

## Correspondence

### Myocardial Depression by Fentanyl and Morphine

To the Editor:—In his article, "Contractile Responses to Morphine, Piritramide, Meperidine, and Fentanyl,"<sup>1</sup> Dr. Strauer concluded that fentanyl was two to four times as potent as morphine in producing myocardial depression at equianalgesic doses. Dr. Padgett and I, in a previously published paper,<sup>2</sup> concluded that fentanyl was  $\frac{1}{2}$  to  $\frac{1}{4}$  as potent as morphine in producing myocardial depression at an equianalgesic dose. This difference may have resulted from any of a number of differences between the two studies:

- 1) Species: cat<sup>1</sup> vs. rat<sup>2</sup>
- 2) Temperature: 23–24 C<sup>1</sup> vs. 30 C<sup>2</sup>
- 3) Preliminary anesthesia: pentobarbital<sup>1</sup> vs. none<sup>2</sup>
- 4) Frequency of stimulation: 20/min<sup>1</sup> vs. 15/min<sup>2</sup>
- 5) Strength of stimulation: 15–20 per cent above threshold<sup>1</sup> vs. 10 per cent above threshold<sup>2</sup>
- 6) Mechanical property evaluated: isotonic shortening<sup>1</sup> vs. peak developed isometric tension and maximum rates of tension generation and relaxation<sup>2</sup>
- 7) Method of preparing drugs: not stated<sup>1</sup> vs. prepared fresh daily from powder<sup>2</sup>
- 8) Position of each muscle on its length-tension curve: not stated<sup>1</sup> vs. peak of curve<sup>2</sup>
- 9) Method of calculating drug effects: comparison with "control values"<sup>1</sup> vs. differences between observed values and expected changes from control values<sup>2</sup>
- 10) Calculation of the point of 50 per cent depression: extrapolation of a curve, presumably manually,<sup>1</sup> vs. an objective statistical technique<sup>2</sup>

The last three points are most important and require amplification.

Dr. Strauer does not state where his muscles were on their length-tension curves. Drugs may have different quantitative effects, even when calculated on a percentage basis, if muscles are not at least close to the same points on these curves.

Of even more significance is the actual position of Dr. Strauer's muscles as revealed by his illustrations. His figures 1 and 3 show the absence of any resting tension at all, even though his figures 4 and 5 indicate that at least 0.2 g should have been present. My experimental results showed that resting tension was decreased 10–20 per cent by high doses of morphine and fentanyl, indicating increases in resting compliance. This would result in increased muscle length at any given preload. If Dr. Strauer's muscles had no resting tension before the drugs were given, the addition of morphine or fentanyl would result in buckling of a muscle held at constant length by a given preload. When the muscle was then stimulated to contract isotonically, a portion of the active state would be consumed in straightening out the buckled muscle before any shortening took place. This would result in a falsely-low velocity of shortening and a falsely-high per cent reduction in performance attributed to the drug.

Dr. Strauer states that his muscles remained "stable" for at least 12–16 hours and that "stable" mechanical conditions were usually reached 30–90 minutes after an analgesic was washed out. However, he does not state that the performance of the muscle actually returned to control values after the drug was washed out. He also does not state that the behavior of his muscles remained absolutely unchanged when no drug was given. If all his muscles received drugs, then he could not evaluate their performance in the absence of drugs. It would be very unusual if his muscles did not vary at all for a period of 12–16 hours, even at a temperature of 23 C. Thus, it would appear that he has made no provision for effects due to time alone.

Dr. Strauer implies that he added sequential drug doses to produce higher and higher concentrations, and did not wash out each dose before adding the next one. If he calculated his drug effects as differences between ob-

TABLE 1. Fentanyl and Morphine Muscle-bath Concentrations and Their Relative Myocardial Depressant Potencies

Index of Contractility	Bath Concentrations Producing 50 Per Cent Depression of Contractility				Relative Myocardial Depressant Potency	
	Fentanyl		Morphine		Fentanyl/morphine	
	$\mu\text{g/ml}$	Molar	$\mu\text{g/ml}$	Molar	$\mu\text{g/ml}$	Molar
Maximum rate of isotonic shortening <sup>1</sup>	10	$1.9 \times 10^{-5}$	$2.0 \times 10^2$	$2.6 \times 10^{-3}$	200	137
Peak developed isometric tension <sup>2</sup>	169	$3.2 \times 10^{-4}$	$7.6 \times 10^2$	$1.0 \times 10^{-2}$	45	31
Maximum rate of tension development <sup>3</sup>	85	$1.6 \times 10^{-4}$	$4.8 \times 10^2$	$6.3 \times 10^{-2}$	56	39
Maximum rate of tension relaxation <sup>2</sup>	95	$1.8 \times 10^{-4}$	$3.8 \times 10^2$	$5.0 \times 10^{-2}$	40	28
Average <sup>2</sup>	116	$2.2 \times 10^{-4}$	$5.4 \times 10^2$	$7.1 \times 10^{-2}$	47	33

served values and initial control values, the magnitude of the drug effects would be falsely high in the higher dose ranges.

In our experiments, Dr. Padgett and I took the effects of time into account by performing five experiments exactly according to the protocol, except that no drug was added. These data were used to determine expected changes in the muscle preparation due to time alone; the drug-effect calculations were based on this consideration.

The problem of falsely-high drug effects is relatively more important for fentanyl than for morphine because large changes were observed with lower doses of fentanyl than of morphine. In these lower dose ranges, as plotted on a semilogarithmic curve, small changes in dose produce much greater shifts in the dose-response curve than at higher doses. Dr. Strauer's dose-response curve for fentanyl is probably too steep, and he has probably compared the effects of morphine and fentanyl on nonparallel portions of their dose-response curves. This would make it impossible for him to make any sort of an objective evaluation of the relative myocardial depressant potencies of fentanyl and morphine. (The absence of any information with regard to variation, such as the standard error, makes it even more difficult for Dr. Strauer to validate his dose-response curves.)

In our studies, the average dose of fentanyl which produced 50 per cent depression (table 1) was 11.6 times greater than the dose reported by Dr. Strauer (116 vs. 10  $\mu\text{g/ml}$ ); our comparable morphine dose was only 2.7 times as large ( $5.4 \times 10^2$  vs.  $2 \times 10^2$   $\mu\text{g/ml}$ ). These differences could very well be due to the sev-

eral considerations outlined above and to the temperature difference: at Dr. Strauer's lower temperature, smaller doses would be needed to produce a given degree of depression. All these points particularly apply to the large dose differential for fentanyl, and explain how Dr. Strauer could have calculated a much higher relative myocardial depressant potency of fentanyl than Dr. Padgett and I.

Dr. Strauer reported that, on a weight basis, fentanyl was 200 times as potent as morphine in producing myocardial depression. My comparable figure would be 47 on a weight basis and 33 on a molar basis (table 1). Dr. Strauer used the figures of 50 and 100 as the relative analgesic potencies of fentanyl and morphine (on a weight basis) and I used the figure of 130 (on a molar basis). Dividing these figures into the factor representing the myocardial depressant potency of fentanyl relative to morphine results in the myocardial depressant potency of fentanyl relative to morphine at an equianalgesic dose. In this way, Dr. Strauer arrived at the figures of 2-4 on a weight basis, and I arrived at the figure of 0.25 on a molar basis.

Whether the weight or the molar basis is used, if the myocardial depressant potency of fentanyl relative to morphine is taken as reported by Dr. Padgett and myself the relative myocardial depressant potency of fentanyl at an equianalgesic dose is much less than one: 0.25 (*i.e.*, 33/130) or 0.47 (*i.e.*, 47/100). Even when the figure of 50 is taken as the relative analgesic potency of fentanyl compared with morphine, one can still infer that fentanyl and morphine are, at worst, no more than

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<sup>1</sup> to be much too high. Using the smaller relative myocardial depressant potency figures as previously published,<sup>2</sup> 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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2. Goldberg AH, Padgett CH: Comparative effects of morphine and fentanyl on isolated heart muscle. *Anesth Analg (Cleve)* 48:978-982, 1969

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*To the Editor:*—As a result of his investigation, Dr. Goldberg<sup>1</sup> concluded that fentanyl produced inotropic effects on isolated left ventricular trabeculae carneae of rats which were approximately a third to a fourth the effects of equianalgesic doses of morphine. In our experiments,<sup>2</sup> 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 ( $0.21 \pm 0.06$  g/mm<sup>2</sup>) and afterload ( $0.44 \pm 0.09$  g/mm<sup>2</sup>) 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 ( $\Delta l, dl/dt_{max}$ ) and isometric ( $P_0, dT/dt_{max}$ ) 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  $dl/dt_{max}$  (page 307<sup>2</sup>).

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<sup>2</sup>:  $0.41 \pm 0.05$  g/mm<sup>2</sup>). 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  $L_{max}$  was selected.

Resting length-tension relationships were not affected by morphine or fentanyl.<sup>2</sup> In contrast, Dr. Goldberg's experiments<sup>1</sup> indicated progressive decreases in initial resting tension by all doses of morphine and by the two highest concentrations of fentanyl (page 980<sup>1</sup>). 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,<sup>1</sup> distensibility of the usual equipment (not stated<sup>1</sup>) 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.