bypass surgery. All patients had ejection fractions of 0.5 or greater, and 19 of them were chronically taking propranolol or metoprolol. Patients were assigned randomly to receive either fentanyl 100 $\mu g \cdot kg^{-1}$ (Group 1) or sufentanil 15 $\mu g \cdot kg^{-1}$ (Group 2). The doses are representative of those being recommended for use in cardiac surgery.

Preoperative medication consisted of morphine sulfate 0.1 $mg \cdot kg^{-1}$ im and scopolamine 0.3–0.4 mg im, given 1–1.5 hours prior to induction of anesthesia. Peripheral venous, pulmonary arterial, and radial arterial lines were inserted under local anesthesia. Baseline hemodynamic measurements were made, and 100% oxygen was administered via mask.

After a control arterial blood sample was drawn for determination of a plasma histamine concentration, anesthesia was induced with either fentanyl 100 $\mu g \cdot kg^{-1}$, administered at a rate of 400 $\mu g \cdot min^{-1}$ iv, or sufentanil, 15 $\mu g \cdot kg^{-1}$, administered at a rate of 60 $\mu g \cdot min^{-1}$ iv. The dose and infusion rate of fentanyl are those commonly utilized in our institution. The dose of sufentanil is that utilized by Sebel and Bovill.[2] Since both drugs were supplied in a concentration of 50 $\mu g \cdot ml^{-1}$, the infusion rates were selected to give the same infusion time for both narcotics. Metocurine, 0.3 $\mu g \cdot kg^{-1}$ iv, was infused concurrently with the study medication at a rate of 2 $mg \cdot min^{-1}$. We previously have shown that metocurine does not release histamine when given at this rate.[4] Respiration was controlled to prevent hypercarbia.

Phasic and mean arterial pressure (MAP), heart rate (HR), pulmonary artery pressure (PA), mean central venous pressure (CVP), and pulmonary capillary wedge pressure (PCWP) were recorded on an eight-channel recorder with an oscilloscope. Cardiac output (CO) was measured by thermodilution using an Edwards Laboratory computer. Systemic vascular resistance (SVR) was calculated as $[(MAP - CVP)/CO] \times 80$ dynes $\cdot$ sec $\cdot$ cm^{-5}.

Hemodynamic measurements were made, and blood samples for histamine were obtained after one-third of the total narcotic dose had been administered, and at 2 and 5 min after the completion of narcotic infusion. Each 10-ml sample was drawn into a heparinized tube (Vacutainer,® Becton-Dickenson, Rutherford, New Jersey) and placed on ice immediately. Tubes were centrifuged at 2,000 rpm for 10 min, and the plasma layer was put into polypropylene tubes (Falcon 2063) and stored at −70° C. Plasma histamine levels were determined with the use of the radioenzymatic assay described by Moss *et al.*,[5] which has a sensitivity of 100 $pg \cdot ml^{-1}$. Baseline plasma histamine in our laboratory is normally less than 2 $ng \cdot ml^{-1}$.

Data were analyzed by analysis of variance.

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TABLE 1. Demographics

	Fentanyl	Sufentanil	P
Male/female	9/1	10/0	NS
Age (yrs)	59.9 ± 2.0*	53.5 ± 3.3	NS
Range	(50–72)	(32–66)	
Height (cm)	173.0 ± 2.0	179.3 ± 1.5	0.0338
Range	(162.6–182.9)	(170.2–185.4)	
Weight (kg)	73.3 ± 2.6	86.5 ± 2.9	0.0062
Range	(60–92)	(75–99)	
Beta-adrenergic receptor blocker ($mg \cdot day^{-1}$)			
Propranolol	174.3 ± 56.0	94.3 ± 24.0	NS
Range	(60–480)	(30–160)	
Metoprolol	187.5 ± 37.5	133.3 ± 33.3	NS
Range	(150–225)	(100–200)	

* Mean ± SEM.

RESULTS

Demographic data on the 20 patients are listed in table 1. The patients in the sufentanil group had larger mean heights and weights. The daily doses of beta adrenergic receptor blockers were not significantly different.

All patients lost consciousness within 5 min after receiving the narcotic. Chest wall rigidity occurred in six patients in Group 1 and in four patients in Group 2. All episodes of rigidity responded to the administration of metocurine, and no patient became significantly hypercarbic.

Both groups had significant decreases in MAP and SVR. The maximal effects occurred after one-third of the drug had been infused (fig. 1) and persisted throughout the study period. There were no significant between-group differences. One patient in the fentanyl group required phenylephrine for hypotension. This patient had a decrease in MAP from 80 to 50, and SVR went from 1,361 to 796 dynes · sec · cm^{-5}. Plasma histamine did not increase.

Although the baseline values for plasma histamine were statistically significantly different (fentanyl 859 ± 91, sufentanil 1,725 ± 244; $P < 0.003$), these mean values were within the range of normal for our laboratory.‡ No significant changes in plasma histamine occurred during the study period in either group.

There were no significant changes from control for mean HR and CO values at any time point in either group. There were small but statistically significant changes in CVP, PA, or PCWP in both groups (table 2). None of the between-group comparisons were statistically significant.

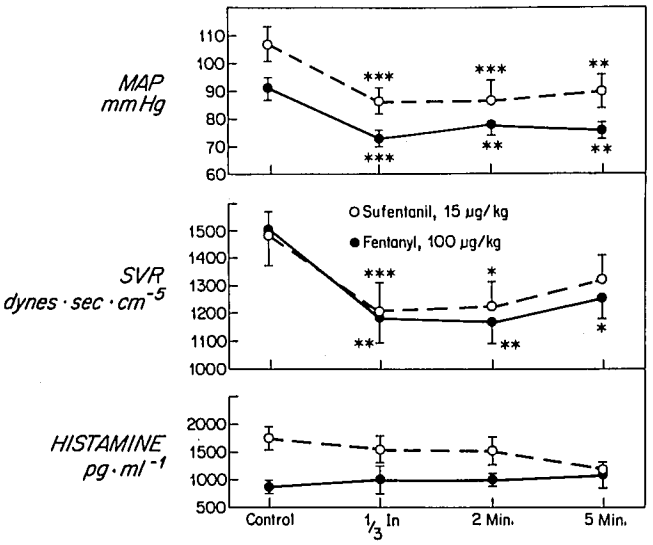

FIG. 1. Mean arterial pressure, systemic vascular resistance, and plasma histamine concentrations for Groups 1 and 2. Significant changes from control are indicated by *($P < 0.05$), **($P < 0.01$), or ***($P < 0.001$).

DISCUSSION

Anesthetic techniques utilizing oxygen and high doses of narcotics may be most useful during induction of anesthesia. The relative lack of cardiovascular depression is particularly advantageous when there is no surgical stimulus. Maintenance of narcotic anesthesia, on the other hand, frequently requires the use of supplemental anesthetics and vasoactive drugs.[6]

There has been some debate recently over the relationship between plasma histamine concentration to the cardiovascular responses produced by intravenously administered narcotics.[7,8] There seems little doubt that basic drugs like morphine can cause significant elevation in plasma histamine, and these changes correlate well with vasodilation and hypotension.[4] The cardiovascular effects of high doses of morphine can be blocked partially by

TABLE 2. Maximal Changes in Hemodynamic Values from Control*

Parameter	Fentanyl	Sufentanil
HR ($beats \cdot min^{-1}$)	0.0 ± 2.0	−1.2 ± 0.8
CO ($l \cdot min^{-1}$)	−0.1 ± 0.3	−0.2 ± 0.2
CVP (mmHg)	+3.0 ± 0.5†	+2.4 ± 0.7†
PA (mmHg)	+1.7 ± 0.6†	+0.6 ± 1.4
PCWP (mmHg)	+2.0 ± 0.6†	+1.0 ± 0.7

† Significantly different from control value ($P < 0.05$).
* Mean ± SEM.

‡ Two sufentanil-treated patients had abnormally high histamine levels on entry into the operating room, thus accounting for the elevated average value in this group. These values were confirmed by duplicate assays. The plasma histamine levels in both patients decreased during sufentanil infusion.

pretreatment with antihistamines.[9] A more direct approach to the problem is simply to use drugs like fentanyl that do not release histamine.

We administered sufentanil in a dose and at an infusion rate representative of those being evaluated in cardiac surgery and found no evidence of histamine release. That is not to say we found no cardiovascular effects. Both fentanyl and sufentanil lowered systemic pressure and peripheral vascular tone. Both drugs presumably reduce central sympathetic tone, and may share morphine's peripheral effects on capacitance and resistance vessels.[10]

In summary, sufentanil produces rapid loss of consciousness, moderate decreases in systemic pressure and peripheral resistance, and no histamine release. In these respects it is clinically indistinguishable from fentanyl.

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Intracranial Pressure, Mean Arterial Pressure, and Heart Rate Following Midazolam or Thiopental in Humans with Brain Tumors

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Midazolam maleate is a water-soluble benzodiazepine that recently has been recommended as an effective intravenous agent for induction of anesthesia.[1–3] Midazolam has a short onset and duration of action,[4] is nonirritating to veins,[5] relieves anxiety,[3] produces antegrade amnesia,[6] and is a mild respiratory depressant.[7]

No significant cardiovascular differences have been demonstrated between midazolam (0.25 mg/kg) and thiopental (4 mg/kg) when either drug is intravenously administered to healthy surgical patients for induction of anesthesia,[8] and midazolam has minimal cardiovascular effects even when administered to patients with ischemic heart disease who are undergoing coronary artery bypass surgery.[9]

Midazolam (0.2 mg/kg) decreases cerebral blood flow (CBF) by 35% in humans[10] and 55% in dogs and produces dose-related decreases in cerebral metabolic rate of oxygen ($CMRO_2$) in dogs to a maximum of 55% after 10 mg/kg.[11] Thiopental in equivalent doses has similar effects on CBF and $CMRO_2$.[12]

The effect of midazolam and thiopental on intracranial pressure (ICP), mean arterial pressure (MAP), and heart

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