Contractile Responses to Morphone, Piralamide, Meperidine, and Fentany1

A Comparative Study of Effects on the Isolated Ventricular Myocardium

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The effects of four analgesics on myocardial contractility were studied in isolated cat papillary muscle preparations. At low doses, both morphone (1-10 µg/ml) and piralamide (0.01-1 µg/ml) produced slight, but non-significant, increases in the extent of shortening, the velocity of shortening, the rate of tension development, cardiac work, and cardiac power. No positive inotropic effects of meperidine and fentany1 were detected. At larger doses all analgesics caused dose-dependent decreases in these measures. Equal contractile depressant doses (measured in terms of 50 per cent inhibition of the velocity of isotonic shortening) were: morphone, 2,000 µg/ml; piralamide, 1,000 µg/ml; meperidine; 100 µg/ml; fentany1, 10 µg/ml. The results are discussed in relation to equianalgesic potency. (Key words: Morphone; Piralamide; Meperidine; Fentany1; Myocardial contractility.)

Despite the frequent application of analgesics in treatment of the pain of myocardial infarction and as supplements to anesthesia, there are only a few data concerning the effects of analgesics on cardiac mechanics and contractility.10 This study was undertaken to analyze the inotropic actions of some frequently used analgesics in a preparation appropriate for determination of the contractile state of ventricular muscle.

Materials and Methods

Studies were carried out using 28 right ventricular papillary muscles taken from cats (1.5-2.5 kg) anesthetized with pentobarbital, 25 mg/kg, ip. Cross-sectional areas of the papillary muscles averaged 0.92 ± 0.21 mm², and their initial lengths (L₀) averaged 7.9 ± 1.8 mm. Methods used are described in detail elsewhere.15 Following dissection, the muscles were immediately incubated in a magnet containing a Krebs-Ringer solution (Na⁺ 148 mEq, K⁺ 4.0 mEq, Ca²⁺ 5.0 mEq, Mg²⁺ 2.5 mEq, Cl⁻ 128 mEq, HCO₃⁻ 25 mEq, HPO₄⁻ 1.2 mM, and glucose 5.6 mM/liter). When bubbled with Carboxen (95 per cent O₂, 5 per cent CO₂), the pH of the bath was 7.4–7.42, and Pₒ₂ was more than 700 mm Hg. The temperature of the bath was kept constant at 23–24 C by an outer water jacket connected to a circulating constant-temperature water reservoir.

The tendinous end of the papillary muscle was attached to a force transducer (Sanborn FTA 100/1) by a rigid wire connection. The tendinous end of the papillary muscle was attached to a lever arrangement mounted on micro ball bearings. Lever displacement was measured—without mechanical contact—by an induction transducing system (Hottinger Baldwin, Darmstadt, Germany). Through adjustable stops, fixation of the lever and of initial muscle length for isometric studies, as well as complete fixation for isometric studies, could be varied.

The muscles were stimulated supramaximally by square-wave DC impulses 5 msec in duration, 15-20 per cent above threshold (Grass Stimulator S 88), delivered through platinum mass electrodes. Stimulation frequency in all experiments was 20/min. The equipment's sensitivity (tendons, wire connections, lever system) was less than 0.15 mm for a 10-g load. The whole apparatus was mounted on a steel plate firmly established in a sand-mold.

The following tracings were displayed on an oscilloscope (Tektronix 564 B) and simultaneously recorded on a direct-recording apparatus (Hellige/Germany): stimulation frequency (Stim); muscle lengthening (ΔL); first time derivative of muscle lengthening

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Fig. 1. A, Isometric afterloaded contractions of a cat papillary muscle before and after (+) morphine, 1 μg/ml. Tracings from top to bottom: Simulation frequency (Stim.); muscle lengthening (a); first time derivative of muscle lengthening (d1/dt); tension development (T); time derivative of tension development (d2/dt); g = constant. The effect of morphine was observed for 30 minutes after its administration. The tracings represent sequential events from the beginning of morphine infusion to 30 minutes after its administration. The sequence of tracings corresponds to that in A. In contrast to the smaller dose, 1,000 μg/ml were associated with considerable depression of the extent of shortening, velocity of isotonic shortening, and rate of tension development, by amounts averaging approximately 40 per cent of the control values.

B, Isometric afterloaded contractions of a cat papillary muscle before and after (+) morphine, 1,000 μg/ml. The effect of morphine was observed for 30 minutes after its administration. The tracings represent sequential events from the beginning of morphine infusion to 30 minutes after its administration. The sequence of tracings corresponds to that in A. In contrast to the smaller dose, 1,000 μg/ml were associated with considerable depression of the extent of shortening, velocity of isotonic shortening, and rate of tension development, by amounts averaging approximately 40 per cent of the control values.
(dl/dt); tension development (T); first time derivative of tension development (dT/dt). The first time derivatives of muscle lengthening and tension development were obtained both by electrical differentiation (RC circuits, time constant: 1 msec) and from records made at high paper speeds (100 and 250 mm/sec).

Following incubation, papillary muscles were stimulated for 90–120 min to obtain steady-state conditions. Then, using a constant preload and frequency of stimulation, several force–velocity relations (control) were determined for the whole range of afterloads, that is, from preloaded contraction to isometric contraction. Thereafter, using a constant preload, afterload, and frequency of stimulation, the analgesic being studied was infused into the bath solution. In each experiment the effects were observed for 30 minutes, which was adequate for the establishment of a new equilibrium reflecting the effect of the analgesic.

Isotonic shortening (Δl) of muscle (mm) was converted into muscle lengths per contraction (ML). A corresponding calculation was made for the velocity of isotonic shortening (dl/dt max), which was calculated for muscle lengths per second (ML/sec).

Tension development (T) was related to the cross-sectional area of the muscle (g/mm²) (assuming a cylindrical muscle configuration).

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**Fig. 2.** Force–velocity relations before (O) and after (●) morphine, 1,000 µg/ml. The abscissa represents total muscle load (preload + afterload); the ordinate represents peak velocity of isotonic shortening. Note the decreases of both preload velocity (horizontal arrows) and maximum isometric tension (vertical arrows).

**Fig. 3.** Isotonic afterloaded contractions of a cat papillary muscle before and after (↑) piritramide, 100 µg/ml. The sequence of the tracings corresponds to that in figure 1. Note the initial depression of muscle activity and the normalization approximately 20–25 minutes after administration of piritramide.
Likewise, the rate of tension development, $dT/dt$, was calculated, so that $dT/dt_{\text{max}}$ (g/sec) became g/mm²/sec. Cardiac work $(K \times \Delta l)$ was calculated as the product of tension development and the extent of shortening, $K \times \Delta l$ (g × mm) : $K \times \Delta l$ (g/mm² × ML). Cardiac power was calculated as the product of tension development and the velocity of isotonic shortening. $K \times dl/dt$ (g×mm/sec):$K \times dl/dt_{\text{max}}$ (g/mm²×ML/sec).

Each muscle was used to test no more than ten bath concentrations and no more than two analgesics. The muscles remained stable for at least 12–16 hours. After an analgesic had been washed out, stable mechanical conditions were usually reached in 30 to 90 minutes. Muscles which began to deteriorate during the time of examination were discarded, and they were not included in the results. The final concentrations of the analgesics in the bath were: morphine (µg/ml), 0.1, 1, 10, 100, 1,000, 2,000; piritramide (µg/ml), 0.1, 1, 10, 100, 1,000, 1,500; meperidine (µg/ml), 0.1, 1, 10, 100; fentanyl (µg/ml), 0.1, 1, 5, 10. The total number of measurements performed was 137. Changes induced by drugs were compared with control values by t test for paired data.

**Results**

**MORPHINE**

A concentration of 0.1 µg/ml in the bath had no effect on muscle response. At higher concentrations (1–10 µg/ml) a positive inotropic effect was observed. When the concentration exceeded 100 µg/ml, a negative inotropic effect resulted. Typical effects of morphine (1 µg/ml and 1,000 µg/ml) are shown in figure 1, in representative tracings of isotonic contractions with constant preload and afterload.

With morphine, 1,000 µg/ml, the curve describing force–velocity relations was shifted downward, with decreases of both preload velocity and maximum isometric tension (fig. 2). This depression of force–velocity curves indicates that the heart muscle developed lower muscle tension at the same contraction velocity or lower contraction velocity at the same muscle load. For morphine, the dose that produced 50 per cent inhibition of $dl/dt_{\text{max}}$ was 2,000 µg/ml (see fig. 5). It must be noted that those doses of the analgesics associated with 50 per cent reduction of the velocity of isotonic shortening reduce other factors of cardiac performance approximately proportionately: doses producing 50 per cent inhibition of $dl/dt_{\text{max}}$ decreased shortening by 48 per cent ($P < 0.001$), the rate of isometric tension development by 55 per cent ($P < 0.01$), cardiac work by 46 per cent ($P < 0.001$), and cardiac power by 54 per cent ($P < 0.001$). Thus, velocity factors as well as load-dependent factors were affected nearly to the same degree as $dl/dt_{\text{max}}$.

**MEPERIDINE**

No positive inotropic effects were observed after administration of meperidine. Considerable depression of muscle mechanics ($\Delta l$, $dl/dt$, $dt_{\text{max}}$).

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**Fig. 4.** Force–velocity relations before (○) and after (●) piritramide, 100 µg/ml. The abscissa represents total muscle load (preload + afterload); the ordinate represents peak velocity of isotonic shortening. Note the depression of force–velocity relations 5 minutes after the administration of piritramide and the nearly complete normalization at 30 minutes.
dt/dt) became apparent at doses greater than 1 μg/ml. Compared with morphine, the concentrations that produced equal degrees of depression of muscle mechanics were approximately 20 times lower. Thus, the contractile depressant potency of meperidine was approximately 20 times greater than that of morphine.

**Fentanyl**

Fentanyl had no significant effect on muscle mechanics at concentrations of 0.01–1 μg/ml. At higher concentrations negative inotropic effects were observed. At a concentration of 5 μg/ml, muscle mechanics (ΔI, dl/dt, dT/dt) were depressed by 30 per cent, and at a concentration of 10 μg/ml, by 50 per cent. Compared with morphine, equal contractile depressant effects were observed at concentrations 200 times lower.

**Pirritramide**

At low concentrations (0.01–1 μg/ml), pirritramide produced non-significant increases of muscle mechanics (ΔI, dl/dt, dT/dt). However, at higher concentrations, to a maximum of 1,500 μg/ml, depression was observed but tended to be transient: immediately after the infusion an initial depression became apparent (fig. 3); within 6–8 minutes thereafter, muscle mechanics (ΔI, dl/dt, dTmax/dt) increased, progressively approaching control values, which were achieved approximately 20–25 minutes after administration. This transitory cardiac depression shifted the force–velocity curve downward (fig. 4), but it returned towards the control curve, which was almost reached at the end of the 30-minute period.

Dose–response curves in terms of effect on isotonic contraction velocity (mean values of the
per cent change of $dl/dt_{\text{max}}$) were constructed for all analgesics (fig. 5). At low concentrations, both morphine and piritramide produced slight, but not significant, increases of the velocity of isotonic shortening. At high concentrations, considerable decreases of the velocity of isotonic shortening were produced by all analgesics. Doses which produced 50 per cent reduction of the velocity of isotonic shortening were: fentanyl, 10 $\mu$g/ml; meperidine, 100 $\mu$g/ml; piritramide, 1,000 $\mu$g/ml; morphine, 2,000 $\mu$g/ml.

### Discussion

Alterations of myocardial contractility are indicated by changes of the extent of shortening, the velocity of shortening, and the rate of tension development with a constant preload, afterload, and frequency of stimulation; or shifts of the curve describing force–velocity relations associated with changes of preload velocity and/or maximum isometric tension ($P_{\text{m}}$) with a constant preload and frequency of stimulation. The data presented herein demonstrate that the analgesics investigated produce dose-dependent depression of the extent of shortening, the velocity of shortening, and the rate of tension development. Moreover, at a constant preload and stimulation frequency, the force–velocity curve shifted toward lower values for both preload velocity and maximum isometric tension. Thus, it can be concluded that large doses of these analgesics exert negative inotropic effects on the isolated ventricular myocardium.

Since these experiments were performed in vitro, at a low frequency of stimulation (20/min) and a low bath temperature (23–24 C), application of the data obtained to clinical conditions is difficult. However, it may be reasonable to consider the relevance for man of doses associated with 50 per cent reduction of muscle mechanics. Clinical studies, as well as pharmacologic animal experiments, have indicated marked differences among the equianalgesic potencies of the four analgesics investigated. Compared with morphine (potency of 10 mg = 1), the analgesic potency of fentanyl (0.1–0.2 mg) is approximately 50–100-fold greater and that of piritramide (5–10 mg), 1–2-fold greater, whereas the analgesic potency of meperidine (70 mg), is a tenth to a fifth as great. Accordingly, the relative contractile depressant potencies of the analgesics, related to 50 per cent inhibition of $dl/dt_{\text{max}}$, have been estimated. As shown in table 1, the relative contractile depressant potencies of morphine, fentanyl, and piritramide seem very similar, whereas that of meperidine at equianalgesic doses is 100–200-fold greater.

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### Table 1. Equianalgesic Potencies of the Four Analgesics Investigated Related to 50 Per Cent Depression of Contractility

<table>
<thead>
<tr>
<th>Analgesic Doses</th>
<th>Bath Concentrations that Produced 50 Per Cent Depression of Contractility (mg/ml)</th>
<th>Relative Contractile Depressant Potencies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>10</td>
<td>2,000</td>
</tr>
<tr>
<td>Meperidine</td>
<td>70</td>
<td>100</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>0.1–0.2</td>
<td>50–100</td>
</tr>
<tr>
<td>Piritramide</td>
<td>5–10</td>
<td>1–2</td>
</tr>
</tbody>
</table>

* Equianalgesic potencies have been estimated in accordance with the equianalgesic doses (mg). Estimations are referred to the potency of an equianalgesic dose of morphine (= 1). Note the similar relations between contractile and the analgesic effects of morphine, fentanyl, and piritramide, whereas an equianalgesic dose of meperidine produces an approximately 100–200-fold decrease in contractility.

† Related to 50 per cent reduction of $dl/dt_{\text{max}}$. 

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Obstetrics

MATERNAL AND FETAL LIDOCAINE LEVELS During continuous epi-
dural analgesia the authors measured serum lidocaine levels in maternal and fetal blood simultaneously. Lidocaine, 1 per cent with 1:200,000 epinephrine, was used for all epidural injections, given on an hourly basis during labor with an addi-
tional injection at the time of delivery. Serial samples of venous blood were drawn from the mother and the fetal scalp; the results indicate that the maximum level of serum lidocaine occurs 20 minutes after epidural injection. The serum level is correlated with the total dose administered, increasing by small increments with each additional injection. The maximum serum levels found were well below the re-
ported toxic levels of lidocaine and were significantly less than those reported to occur following paracervical block. This is attributed to the smaller mass of lido-
caine used in the epidural technique. The authors suggest that if continuous epi-
dural analgesia is conducted in the manner described, maternal and fetal morbidity and mortality will be significantly less than with paracervical block. (Fox, G. S., and others: Intrauterine Fetal Lidocaine Concentrations during Continuous Epidural Anesthesia, Am. J. Obstet. Gynecol. 110: 896-899 1971.)