MYOCARDIAL SPARING EFFECT OF FENTANYL DURING HALOTHANE ANAESTHESIA IN DOGS

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SUMMARY
The cardiovascular effects of fentanyl (Sublimaze) were studied in seven mongrel dogs. A constant infusion of the drug was used to produce an apnoeic end-point while concomitant cardiovascular changes were monitored. After one hour the infusion was repeated while ventilation was controlled and atropine was given to eliminate the haemodynamic effect of changes in PaCO₂ and heart rate. When PaCO₂ was allowed to increase fentanyl reduced heart rate and mean arterial pressure markedly while left ventricular dp/dt was depressed moderately at the time of respiratory arrest. When heart rate and PaCO₂ were kept constant there was little variation in the cardiovascular measurements during fentanyl infusion. We conclude that fentanyl allows relative myocardial sparing in dogs when used at clinically effective concentrations.

The cardiac effects of fentanyl are considered to be less depressant than those of other narcotics such as morphine (Mostert et al., 1971) and meperidine (Freye, 1974). While the respiratory effects of fentanyl have been well documented, there is no available data to allow comparison of depression of respiration with other side effects of this powerful narcotic. This study was designed to compare ventilatory depression with concurrent cardiac events during constant fentanyl infusion in dogs. The end-point was the production of apnoea lasting for 30 sec or longer.

METHODS
Seven mongrel dogs weighing 10–13 kg were anaesthetized with halothane, nitrous oxide and oxygen using a circle system with carbon dioxide absorber. After tracheal intubation, the dogs breathed 1.2–1.5% inspired halothane for 1 hr.

End-tidal Pco₂, tidal volume, respiratory rate, heart rate, and central aortic arterial pressure were measured continuously. A 12-cm 16 gauge Teflon catheter (Angiocath) was placed percutaneously into the left ventricle and coupled directly to a Statham P-23Db transducer for pressure recording. The signal was differentiated (Grass Differentiator: 90% rise time 1.8 msec) to give a continuous recording of left ventricular dp/dt. Response linearity in this system probably exceeds 40 Hz. Arterial Po₂, Pco₂ and pH were measured frequently and any metabolic abnormalities were corrected. Body temperature was maintained between 36.5 and 37.5°C.

Fentanyl citrate (50 μg/ml) was administered i.v., using an infusion pump, at rates from 0.4 μg/kg/min to 0.8 μg/kg/min while the dogs were breathing spontaneously. The infusion was maintained until the dogs had been apnoeic for 30 sec, at which point the fentanyl was discontinued and recovery was allowed over a 1-hr period. Controlled ventilation was then established with a Harvard respirator keeping PaCO₂ constant (33–40 mm Hg) in order to abolish the carbon dioxide influence on cardiac function. Atropine sulphate 1 mg/kg was given in an attempt to achieve a constant heart rate. When a steady state was reached the fentanyl infusion was re-established at the same rate. However, the infusion was continued so that the amount of fentanyl given exceeded by 50–100% that required previously to produce apnoea. In two dogs, showing tolerance to fentanyl, the dose given during constant ventilation exceeded the apnoea dose by at least 100%. These larger doses during controlled ventilation were given to minimize the possible effect of tolerance to the circulatory effects of fentanyl which has been reported (Freye, 1974). In several of the animals, duplicate runs were made to verify reproducibility of the drug effect. Only the original study is reported from these dogs (table I).
Table I. The cardiovascular effects of fentanyl infusion at the point of respiratory arrest during spontaneous (SR) and controlled respiration (CR). The following measurements are given: heart rate (HR), mean arterial pressure (MAP), peak rate of increase of left ventricular pressure (peak dp/dt), maximum left ventricular pressure (LVP), and left ventricular end diastolic pressure (LVEDP).

<table>
<thead>
<tr>
<th>Dog</th>
<th>Fentanyl (µg/kg)</th>
<th>HR (% change)</th>
<th>MAP (% change)</th>
<th>Peak dp/dt (% change)</th>
<th>LVP (% change)</th>
<th>LVEDP (% change)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SR (µg/kg)</td>
<td>CR</td>
<td>SR (µg/kg)</td>
<td>CR</td>
<td>SR (µg/kg)</td>
<td>CR (µg/kg)</td>
</tr>
<tr>
<td>1</td>
<td>21.2</td>
<td>100.0</td>
<td>-78 -7</td>
<td>-44 +3</td>
<td>-28 -2</td>
<td>-27 0 +2 +1</td>
</tr>
<tr>
<td>2</td>
<td>28.8</td>
<td>24.0</td>
<td>-58 -29</td>
<td>-54 -13</td>
<td>-34 -12</td>
<td>-33 -27 0 0</td>
</tr>
<tr>
<td>3</td>
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<td>-</td>
<td>-30 -10</td>
<td>-4 -4</td>
<td>+5 -4</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>12.6</td>
<td>18.0</td>
<td>-32 -15</td>
<td>-28 -22</td>
<td>-18 -2</td>
<td>-20 -7 +1 -1</td>
</tr>
<tr>
<td>5</td>
<td>12.0</td>
<td>24.0</td>
<td>-44 +1</td>
<td>-19 +15</td>
<td>+4 +4</td>
<td>- +4 - +6 +6</td>
</tr>
<tr>
<td>6</td>
<td>13.6</td>
<td>25.0</td>
<td>-39 -5</td>
<td>-14 -9</td>
<td>+2 +8</td>
<td>-6 +10 +6 +4</td>
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<tr>
<td>7</td>
<td>38.4</td>
<td>90.0</td>
<td>-47 -18</td>
<td>-25 -9</td>
<td>-14 0</td>
<td>-16 0 +5 0</td>
</tr>
</tbody>
</table>

Mean ± SEM: 20.9 ± 3.7 47% -12* 28* -5.8 -16* -0.7 -16.2 -1.7 +3 +1.7

Significant from own control: *P<0.05; †P<0.01.
Significant difference between spontaneous and controlled respiration: ‡P<0.05; §P<0.01.

RESULTS

Table I shows the cardiovascular effects of fentanyl infusion at the point of respiratory arrest during spontaneous respiration (SR) and at the dose-equivalent point during controlled respiration (CR). The following measurements are given: heart rate (HR), mean arterial pressure (MAP), peak rate of increase of left ventricular pressure (LV dp/dt), left ventricular pressure (LVP), and left ventricular end diastolic pressure (LVEDP).

At the "apnoeic" points during spontaneous respiration, the heart rate was influenced more (47% reduction) than other cardiovascular variables. The mean arterial pressure was decreased by 28% while ventricular pressure remained relatively unchanged during controlled respiration. Sparing of ventricular function (little change in peak LV dp/dt) is noted during both ventilation modes (see text).

![Graph](image-url)
peak LV $\frac{dp}{dt}$ was reduced by only 16%. LVEDP, or preload, increased by 3 mm Hg.

During controlled ventilation and following atropine i.v., all of the cardiac variables were affected less by fentanyl, and in particular, myocardial contractility as indicated by LV $\frac{dp}{dt}$ was not affected in six of the seven dogs. However, in this part of the experiment, heart rate (which averaged 137 beats/min during control conditions) still decreased by 12%, with fentanyl infusion in spite of the vagolytic action of atropine.

In figure 1 are shown the time course of the respiratory and circulatory changes during fentanyl infusion from a duplicate study in one of the dogs. The largest changes occurred during spontaneous respiration. The arterial pressure decreased by 41% at the point of apnoea and the heart rate decreased by 47% while peak LV $\frac{dp}{dt}$ decreased by only 10%. Arterial $P_{CO_2}$ increased from 35 mm Hg to 55 mm Hg at the point of apnoea. During controlled respiration $P_{CO_2}$ was maintained at 33 mm Hg and the changes in heart rate, arterial pressure and peak LV $\frac{dp}{dt}$ were negligible.

**DISCUSSION**

These results indicate a marked difference between the respiratory and circulatory effects of fentanyl. With spontaneous ventilation, the reduction in heart rate (47%) when apnoea was reached suggests a vagomimetic effect by fentanyl. Atropine 1 mg/kg reduced this effect during fentanyl infusion, since heart rate decreased by an average of 12% in the controlled ventilation series. It is possible that the vagal nerve endings to the heart were not blocked completely by atropine, or that fentanyl may have a direct negative chronotropic effect on the heart. We have found that i.v. atropine sulphate 1 mg/kg in dogs blocks nearly all the chronotropic response to direct vagal stimulation for about 30 min. Since many of our periods of study lasted longer than this, the vagus may have recovered susceptibility to drug stimulation later in the infusion. This could explain the mild slowing of the heart rate during controlled ventilation.

While mean arterial pressure decreased by 28% following fentanyl during spontaneous respiration, there was no significant change when fentanyl followed atropine during controlled eucapnic ventilation. Moreover, LV $\frac{dp}{dt}$ decreased slightly (16%) during spontaneous ventilation, but was unchanged during controlled ventilation. These last data suggest a relative sparing of myocardial contractility by fentanyl during spontaneous ventilation and complete sparing during controlled ventilation.

In our investigation, cardiac preload and afterload remained nearly constant following atropinization and controlled respiration. With both these variables and heart rate relatively stable, any change in cardiac contractility will be reflected in changes in peak LV $\frac{dp}{dt}$ (Mason, 1969). No significant change in peak LV $\frac{dp}{dt}$ was observed in our controlled respiration dogs following the infusion of fentanyl. While the heart rate decreased significantly, even after the administration of atropine, a reduced heart rate generally produces a decrease in peak LV $\frac{dp}{dt}$ (Wallace, Skinner and Mitchell, 1963). Therefore, if a correction factor should be applied to our measured peak LV $\frac{dp}{dt}$, it would be to increase the value.

The effects of carbon dioxide and atropine on myocardial function must be considered in this experiment. In intact dogs and man, hypercapnia generally results in increased myocardial performance (Blackburn et al., 1972; Prys-Roberts et al., 1967). In this study, however, there was a reduction in LV $\frac{dp}{dt}$ during spontaneous respiration when hypercapnia was present. With sustained eucapnea there was no change in this measurement following fentanyl infusion. Consequently, $P_{CO_2}$ changes alone cannot explain the observed preservation of cardiac contractility during fentanyl administration, and the decrease in LV $\frac{dp}{dt}$ during spontaneous respiration may be attributable to the marked reduction in heart rate. Additionally, atropine itself has been shown to have no direct effect on canine myocardial contractility (Reitan, Fraser and Eisele, 1973).

In vitro studies have shown that fentanyl is either more depressant (Strauer, 1972) or less depressant (Goldberg and Padget, 1969) than morphine on animal cardiac muscle preparations. Interestingly, in either case, the perfusate drug concentration necessary for depression of muscle mechanics greatly exceeded expected clinical values. In our laboratory, 50 µg given as a bolus to a 10-kg dog produces apnoea and somnolence within 2 min. Assuming an initial distribution space of 10% of body weight, the drug concentration for this effect becomes approximately 0.05 µg/ml or 1.4 x 10^{-7} M. Neither Strauer nor Goldberg saw significant contractility changes until perfusate concentrations were at least 100 times this value (Strauer, 1972; Goldberg and Padget, 1969).

Human studies have shown little change in myocardial function following the administration of fentanyl (Tammisto, Takki, and Toikka, 1970; Ferrari et al., 1974). Canine experiments by Freye...
demonstrated that fentanyl in moderate and high doses (up to 0.16 mg/kg) had little effect on ventricular function (Freye, 1974).

In conclusion, our study shows that fentanyl, in clinically useful concentrations, causes a significant lowering of mean arterial pressure and heart rate in the spontaneously breathing dog. LV $\frac{dp}{dt}$, an indicator of ventricular function, was reduced only moderately. However, when heart rate and $P_{aCO_2}$ remained reasonably constant, there was no significant myocardial depression at fentanyl infusion concentrations in excess of the usual apnoeic doses of the drug. The role of drug interaction between halothane, nitrous oxide, and fentanyl cannot be discounted, nor can it be assessed from this study.

REFERENCES


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EFFET D’EPARGNE DU FENTANYL SUR LE MYOCARDE PENDANT L’ANESTHESIE DE CHIENS PAR L’HALOTHANE

RESUME
Les effets cardiovasculaires du fentanyl (Sublimaze) ont été étudiés sur sept chiens bâts. Une infusion constante de la drogue a été utilisée pour produire un point d’aboutissement apnoeique pendant que l’on surveillait les variations cardiovasculaires accessoires. Cette infusion a été répétée une heure plus tard sous ventilation contrôlée et on a admis le fentanyl, pour éliminer l’hémodynamique des variations des battements de coeur et du $P_{aCO_2}$. Lorsqu’on a laissé augmenter le $P_{aCO_2}$, le fentanyl a réduit efficacement les battements de coeur et la pression artérielle moyenne pendant que le $\frac{dp}{dt}$ ventriculaire gauche se stabilisait légèrement au moment de l’arrêt respiratoire. Lorsque les battements de coeur et le $P_{aCO_2}$ ont été maintenus constants, il n’y a eu que peu de variations dans les mesures cardiovasculaires pendant l’infusion de fentanyl. Nous en concluons que le fentanyl permet un effet d’épargne relatif du myocarde chez les chiens, lorsqu’on l’utilise à des concentrations cliniquement efficaces.

$\frac{dp}{dt}=$changement dans la pression/changement dans le temps.

DIE MYOKARDIALE SPARWIRKUNG VON FENTANYL WAHRND EINER HALOTHANNARKOSE BEI HUNDEN

ZUSAMMENFASSUNG

EFECTO LIMITADO MIOCARDIAL DEL FENTANYL DURANTE LA ANESTESIA DE HALOTANO EN PERROS

SUMARIO
Se estudiaron los efectos cardiovasculares del fentanil (Sublimaza) sobre siete perros mestizos. Se utilizó una infusión constante de la droga para producir un punto final apneico, mientras se controlaban los cambios cardiovasculares concomitantes. Después de una hora, se repitió la infusión mientras se vigilaba la ventilación y se suministraba atropina para eliminar un efecto hemodinámico de cambios en el ritmo cardíaco y el $P_{aCO_2}$. Cuando se mantuvo que aumentara el $P_{aCO_2}$, el fentanil redujo sensiblemente el ritmo cardíaco y la presión arterial media, mientras que el $\frac{dp}{dt}$ ventricular izquierdo se rebajaba moderadamente en el momento de la detención respiratoria. Cuando el ritmo cardíaco y el $P_{aCO_2}$ se mantuvieron constantes, hubo poca variación en los índices cardiovasculares durante la infusión de fentanil. Llegamos a la conclusión de que el fentanil permite una pausa relativa del miocardio en los perros, cuando se utiliza en concentraciones clínicamente eficaces.