equally depressant at equianalgesic doses (47/50 = 0.94).

In short, I have presented reasons for believing Dr. Strauer's myocardial depressant potency of fentanyl relative to morphine to be much too high. Using the smaller relative myocardial depressant potency figures as previously published, the conclusion is that fentanyl is less of a myocardial depressant than morphine at an equianalgesic dose, rather than the reverse.

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REFERENCES


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To the Editor.—As a result of his investigation, Dr. Goldberg concluded that fentanyl produced inotropic effects on isolated left ventricular trabeculae carnea of rats which were approximately a third to a fourth the effects of equianalgesic doses of morphine. In our experiments, fentanyl was two to four times as potent as equianalgesic doses of morphine in producing myocardial depression in isolated right ventricular cat papillary muscles. This discrepancy may be the result of species differences or variations in stimulation frequency or temperature. However, apart from these differences, some other differences should be considered.

In our experiments, a constant preload (0.21 ± 0.06 g/mm²) and afterload (0.44 ± 0.09 g/mm²) were used, and actively developed muscle tension (afterload contraction) was continuously recorded (figs. 1 and 3). Thus, constancy of both initial muscle length and tension development was established. Moreover, the effects of analgesics on isotonic (ΔL, Δl/dtmax) and isometric (P0, ΔT/Δtmax) contractions were studied in each experiment by determination of force-velocity relations over the whole range, from preload contraction to isometric contraction. Velocity factors as well as load-dependent factors were affected to nearly the same degree as Δl/dtmax (page 307). The position of each muscle on its length-tension curve was on its ascending limb, approximately 40-50 per cent below that resting tension associated with the peak active tension development (preload ½: 0.41 ± 0.05 g/mm²). This position enables contraction and relaxation of the muscle independent of influences of the parallel-elastic element, which may become important at larger initial resting tensions. Since pharmacologically induced changes of parallel and series elasticity of cardiac muscle are not yet clearly identified, a preload associated with a shorter initial muscle length than Lmax was selected.

Resting length-tension relationships were not affected by morphine or fentanyl. In contrast, Dr. Goldberg's experiments indicated progressive decreases in initial resting tension by all doses of morphine and by the two highest concentrations of fentanyl (page 980). However, when fixed at the peak of the length-active tension curve, a decrease in initial resting tension will necessarily be associated with a decrease in actively developed muscle tension. Thus, provision for constant initial muscle length was not made, and a greater negative inotropic response to morphine will appear in Dr. Goldberg's experiments. In our experiments, equipment distensibility was kept negligibly small (less than 0.15 mm for a 10-g load) by using rigid wire connections. However, in isometric contractions associated with peak tension development, distensibility of the usual equipment (not stated) can lead to changes in initial muscle length simulating decreases in resting tension or increases in resting compliance. Therefore, changes in diastolic length-tension relationships are of value provided distensibility of the system excepting the muscle itself can be excluded as a variable.
The exact characteristics of diffusion of analgesics into cardiac muscle tissue remain to be investigated. However, it seems likely that large diameters of isolated cardiac tissue will make diffusion of agents and of oxygen more difficult. With regard to oxygen diffusion, in our experiments 2 muscles with small cross-sectional areas were selected (0.92 ± 0.21 mm²). The diameters of the muscles were 1.08 ± 0.05 mm, thus facilitating oxygen diffusion. In Dr. Goldberg's experiments, 1 cross sections of trabeculae averaged 1.72 mm² (page 979 1), which corresponds to an average diameter of approximately 1.5 mm. This diameter may be too great for sufficient oxygen diffusion (30°C) and possibly too great for homogeneous diffusion of morphine and fentanyl into the core of the muscle.

With these precautions to ensure oxygenation and with selected wall thickness (diameter ≤ 1.0–1.1 mm), temperature (24°C), frequency of stimulation (20/min), preload (<0.25 g/mm²) and afterload (<0.5 g/mm²), isolated cat papillary muscles have mechanical stability for more than 12–16 hours. In eight unreported control experiments, cardiac muscle mechanics were determined after 12 hours. Isotonic shortening and isotonic contraction velocity increased only 2–3 per cent compared with control and P₀, the maximum isometric muscle tension, and dT/dtₘₐₓ decreased only 4.3–5 per cent. These changes were statistically non-significant (t test). Even using cumulative increases in drug concentration, calculated pharmacologic effects can therefore be compared with control values, since changes of cardiac muscle mechanics owing to time alone are small and non-significant. Changes with time are even more irrelevant when large differences in cardiac mechanics (e.g., 50 per cent inhibition vs. control) are considered or when drug effects are compared with control after the drug has been washed out and after a new control value has been reached. 2

Measurement of pharmacologic effect in terms of 50 per cent inhibition of biological activity is a standard method of study. However, it may be of interest to compare the relative contractile depressant effects of morphine and fentanyl at lower doses which may be more relevant to plasma concentrations of analgesics in man. As evidenced by figure 5 2 and table 1, 2 the relative contractile depressant potency of fentanyl is 2–4 at 50 per cent inhibition of isotonic contraction velocity; at 40 per cent inhibition this factor is 1.7–3.4, at 30 per cent inhibition 1.5–3, at 20 per cent inhibition 1–2, at 10 per cent inhibition 0.5–1. Thus, in lower dose ranges no considerable contractile differences appear; however, a lower contractile depressant potency of fentanyl (=0.5–1) relative to morphine (=1) will not be present, not even at small bath concentrations.

In all experiments, effects of analgesics on myocardial contractility were observed for 30 minutes. 2 This observation time was sufficient to provide a new equilibrium after each addition of analgesic. 2 In Dr. Goldberg's experiments, 15-minute intervals were used. 3 The time courses of the effects of morphine and fentanyl on cardiac muscle mechanics (table 1) are quite different. At 15 minutes, decreases of isotonic contraction velocity as well as other measures (shortening, tension development, rate of tension development) were −46 per cent (morphine) and −34 per cent (fentanyl), whereas at 30 minutes decreases of −50 per cent (morphine) and −49 per cent (fentanyl) resulted. Calculations made at 15-minute intervals, therefore, will be associated with smaller decreases of isotonic

<table>
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<th>Time of Observation (min)</th>
<th>Mean Decreases (Per Cent) of Isotonic Contraction Velocity (d/dtₘₐₓ)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Morphine (2.000 µg/ml)</td>
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<tr>
<td>5</td>
<td>−32</td>
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<tr>
<td>10</td>
<td>−40</td>
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<td>60</td>
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contraction velocity for fentanyl than for morphine, and will thus underestimate the contractile depressant potency of fentanyl. Under steady-state conditions (30 min), however, decreases of isotonic contraction velocity were similar for the two agents.²

For the reasons presented, I think the contractile depressant potency of fentanyl was underestimated in Dr. Goldberg’s experiments.¹ Our experiments ² provided evidence of a greater contractile depressant potency of fentanyl in comparison with morphine when related to 50 per cent inhibition of cardiac muscle mechanics. Even at low contractile depressant doses (associated with 10–30 per cent inhibition of cardiac muscle mechanics), the contractile depressant potencies of the two agents (morphine, fentanyl) are nearly equal at best. There seems to be no reason why, with regard to myocardial contractility, fentanyl should be given preference to morphine.

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Literature Briefs

Literature briefs were submitted by Drs. L. Brand, L. Cooperman, B. Dalton, M. Gold, A. Goldblatt, J. Harp, L. C. Mark, H. Rackow, and G. Rockwell. Briefs appearing elsewhere in this issue are part of this column.

Circulation

MYOCARDIAL FUNCTION AFTER INFARCTION. The increasing prevalence of chronic postinfarction heart failure prompted a study of 50 such patients (including seven women) utilizing cardiac catheterization, quantitative biplane angiography, and selective coronary cineangiography. Each patient was maximally treated with digitalis and diuretics and was without peripheral edema. The cardiac indexes were less than 2.5 l/min/m² in 26 patients. Many of the patients with normal cardiac indexes had elevated filling pressures, evidence of left ventricular dilatation, and diminished ejection fractions. Left ventricular end-diastolic pressures were greater than 12 mm Hg in 33 patients, while left ventricular end-diastolic volumes were greater than 110 ml in 43 patients, the latter indicative of a diminution in ejection fraction to less than 0.5. A localized abnormality of ventricular contraction was evident in 38 patients. The presence of mitral regurgitation (2.1 ± 11 l/min/m², with a range of 0.54 to 4.2 l/min/m²) was associated significantly with elevation of left ventricular end-diastolic volume and pressure and a low cardiac index, and was more common with occlusive right-coronary-artery disease. Several of the preceding abnormalities were found in most patients: 17 had five and nine had all six. The coronary disease index, with an aggregate vessel-blockage score of 0 to 4 points for each of the three main arteries, was 6.3 ± 2 (range 3–10) for 42 patients in whom angiography was possible. This index correlated poorly with hemodynamic values. (Baxley, W. A., and others: Left Ventricular Anatomical and Functional Abnormalities in Chronic Post-infarction Heart Failure, Ann. Intern. Med. 74: 499–508, 1971.)