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Acute Tolerance to Fentanyl during Anesthesia in Dogs

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The effect of fentanyl on increases in heart rate and mean arterial pressure elicited by electric stimulation of a branch of the radial nerve was studied in anesthetized, paralyzed, and artificially ventilated dogs. In one group, a bolus of 100 μg/kg of fentanyl depressed the evoked changes in heart rate and arterial pressure by 82 and 75%, respectively, by 5 min, and recovery occurred within 90 min. A second group was given increasing bolus doses of fentanyl from 1.5 to 100 μg/kg every 20 min for 200 min. The doses and intervals were chosen to give a logarithmic increase in plasma concentration of fentanyl to include a final bolus dose of 100 μg/kg and were predicted by a two-compartment pharmacokinetic model derived from data of the first group. In the second group, the bolus dose of 100 μg/kg after 5 min had no significant effect on evoked cardiovascular responses. Over the following 2 h, the evoked changes in heart rate and arterial pressure increased above those preceding the 100 μg/kg dose. An additional bolus dose of 100 μg/kg given 2 h after the first did not depress the evoked reflexes below the control values. It was concluded that tolerance to the effects of fentanyl can occur within 3 h and that for evoked responses to arterial pressure, rebound withdrawal effects can be seen within an additional 90 min. (Key words: Anaesthetics, intravenous: fentanyl. Blood pressure: drug effects. Heart: pulse rate. Tolerance: narcotics.)

THE PHENOMENA of tolerance and dependence have been the subject of considerable investigation, particularly in relation to narcotic analgesic drugs, and many hypotheses have been proposed to explain them.[1,2] It has long been established that tolerance to narcotic drugs can develop at different rates, so that under appropriate conditions it can occur within a few days, hours, or even minutes. Examples of the diverse effects to which acute tolerance has been demonstrated in either conscious or anesthetized animals are analgesia,[3] hypothermia,[4] and increased motor activity.[5]

Compared with morphine and other similar narcotics, fentanyl has been much less investigated, and the only studies on acute tolerance have been related specifically to its analgesic effects in conscious rats during 2–5 days.[6,7] Recently, in a clinical report, where large amounts of fentanyl had been administered by infusion during several days, its anesthetic effects were markedly reduced, suggesting the development of tolerance.[8]

During anesthesia, when motor reflexes are obtunded by muscle relaxants, evidence of depression of the effects of nociceptive stimulation must be sought in autonomic reflexes. The purpose of the present study was to determine whether tolerance to the depressant effects of fentanyl on somatocardiovascular reflexes can develop within a time relevant to the duration of routine surgery and anesthesia.

Methods

Experiments were performed on two groups, each consisting of five dogs weighing between 9.5 and 15.9 kg. Anesthesia was induced with methohexitone (12.5 ± 0.5 mg/kg), after which they were intubated and artificially ventilated with oxygen-enriched air. Cannulae were inserted into the left femoral artery and through each femoral vein into the inferior vena cava (IVC), the one positioned in its abdominal portion for the administration of drugs and infusions and the other in its thoracic portion for blood sampling for fentanyl concentrations. Anesthesia was maintained, using a 1% solution of a-chloralose in an initial dose of 32 ± 1 mg/kg, followed by a continuous infusion of 14 ± 1 $mg \cdot kg^{-1} \cdot h^{-1}$ throughout each experiment, and the animals were paralyzed with suxamethonium (1 mg/kg every 30 min). Esophageal temperatures were maintained between 36.5 and 38.5° C. Pa_{O_2}, Pa_{CO_2}, and arterial *p*H (Radiometer® ABL 1) were maintained in the ranges of 107–116 mmHg, 40–42 mmHg, and 7.25–7.31, respectively, by alteration of the tidal volume, inspired oxygen concentration, and, when necessary, the administration of NaH_{CO_3}. These values were statistically comparable in the two groups of dogs. The hematocrit was maintained in the range of 40–43% by the infusion

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of 0.9% NaCl solution (approximately 8–10 $ml \cdot kg^{-1} \cdot h^{-1}$).

The mean arterial and airway pressures were measured using calibrated Statham® strain gauges and displayed together with the ECG and the beat-by-beat heart rate (Devices® 4522) on an ultraviolet light recorder (SE Laboratories, type 2112).

The lateral branch of the superficial (cutaneous) branch of the left radial nerve was exposed in the foreleg, desheathed and cut distally, and mounted on silver electrodes in a mineral oil pool. Ten-second trains of supramaximal stimuli (Grass S 88® stimulator) were applied to the desheathed nerve (intensity 50 V, duration 0.5 ms, frequency 30 Hz) and the evoked changes in heart rate (ΔHR) and mean arterial pressure ($\Delta\overline{AP}$) were observed. Each train of stimuli was triggered by the R wave of the ECG during the end-expiratory phase of respiration in order to eliminate variation due to the effect of changes in baroreceptor activity during the cardiac and respiratory cycles.[9] In dogs anesthetized with a-chloralose by continuous infusion, provided that blood gas tensions and mean arterial pressure are controlled, there is no change in somato-cardiovascular reflexes for periods in excess of 24 h, provided that the nerves remain in good condition.†† The increases in heart rate and arterial pressure were measured as the peak responses from the average level during a maximum of five respiratory cycles (approximately 30 s) after recovery from previous stimulation. ΔHR and $\Delta\overline{AP}$ were calculated as the mean value of five such responses at the relevant times.

Following control responses in Group 1, fentanyl 100 μg/kg was administered during 30 s, and the changes in ΔHR and $\Delta\overline{AP}$ were observed at 5, 10, 15, 30, 50, 70, 90, and 120 min. At the same times, venous blood samples (4 ml) were taken from the intrathoracic IVC catheter, and the plasma was separated and stored at −20° C, to be analyzed subsequently for fentanyl concentration by radioimmunoassay (sensitivity 2 pg/ml plasma), using a modification‡‡ of a technique described by Michiels *et al.*,[10] in which the cross-reaction of possible metabolites of fentanyl with antifentanil antibody is negligible. The coefficient of variation for duplicate estimations was 0.62%.

From the time-concentration data of dogs in Group 1, a two-compartment open model was derived.[11] The model then was used to determine the dosing strategy for the second group of dogs (Group 2). A series of doses was calculated, which, when given at 20-min intervals for 180 min, would yield a logarithmically increasing series of plasma concentrations (sampled 16 min after each dose), such that the final dose would be 100 μg/kg. The method is described in detail in the Appendix.

After the above procedure, dogs in Group 2 were given 1.5, 1.7, 2.5, 4.0, 6.3, 10.0, 15.0, 25.0, 40.0, 63.0 and 100.0 μg/kg at 20-min intervals. Plasma fentanyl concentrations were measured 16 min after each dose. Responses for HR and AP were recorded before any fentanyl was given (control a) and following the 63 μg/kg (control b). After the 100 μg/kg (test 1) dose, the responses were recorded for 120 min and plasma concentrations of fentanyl measured as for dogs in Group 1. A second (test 2) dose of 100 μg/kg then was given and the responses recorded for a further 30 min.

In these experiments, a volume of approximately 50 or 100 ml of blood (equal to the total volume taken for blood samples) was collected (into heparin) before surgical dissection, *i.e.*, approximately 2 h before control responses were obtained. After collection of each blood sample during the study, an equal volume of the collected "control" blood was transfused.

Statistical comparison of the data between groups was performed by one-way analysis of variance, followed by two-tailed unpaired *t* tests. Within-group changes were analyzed by two-way analysis of variance followed by two-tailed paired *t* tests. Where appropriate, regression analysis by the method of least squares and analysis of covariance were used. $P < 0.05$ was considered as statistically significant. All data in the text are expressed as mean ± SE.

Results

Examples of the evoked cardiovascular responses from one dog from each group are shown in figure 1, where it can be seen that without conditioning with fentanyl (Group 1), 100 μg/kg caused a decrease of approximately 85% in ΔHR and 70% in $\Delta\overline{AP}$, with recovery at 90 min, whereas in Group 2 the initial bolus dose of 100 μg/kg had almost no effect, and the responses increased significantly above control by 90 min. However, there was no recovery of the effect of the drug on resting heart rate and arterial pressure in both dogs throughout the period of observation (compare controls a and b for Group 2 in fig. 1).

The results of all five dogs in each group are presented in figure 2. During the control periods in both groups, there were no significant differences in either the resting heart rates and arterial pressures or in ΔHR and $\Delta\overline{AP}$, which were in the ranges of 42–90 beats/min and 36–77 mmHg, respectively. In Group 1, following the bolus

†† Whitwam JG: Responses in the sympathetic nerves of the dog. Ph.D Thesis, University of Leeds, 1971.

‡‡ Bower S: The measurement and distribution of fentanyl in blood. Ph.D Thesis, University of Newcastle-Upon-Tyne, 1980.

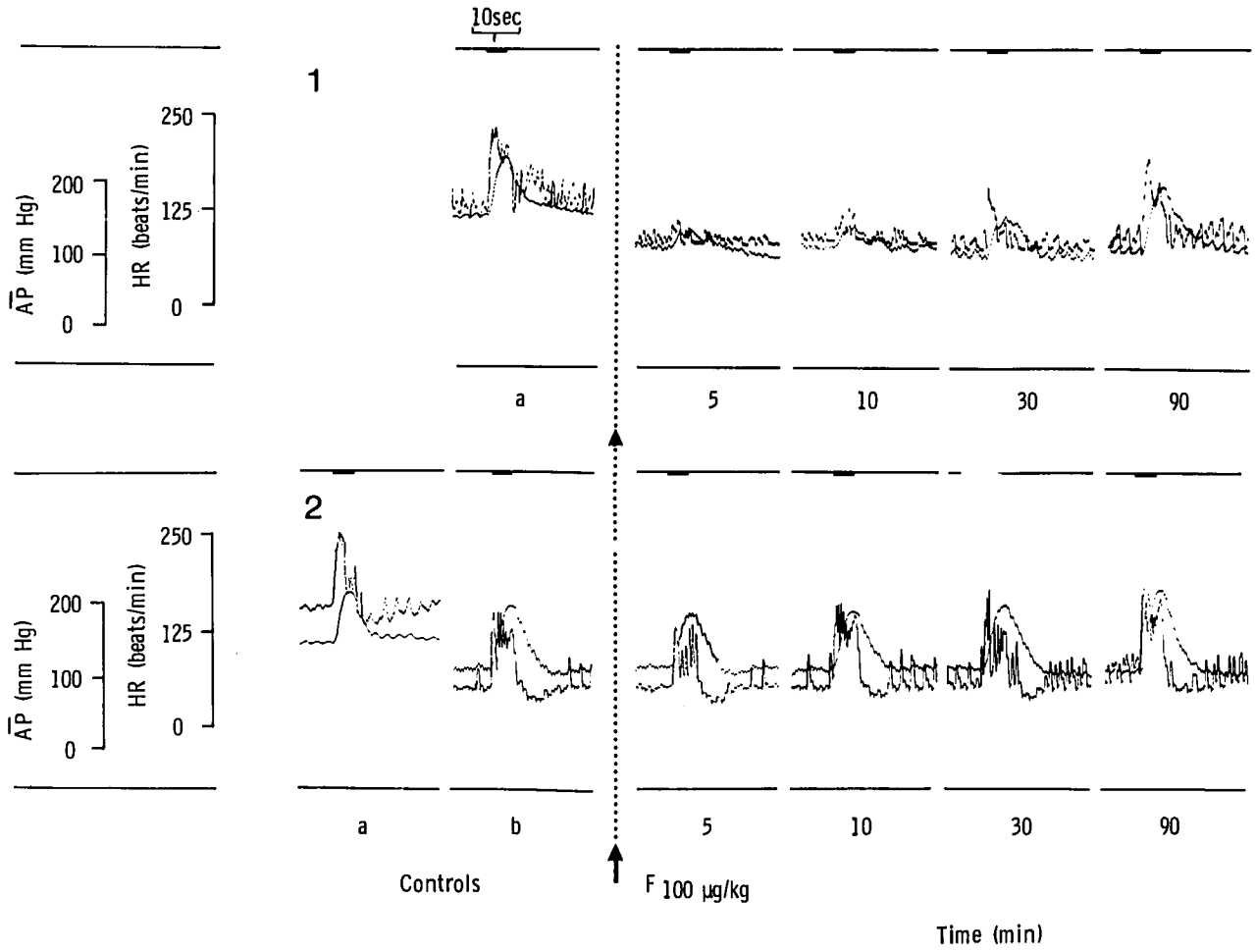

FIG. 1. Examples of spontaneous and reflexly evoked changes in heart rate (HR) and mean arterial pressure ($\overline{AP}$) in one dog from Groups 1 and 2. (Upper line HR and lower line $\overline{AP}$ in both traces.) Group 1: effect of a bolus dose of 100 µg/kg of fentanyl. Group 2: Controls a and b: before and after conditioning with incremental doses of fentanyl (see text), followed by a bolus of 100 µg/kg of fentanyl. Upper trace Group 1, lower trace Group 2, 10-s trains of electrical stimuli (50 V, 0.5 ms duration, 30 Hz) indicated by thickened marker line at the top.

dose of 100 µg/kg, the mean ΔHR and $\Delta\overline{AP}$ were reduced at 5 min by 82% and 75%, respectively ($P < 10^{-8}$). Thereafter, gradual recovery occurred, but the responses still were significantly reduced at 70 min ($P < 0.025$ for ΔHR and $P < 0.04$ for $\Delta\overline{AP}$), complete recovery requiring 90 min.

In Group 2 dogs, the responses obtained during control periods a and b (*i.e.*, before and at the end of conditioning) did not differ significantly. Five minutes after the first test dose of fentanyl, $\Delta\overline{AP}$ showed no significant change but ΔHR was reduced by 16 beats/min ($P < 0.01$), compared with the responses during control period b. Thereafter, both ΔHR and $\Delta\overline{AP}$ increased gradually throughout the period of observation, so that 90 min later they were significantly higher than during control period b (ΔHR $P < 0.05$; $\Delta\overline{AP}$ $P < 0.02$). When compared with the values in control period b at 120 min, ΔHR had increased by 14% ($P < 0.02$) and $\Delta\overline{AP}$ by 29% ($P < 0.02$), while when compared with values in control period a, only $\Delta\overline{AP}$ had increased significantly ($P < 0.05$) above them at 90 min and continued to increase throughout the period of observation ($P < 0.025$ at 120 min). However, ΔHR at this time did not increase significantly above the values in control period a (*i.e.*, in "fentanyl-naive" animals).

The decreasing concentrations of fentanyl in Group 1 dogs yielded an aggregate two-compartment kinetic model with an apparent initial distribution volume of 2,996 ml/kg and intercompartmental and total clearances of 281 and 52 $ml \cdot kg^{-1} \cdot min^{-1}$, respectively.

During the Group 2 conditioning period, the measured plasma fentanyl concentrations increased in an approximately logarithmic manner (fig. 3) and did not differ greatly from those predicted by the kinetic model. The decay of plasma concentration following a 100 µg/

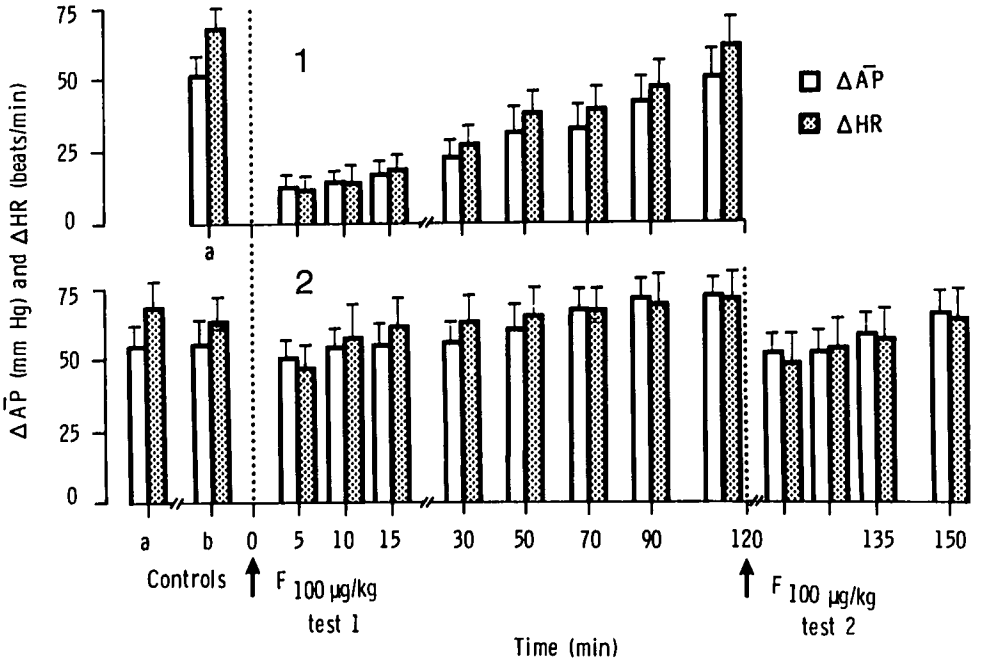

FIG. 2. Changes with time of evoked cardiovascular reflexes (ΔHR and $\Delta\overline{AP}$) in five dogs in Groups 1 and 2 (mean ± SE). Group 1: Responses before (a) and after a bolus dose of 100 μg/kg of fentanyl. Group 2: Controls a and b: before and after 3 h of conditioning with fentanyl (see text) followed by two test bolus doses of 100 μg/kg of fentanyl (test 1 and test 2).

kg dose in the fentanyl-naive (Group 1) and the "fentanyl-conditioned" dogs (test dose 1 to Group 2) are shown in figure 3. During the first 5 min, *i.e.*, when the plasma fentanyl level was falling rapidly, the concentrations in Group 1 were only 50% of the values for Group 2. During the slower plasma decline in the subsequent 120 min, they ranged between 31 and 39% of those at the same relative times in Group 2.

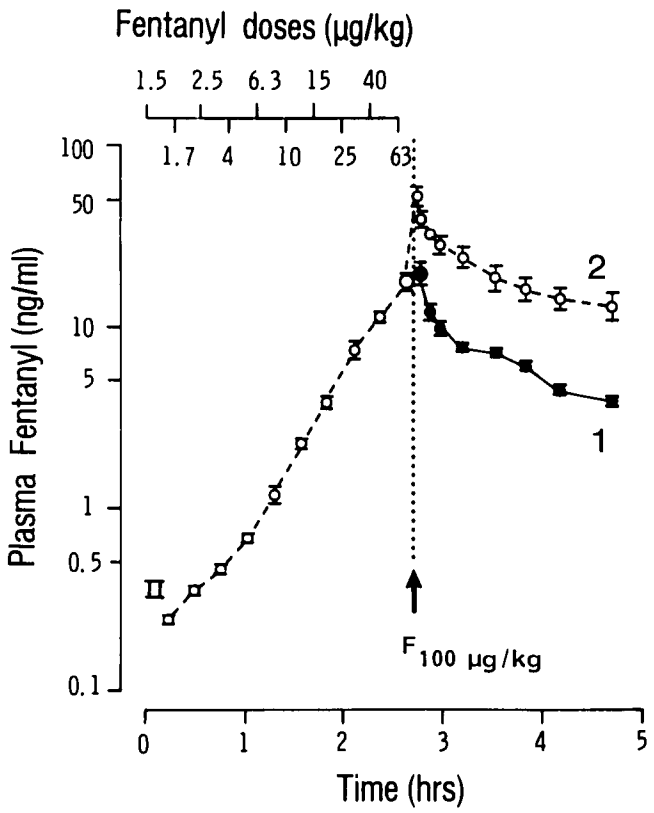

FIG. 3. Plasma fentanyl concentrations (mean ± SE) during treatment with logarithically increasing doses of the drug (Group 2) and following a bolus dose of 100 $\mu g \cdot kg^{-1}$ (Groups 1 and 2).

The effect of fentanyl on the evoked cardiovascular responses expressed as percentage depression exhibited a linear relationship to the log fentanyl concentrations, following the bolus of 100 μg/kg in both groups (fig. 4). For ΔHR r = 0.88 in Group 1 and r = 0.79 in Group 2 and for $\Delta\overline{AP}$ r = 0.87 for Group 1 and r = 0.95 for Group 2. The slopes of the regression lines for both ΔHR and $\Delta\overline{AP}$ were not significantly different (by analysis of covariance), with a parallel shift to the right for Group 2. The calculated "acute tolerance index" or relative potency between the tolerant and nontolerant states (expressed as a ratio of equipotent concentrations, as suggested by Aston[12]), under the conditions of this study was 3.0 for ΔHR and 2.7 for $\Delta\overline{AP}$, indicating that the fentanyl-conditioned animals were approximately three times less responsive to a bolus of 100 μg/kg of fentanyl than the fentanyl-naive animals.

Discussion

The present study shows that conditioning an animal for 3 h with fentanyl can induce tolerance to the depressant effect of the drug on evoked cardiovascular reflexes, although its effects on resting heart rate and arterial pressure persist throughout the same period of observation. Under these experimental conditions, fentanyl became approximately three times less potent in

the tolerant animals, a ratio that coincides with the findings of Colpaert *et al.*[7] for the magnitude of analgesia produced by fentanyl in drug-conditioned conscious rats. Many authors have described the development of acute tolerance to the effects of opiates and particularly morphine on the circulation (*e.g.*, Martin and Eades,[13] Medina and Bermudez,[14] Fennessy and Rattray[15]). However, this is the first systematic study of the development of tolerance to the effects of a narcotic analgesic on cardiovascular responses evoked by controlled reproducible nociceptive stimulation during anesthesia, apart from one observation on one dog reported by Schmidt and Livingston[16] in which the sciatic nerve was stimulated and tolerance to the effects of morphine on the evoked blood pressure response was demonstrated. In the dog these responses are mediated by sympathetic reflexes evoked by afferent fibers in Groups 3 (small myelinated) and 4 (unmyelinated) and inhibition of cardiomotor vagal activity.[17]

It has been known for a long time[18,19] that the rate and degree of development of tolerance to narcotics depends on the size of the dose and the time interval between doses, so that maximal acute tolerance is reported with a "staircase" incrementation of doses administered at such intervals that each succeeding dose is given before complete decay of its predecessor. The interval of 20 min was chosen here on the basis of the kinetic model, which suggested that this time represents the transition between distributional and elimination phases. The conditioning dose regimen (also predicted from the model) yielded a series of concentrations that increased, as intended, logarithmically (fig. 3).

Since the kinetic characteristics of individual dogs varied considerably and the groups were small, the small differences between "predicted" and "actual" concentrations were to be expected. However, it should be noted that previously reported kinetic models for fentanyl in the dog[20] differ considerably from that derived here and might be explained by the different sampling sites used.

During the drug-conditioning period, the cardiovascular reflexes were not tested, as nociceptive stimulation has been reported to antagonize and even prevent the development of tolerance to the analgesic effects of fentanyl.[7,21] All that can be said from this study is that tolerance to somatocardiovascular reflexes had occurred within 3 h, a time similar to that reported for the onset of tolerance to the hypotensive effects of morphine.[14,16] It seems unlikely that this observation is in some way related to the presence of chloralose, since acute vascular tolerance to morphine, meperidine, and methadone has been demonstrated in dogs anesthetized with thiopentone,[22] to morphine in cats anesthetized with pentobarbitone,[14] while Schmidt and Livingston[16] demonstrated

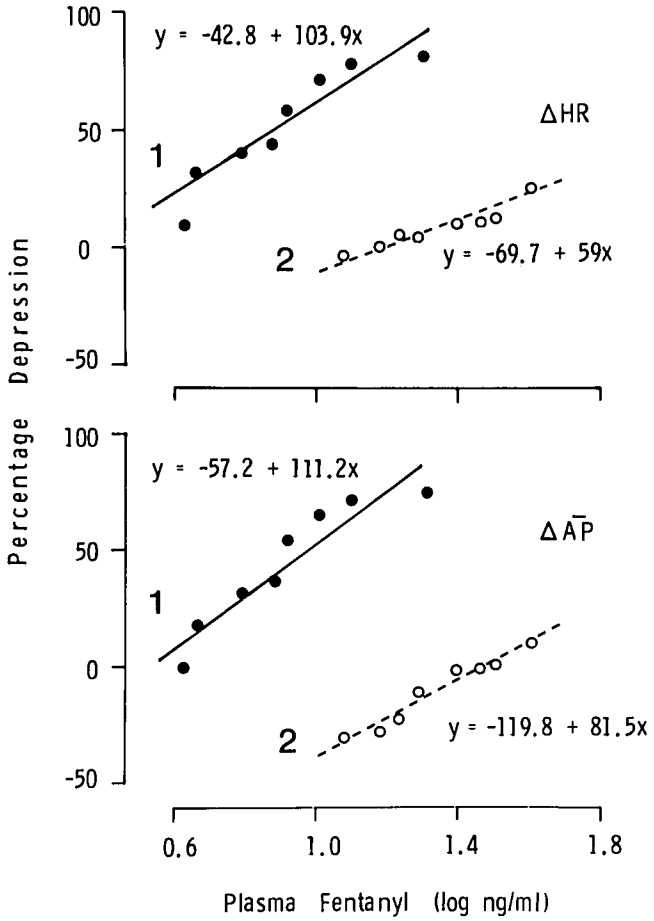

FIG. 4. Log concentration–effect lines for ΔHR and $\Delta\bar{A}P$ (expressed as percentage depression from controls) following a bolus of 100 μg/kg of fentanyl (test dose 1 in group 2), in nontolerant (Group 1) and tolerant animals (Group 2). Ordinate percentage depression, Abscissa plasma fentanyl concentrations ($\log_{10}$ ng/ml).

tolerance to morphine in the presence of several anesthetics including barbiturates, ether, and urethane. It also seems unlikely that significant changes occurred in the plasma protein binding of fentanyl during the course of these experiments, as the temperature, blood gases, arterial *p*H, and hematocrit were maintained within narrow limits and well within any changes that could significantly affect binding of the drug.[23] Since each sample volume was replaced with plasma, it is unlikely that the plasma protein concentration changed significantly during each experimental period.

Schmidt and Livingston[16] suggested that acute tolerance to the effects of morphine on the circulation were due to a combination of central effects in the brain and a direct effect on peripheral blood vessels, and Haggart§§ suggested that peripheral tolerance to the vasodilator

§§ Haggart J: On the mechanism of the vascular action of morphine. Dissertation abstracts 15:1631–1632, 1955.

effect of morphine is at least one contributing factor in the development of tolerance to morphine hypotension. Several authors also have proposed that depletion of histamine depots may be a modulating factor in the development of peripheral vascular tolerance to morphine.[14] Evans *et al.*[24] suggested that the circulatory effects of morphine in the cat (but not in the rat) were mediated largely by an effect on the vasomotor center and the peripheral release of histamine. However, these considerations do not apply to fentanyl, since it does not cause histamine release.[25] The cardiovascular effects of fentanyl are mediated centrally, causing an increase in vagal activity and a decrease in sympathetic activity by an action on the medulla[26] leading to bradycardia and hypotension.

Tolerance to the opiates develops more rapidly when larger doses are used[15,27] and is closely associated with the concurrent development of dependence,[28] characterized by withdrawal and "rebound" phenomena. It is of interest that in the present study, in Group 2 following conditioning and the first test dose, withdrawal of the drug was associated with a rebound increase of $\Delta\overline{AP}$ to above control values, but this did not apply to ΔHR. This is in keeping with previous ideas that tolerance of the effect of opiates on arterial pressure is greater than that of their effects on heart rate.[18,19] The second test dose of fentanyl removed this rebound component and restored the response to control values. Thus, it could be argued that once tolerance has developed, further opiate administration will not depress the cardiovascular reflexes to somatic nerve stimulation but are necessary to maintain the status quo and to avoid enhanced cardiovascular reflexes due to the $\Delta\overline{AP}$ rebound phenomenon, which in the present study occurred within 90 min. In drug addicts, the cardiovascular response to noxious stimulation has been shown to be greater than in normal subjects and to be associated with slower recovery.[29] The rebound observed in the present study could be a similar phenomenon but on a much shorter time scale.

In conclusion, the results of this study show that conditioning with fentanyl caused tolerance to this drug so that large doses became ineffective in depressing somatocardiovascular reflexes. Withdrawal of the drug was associated with enhanced responses in arterial pressure to somatic nerve stimulation, which could be interpreted as an example of the phenomenon of "rebound," which in these experiments occurred in less than 90 min.

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Appendix

The dosing strategy in this study required the computation (from a two-compartment open kinetic model) of a series of bolus doses, which would yield specified concentrations in the central compartment 16 min after each. While the problem can be solved by successive approximation, using standard "forward" equations, a more elegant approach is to develop explicit equations that solve the model for dose rather than concentration.

Thus, given that:

C_1, C_2 = desired concentration (ng/ml) in central and peripheral compartments at time t

ψ_1, ψ_2 = initial concentrations in central and peripheral compartments

V_1 = apparent volume (ml) of the central compartment

α, β = rate constants (per h) characterizing the decay in concentration after a bolus dose

k_{12}, k_{21} = intercompartmental rate constants (per h)

k_{10} = elimination rate constant (per h)

The dose required to satisfy each time segment can be determined:

$$\text{Where } V = \frac{e^{-\alpha t}}{\alpha(\alpha - \beta)} \quad \text{and} \quad W = \frac{e^{-\beta t}}{\beta(\beta - \alpha)}$$

$$\text{Dose } (\mu g) = \left[\frac{C_1 + V \cdot \psi_2 \cdot k_{12} \cdot \alpha + W \cdot \psi_2 \cdot k_{12} \cdot \beta}{V \cdot \alpha(\alpha - k_{21}) + W \cdot \beta(\beta - k_{21})} - \psi_1\right] \cdot \frac{V_1}{1000}$$

The concentration in the peripheral compartment at time t now can be calculated also:

$$\text{Where } Q = \psi_2(k_{12} + k_{10}) + \psi_1 k_{21}$$

$$C_2 = V \cdot \alpha(\psi_2 \cdot \alpha - Q) + W \cdot \beta(\psi_2 \cdot \beta - Q)$$

Now, since C_1 and C_2 become the initial concentrations (ψ_1, ψ_2) for the next segment, the calculation process continues until the series is complete.

The method is applied here to the two-compartment model, which satisfied the present data, but a similar transformation can be applied to three-compartment equations without difficulty.