

Epidural and Subcutaneous Morphine, Meperidine (pethidine), Fentanyl and Sufentanil in the Rat: Analgesia and Other in vivo Pharmacologic Effects

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The experiments examined the characteristics of analgesia produced by different doses of morphine, meperidine (pethidine), fentanyl, and sufentanil after epidural and subcutaneous injection in rats. The specificity of the analgesia was also determined; other *in vivo* pharmacologic activities (i.e., blockade of pinna and cornea reflexes and production of skeletal muscle rigidity) were monitored as pharmacologic indices of opiate drug activity in the brain. After subcutaneous injection, the opiates produced dose-dependent analgesia, blocked the pinna and cornea reflexes, and induced muscle rigidity. After epidural injection, all four compounds produced dose-dependent analgesia and had greater potency, earlier onset, shorter duration, and greater specificity of analgesic action than was the case after subcutaneous injection. Specificity is defined here as the ratio of the ED₅₀ dose that blocked the pinna reflex to the ED₅₀ dose that produced analgesia. The gains in potency and specificity, but not the gains in onset time and the losses in duration of analgesia, differed considerably among the compounds that were examined. The subcutaneous-to-epidural potency ratio related in a linear manner with the lipid-to-water partition coefficient. The gain in specificity also appeared to be related to lipid solubility. The $\mu\text{g}\cdot\text{kg}^{-1}$ doses at which the opiates produced analgesia in rats correlate well with the potency of these compounds in producing analgesia after epidural injection in humans. The rat epidural preparation reflected the doses, onset, and specificity, but not the duration, of analgesia produced by epidural opiates in humans. (Key words: Analgesics: fentanyl; meperidine (Pethidine®); morphine; sufentanil. Anesthetic techniques: epidural opiates; subcutaneous opiates. Behavioral effects: analgesia; blockade of pinna and cornea reflexes; muscle rigidity. Pain: experimental; thermostimulation.)

PHARMACOLOGIC EVIDENCE¹⁻⁵ INDICATES that the analgesia produced by systemically administered opiates involves a site of action in the brain as well as in the spinal cord, and opiate binding sites have been identified autoradiographically⁶⁻⁸ in both the brain and spinal cord. The finding that injection of opiates into the spinal subarachnoid space of laboratory animals produces

analgesia⁹⁻¹¹ has been the basis for administering opiates to patients by the intrathecal or, more commonly, the epidural route.¹²⁻¹⁷

While epidurally administered opiates often produce satisfactory pain relief, side effects may occur; among these are pruritis, nausea, urinary retention, sedation, and respiratory depression.^{15,18-21} Some of these secondary effects, in particular respiratory depression, likely result from the transport of the opiate to sites in the CNS other than the target segments of the spinal cord. The transport mechanisms may include vascular uptake and transport, uptake into and subsequent release from extradural fat, and direct transfer through the dura and diffusion throughout the cerebrospinal fluid (CSF).^{19,22,23} In addition, opiates differ in terms of lipid solubility, dural permeability,²⁴ and other largely unknown characteristics that determine their fate and pharmacologic activity following epidural administration. A need thus exists^{25,26} for data defining the mechanisms by which epidural opiates produce analgesia and other effects. The development of a technique for the catheterization of the lumbar epidural space in the rat²⁷ permits studies to be carried out in an animal species for which a considerable data base exists on the actions and mechanisms of systemically administered opiates.

In this report we examined *in vivo* pharmacologic activities of opiates given by the epidural and the subcutaneous route in rats. The opiates studied were morphine, meperidine, fentanyl,²⁸ and sufentanil²⁹ and these differ considerably in lipid solubility.³⁰ The experiments reported here characterized the analgesic action of these opiates and determined the relative specificity with which analgesia was produced. Analgesia was measured by means of a tail withdrawal assay²⁸ and was compared with several indices of opiate activity in the brain. Blockade of the pinna and cornea reflexes is a characteristic effect of opiate drugs³¹ and requires an action on the tenth and fifth cranial nerves. Opiate rigidity of skeletal muscle likely originates in the striatum³² and substantia nigra.³³ Blockade of the pinna and cornea reflexes and rigidity were thus monitored in the present experiments as indices of pharmacologic activity of the opiates in the brain.

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Materials and Methods

Male Wistar rats weighing 250 ± 20 g were used. Rats were used only once. The laboratory was air conditioned ($21 \pm 1^\circ$ C; relative humidity $65 \pm 5\%$).

EPIDURAL CATHETERIZATION

The technique of epidural catheterization in rats that was used here is a slight modification of the technique described in detail elsewhere.²⁷ Briefly, under Thalamonal® (Innovar®; 2.5 mg droperidol and 0.05 mg fentanyl per ml; 1.5 ml per rat) and pentobarbital ($3.5 \text{ mg} \cdot \text{kg}^{-1}$) anesthesia, a polyethylene catheter (PE 10) was introduced into the epidural space over a length of 0.5 cm cephalad *via* a hole drilled in the fourth lumbar vertebra. Upon fixation of the catheter to the vertebra, the loose end was subcutaneously tunneled toward the neck region.

The animals were allowed 1 week to recover. During this time they were housed individually in standard rodent cages and had free access to food and tap water. Animals showing any sign of apparent neurologic damage were discarded. After the experiments, the animals were killed and the position of the catheter tip was checked at autopsy. Only the results from those animals wherein the catheter tip appeared to be located in the epidural space and in which no epidural fibrinous tissue reaction surrounding the catheter was found were used for data analysis.

The method of epidural injection has been detailed elsewhere²⁷ and consisted of the administration, through the catheter, of 20 μl of either drug solution or saline in increments of 1 μl . The injection procedure took approximately 60 s to complete.

EXPERIMENTAL DESIGN

One series of experiments determined pharmacologic activities of the opiates after subcutaneous injection in intact rats. A second series of experiments was conducted with animals that received drugs by epidural injection.

Subcutaneous Group. Animals were assigned randomly to receive a subcutaneous injection of either saline (control; $n = 29$) or one of different doses ($n = 7$ per dose) of morphine (0.63, 2.5, 10, and $40 \text{ mg} \cdot \text{kg}^{-1}$), meperidine (1.25, 5, 20, and $80 \text{ mg} \cdot \text{kg}^{-1}$), fentanyl (0.0025, 0.01, 0.04, and $0.16 \text{ mg} \cdot \text{kg}^{-1}$), or sufentanil (0.00063, 0.0025, 0.01, and $0.04 \text{ mg} \cdot \text{kg}^{-1}$). Measurements and scores were obtained once before injection and 15, 30, 45, 60 min, and then every 30 min for up to 7 h after injection. Subcutaneous doses were chosen on the basis of preliminary experiments that determined at what doses the full dynamic range of the effects of every compound was covered.

Epidural Group. The animals were assigned randomly to receive an injection of either saline (control; $n = 15$)

or one of different doses of morphine (0.63, 2.5, 10, 40, and $160 \mu\text{g}$ per rat), meperidine (40, 160, 630, and $2,500 \mu\text{g}$ per rat), fentanyl (0.16, 0.63, 2.5, 10, and $40 \mu\text{g}$ per rat), or sufentanil (0.04, 0.16, 0.63, 2.5, and $10 \mu\text{g}$ per rat). Data were collected on five animals per dose. Tail withdrawal latency was measured and pinna reflex, cornea reflex, and muscle tone were scored once before and 5, 15, 30, 45, 60 min, and then every 30 min up to 7 h after injection. Epidural doses were chosen on the basis of preliminary experiments that determined at what range of epidural doses that analgesia was produced by each compound to an extent that was similar to that of the subcutaneous data. Epidural doses were given on a μg per rat rather than a $\mu\text{g} \cdot \text{kg}^{-1}$ basis because this allowed both the drug concentration and the volume of the epidural injectate to be held constant for the different animals.

ANALGESIA ASSAY

The tail withdrawal procedure (TWR) used here has been described in detail elsewhere.²⁸ Briefly, the rat was placed in a cylindrical rat holder with its tail hanging freely outside the cage. The distal 5 cm of the tail was immersed into a warm ($55 \pm 1^\circ$ C) water bath, and the time for tail withdrawal was measured to the nearest 0.1 s. All readings were made by a single observer. In order to minimize tissue damage, the cut-off time was 30.0 s.

OTHER *IN VIVO* ACTIONS

Overall skeletal muscle tone was scored 0 (normal tone) to 3 (lead pipe rigidity); scores 1 and 2 represent weakly and moderately increased tone, respectively. The pinna reflex was scored 0 (normal reflex) to 3 (absence of any apparent motor response), depending on the response of the animal to gentle mechanical stimulation of the pinna by means of a blunt metal rod (ϕ 0.5 mm); scores 1 and 2 indicate the reflex to be slightly or markedly retarded. The corneal reflex was examined in a similar manner and was also scored 0 (normal reflex) to 3 (absence of any apparent motor response). All scores were assigned by a single observer who was unaware of pharmacologic treatments.

STATISTICAL METHODS

Criterion values were defined for each of the four variables that were examined. Tail withdrawal latency was evaluated using the >6.0 s and the ≥ 10 s criteria. Score 3 was the criterion used to evaluate blockade of pinna and cornea reflexes as well as to evaluate muscle tone.

All raw data were transformed into the percentage of rats out of the number of animals tested that satisfied the criterion. This percentage was then used to compute ED_{50} values according to the method of Finney.³⁴ Differences

between ED₅₀ values were evaluated according to the method of Litchfield and Wilcoxon³⁵ ($\alpha = 0.05$).

DRUGS

Morphine HCl, meperidine HCl, fentanyl citrate, and sufentanil citrate were freshly prepared as aqueous solutions. Injections were made in a volume of 1 ml · 100 g⁻¹ body weight in the subcutaneous experiments and in a volume of 20 μ l per rat in the epidural experiments. Doses of morphine and meperidine are expressed as the salt; doses of fentanyl and sufentanil are expressed as the base.

Results

ANALGESIA: CONTROL DATA

In none of the 251 rats used in the epidural ($n = 110$) and subcutaneous experiments ($n = 141$) did the preinjection latency for tail withdrawal exceed 6.0 s (not shown). Postinjection latency also did not exceed 6.0 s at any interval of time after epidural ($n = 15$) or subcutaneous ($n = 29$) injection of saline. The 6.0 s latency was therefore used as a criterion to define drug-produced analgesia in this assay. A latency ≥ 10 s was used as a second criterion; this criterion defines a more profound analgesia and was used in accordance with earlier studies²⁸ on opiate analgesia.

ANALGESIA: DRUG EFFECTS

Morphine, meperidine, fentanyl, and sufentanil increased the tail withdrawal latency after epidural as well as after subcutaneous injection (fig. 1). Both the magnitude and the duration of the effect increased as a function of the epidural or subcutaneous dose of any of the compounds.

Data were analyzed in terms of the ED₅₀ dose (and 95% confidence limits³⁴; in μ g · kg⁻¹) at which compounds prolonged latency to >6.0 s at any point of time after their administration (table 1; row A). Subcutaneous sufentanil was approximately 9- ($P < 0.05^{34}$), 1,400- ($P < 0.001$), and 4,900-fold ($P < 0.001$) more potent than fentanyl, morphine, and meperidine, respectively. After epidural injection, however, sufentanil was only 8- ($P < 0.05$), 82- ($P < 0.01$), and 900-fold ($P < 0.001$) more potent, respectively.

Data were also analyzed in terms of the ED₅₀ for producing a ≥ 10 s latency (table 1; row B). This ED₅₀ was, of course, always higher than the ED₅₀ value for the >6 s effect. The ratio between these two doses was 2.8, 1.7, 2.2, and 2.0 for subcutaneous morphine ($P < 0.05$), meperidine ($P > 0.05$), fentanyl ($P > 0.05$), and sufentanil ($P > 0.05$), respectively. Similarly, the ratio was approximately 2 ($P > .05$) for epidural morphine, meperidine,

and fentanyl (*i.e.*, 2.4, 2.1, and 2.9, respectively), but 6.0 for epidural sufentanil. Epidural sufentanil was also the only route/drug condition for which the difference between the two ED₅₀ values was statistically significant ($P < 0.05$).³⁶ Remarkably, an earlier study³⁷ also obtained a ratio of 6.0 for epidural sufentanil, while that for intravenous sufentanil again was only 2.5.

Time of peak analgesia was found as the mean (± 1 SEM) time interval after injection at which individual rats reached their highest postinjection latency; the data given in table 1 (row C) reflect results obtained at the lowest dose that produced a median peak latency >6 s at any interval. With all four compounds peak effect was reached earlier ($P < .05$) after epidural than subcutaneous injection, the absolute difference varying only minimally among the compounds (*i.e.*, from 19 to 29 min, table 1, row J). Duration of analgesia was found as follows. From figure 1 it was determined, for each dose, for what length of time the latency curve exceeded 6 s. With subcutaneous morphine, for example, this length of time was 0, 0, 131, and 229 min with the 0.63, 2.5, 10, and 40 mg/kg doses, respectively. A plot was then constructed of this length of time as a function of dose (not shown). The number representing duration in table 1 (row D) consisted of the parameter b (*i.e.*, the slope) of the regression equation $y = a + bx$, which fit (least sum of squares) the data points in this plot. The number thus reflects the rate of progression of the duration of analgesia as a function of dose; drugs with a short duration of action have a shallow slope, whereas the slope is steep with long-acting drugs. With all four compounds, the duration of action was shorter after epidural than subcutaneous injection; the difference in slope of the dose-duration curve was 1.5-fold with morphine and 2.9-fold with meperidine (table 1, row K). Note that after epidural injection the duration of action of morphine was about twice as long as that of other compounds, but it also took about twice as long for epidural morphine to reach peak effect than was the case with the other compounds (table 1; rows C₂ and D₂).

OTHER *IN VIVO* PHARMACOLOGIC EFFECTS

After subcutaneous injection, all drugs blocked the pinna and cornea reflexes and produced skeletal muscle rigidity (fig. 2). Blockade of the pinna reflex (score 3) occurred at ED₅₀ doses (table 1; row E) that were about three-fold higher than those at which analgesia (>6 s) was obtained (table 1; row H₁); this difference was significant ($P < .05$) with morphine and sufentanil. Blockade of the cornea reflex and rigidity occurred at still higher doses (*i.e.*, 6 [fentanyl: blockade of corneal reflex] to 36 [morphine: rigidity] times the lowest of the two analgesic doses; table 1, rows F₁ and G₁; $P < 0.05$).

Epidural morphine in doses up to 160 μ g per rat (640

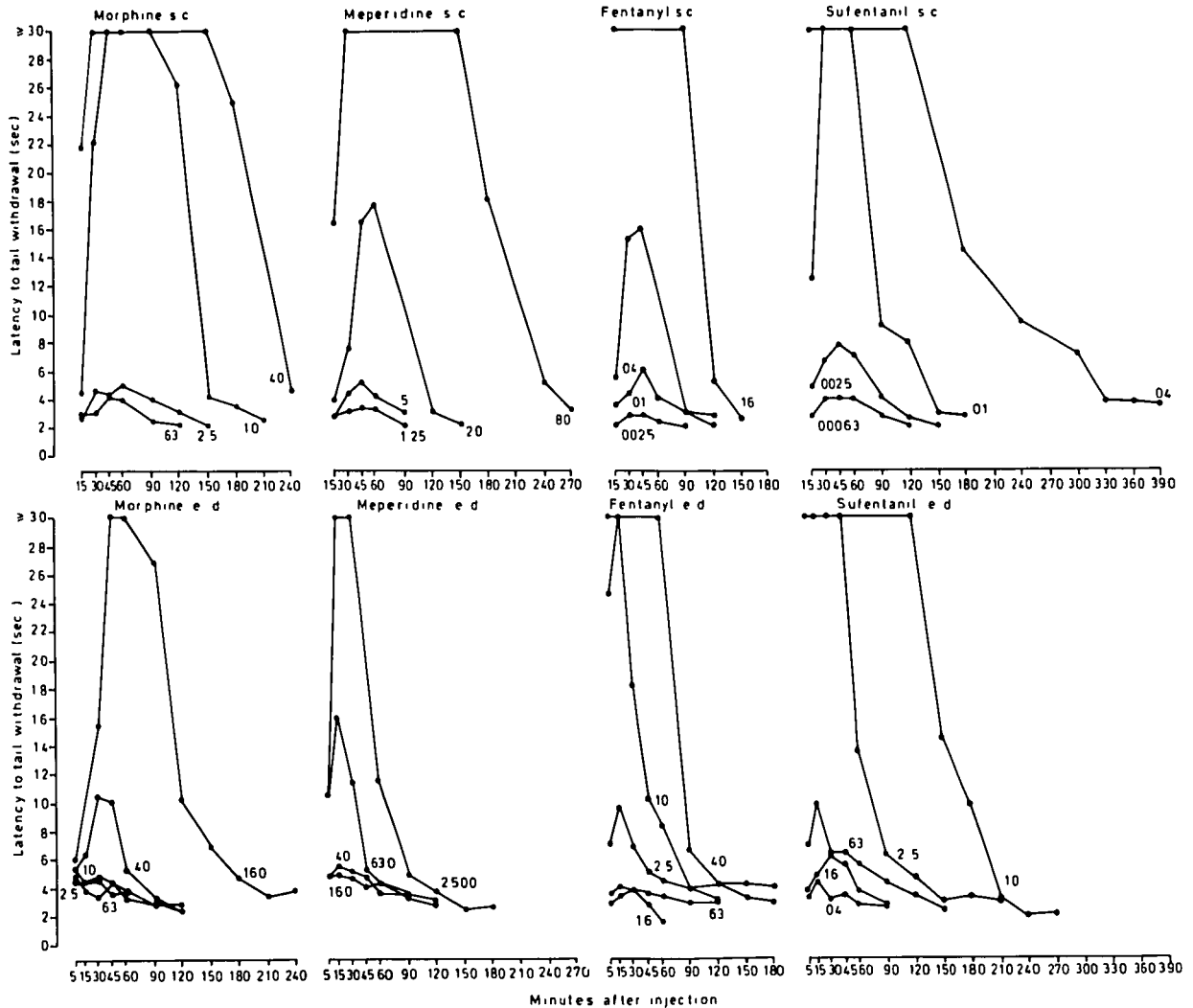


FIG. 1. Analgesia produced by subcutaneous or epidural injection of morphine, meperidine (pethidine), fentanyl, and sufentanil in rats. Data points represent median latency for tail withdrawal²⁸ at each time interval after injection. The numbers appearing in the graphs indicate doses of subcutaneous (in $\text{mg} \cdot \text{kg}^{-1}$; $n = 7$ per dose) or epidural (in μg per rat; $n = 5$ per dose) drug injections. For the sake of clarity, data points were omitted for those times at which drug doses no longer exerted any discernable effect.

$\mu\text{g} \cdot \text{kg}^{-1}$) failed to exert any apparent effect on either the pinna or cornea reflexes or muscle tone (fig. 2; table 1). Doses of 2,500 μg meperidine per rat (10,000 $\mu\text{g} \cdot \text{kg}^{-1}$) exerted some effects on each of these indices (fig. 2) but did not produce scores of 3. Epidural fentanyl and sufentanil did produce scores of 3 with all three indices, but the doses at which these effects occurred were at least 12 times higher ($P < 0.01$) than the analgesic dose (table 1, column H₂).

The specificity of the analgesia thus was greater with all four compounds after epidural injection than after subcutaneous injection (rows H in table 1). The gain in specificity, however, was greater with morphine and meperidine than with fentanyl and sufentanil.

Figure 3 exemplifies the time courses of the effects of sufentanil and fentanyl on the different indices that were

measured in the present experiments. After epidural injection, the peak effects of either compound on the pinna and cornea reflexes and on muscle tone were time-locked with their peak analgesic effects. In addition, analgesia outlasted the other effects; analgesia was still prominent 60 min after sufentanil and 45 min after fentanyl, whereas all other effects had virtually disappeared at these points of time. After subcutaneous injection, the peak effects on the reflexes and on muscle tone were again time-locked with analgesic peak effects, but the analgesia did not outlast the other actions.

Discussion

The experiments reported here examined the analgesia produced by morphine, meperidine (pethidine), fentanyl,

TABLE 1. Characteristics of Analgesia and Other *in vivo* Pharmacologic Effects of Subcutaneous and Epidural Morphine, Meperidine, Fentanyl, and Sufentanil in Rats

Row	Index	Morphine	Meperidine	Fentanyl	Sufentanil
Subcutaneous					
A ₁	TWR > 6 s (ED ₅₀ ; $\mu\text{g} \cdot \text{kg}^{-1}$)	1,810 (920–3,570)	6,380 (3,310–12,290)	12 (6.7–20)	1.3 (0.73–2.3)
B ₁	TWR \geq 10 s (ED ₅₀ ; $\mu\text{g} \cdot \text{kg}^{-1}$)	5,130 (3,930–6,700)	11,120 (7,140–17,310)	26 (16–41)	2.6 (2.0–3.4)
C ₁	Time of peak analgesia (min)	60 \pm 7	43 \pm 5	36 \pm 3	39 \pm 5
D ₁	Duration of analgesia (slope)	197	197	97	172
E ₁	Pinna reflex (ED ₅₀ ; $\mu\text{g} \cdot \text{kg}^{-1}$)	5,430 (4,150–7,100)	15,550 (8,540–28,330)	33 (19–59)	4.5 (2.9–7.0)
F ₁	Cornea reflex (ED ₅₀ ; $\mu\text{g} \cdot \text{kg}^{-1}$)	15,550 (8,540–28,330)	43,020 (25,840–71,620)	70 (54–91)	8.7 (6.7–11)
G ₁	Muscle tone (ED ₅₀ ; $\mu\text{g} \cdot \text{kg}^{-1}$)	65,490 (26,410–162,440)	>80,000	160 (120–210)	21 (12–37)
H ₁	Ratio E ₁ /A ₁	3.0	2.4	2.8	3.5
Epidural					
A ₂	TWR > 6 s (ED ₅₀ ; $\mu\text{g} \cdot \text{kg}^{-1}$)	33 (19–57)	374 (217–644)	3.2 (1.8–5.4)	0.40 (0.23–0.69)
B ₂	TWR \geq 10 s (ED ₅₀ ; $\mu\text{g} \cdot \text{kg}^{-1}$)	80 (46–138)	794 (460–1,370)	9.3 (5.4–16)	2.4 (1.4–4.1)
C ₂	Time of peak analgesia (min)	36 \pm 4	14 \pm 5	16 \pm 4	20 \pm 8
D ₂	Duration of analgesia (slope)	130	67	52	73
E ₂	Pinna reflex (ED ₅₀ ; $\mu\text{g} \cdot \text{kg}^{-1}$)	>640	>10,000	37 (22–64)	5.0 (2.9–8.7)
F ₂	Cornea reflex (ED ₅₀ ; $\mu\text{g} \cdot \text{kg}^{-1}$)	>640	>10,000	50 (29–86)	12 (7.0–21)
G ₂	Muscle tone (ED ₅₀ ; $\mu\text{g} \cdot \text{kg}^{-1}$)	>640	>10,000	79 (46–137)	11 (6.3–19)
H ₂	Ratio E ₂ /A ₂	>20	>27	12	12
Differences Between Routes					
I	Analgesic potency (A ₁ /A ₂)	55	17	3.8	3.3
J	Time of peak analgesia (C ₁ /C ₂)	24	29	20	19
K	Duration of analgesia (D ₁ /D ₂)	1.5	2.9	1.9	2.4
L	Specificity of analgesia (H ₂ /H ₁)	>7	>11	4.3	3.4

TWR = tail withdrawal reflex.

and sufentanil after epidural and subcutaneous injection in rats. The specificity of the analgesia was also determined; that is, other pharmacologic effects (*i.e.*, blockade of pinna and cornea reflexes and production of skeletal muscle rigidity) were monitored in an effort to obtain measurements of opiate drug activity in the brain.

The data indicate that after epidural injection in rats, all four compounds produce dose-dependent analgesia, and have a greater potency, an earlier onset, a shorter duration, and a greater specificity of analgesic action than is the case after an equivalent subcutaneous dose. The gains in time of onset and the losses in duration of analgesic action did not differ much among the four compounds that were examined. Differences among compounds did, however, emerge in terms of the gains in potency and specificity of the analgesic action (table 1).

Morphine, meperidine, fentanyl, and sufentanil are more soluble in fat than in water but differ in their lipid-to-water partition coefficients. Figure 4 presents a plot of the subcutaneous-to-epidural potency ratio (row I in table 1) as a function of the octanol-to-water partition coefficient. The figure indicates that, with the four compounds that were examined, an orderly relationship exists between the subcutaneous-to-epidural potency ratio in producing analgesia and the lipid solubility. The plot also indicates that the relationship is linear in log-log coordi-

ates. Note that it is not the absolute epidural potency, but the subcutaneous-to-epidural *gain* in potency that relates linearly to lipid solubility. Several points would seem to be relevant in considering this relationship. (1) The relationship is unlikely to reflect differences in dural permeability in that at least morphine and fentanyl do not seem to differ much in terms of permeability of isolated human lumbar dura.²⁴ (2) The relationship could be interpreted to reflect differences among drugs in terms of absorption from the subcutaneous injection site and into the circulation.³⁸ However, the ratio of intravenous-to-epidural ED₅₀ values also correlates ($r_s = 1.0$; $P < 0.05$) with lipid solubility (intravenous ED₅₀ values are 2,230, 3,880, 7.7, and 0.46 $\mu\text{g} \cdot \text{kg}^{-1}$ for morphine, meperidine, fentanyl, and sufentanil, respectively; Dr. C. Niemegeers, personal communication). (3) After parenteral but not epidural injection, the compound must cross the blood-brain barrier in order to reach relevant receptor sites; the ability to cross this barrier is, among other factors, determined by lipid solubility,³⁹ so that the potency gain must be expected to relate inversely to lipid solubility.

Differences among the four compounds in the gain in specificity of the analgesia may also relate to lipid solubility. After parenteral injection, analgesia as well as CNS-mediated side effects depend on the penetration into CNS from the circulation, so that the specificity ratio (row H₁

in table 1) must be expected to be similar for different compounds, regardless of their lipid solubility. After epidural injection, vascular absorption may occur *via* the azygos vein into the inferior vena cava,²⁵ and this absorption must be expected to be proportional to lipid solubility. Vascular absorption, penetration of the blood-brain barrier, and also, gain in analgesic potency are all proportional to lipid solubility and combine to explain the greater specificity gain of morphine and meperidine relative to that of fentanyl and sufentanil (row L in table 1).

That epidural opiates produced analgesia (fig. 1), that analgesic doses were lower, and that the onset of analgesic effect was earlier compared with subcutaneous injection can be understood from accepted concepts. Specifically,

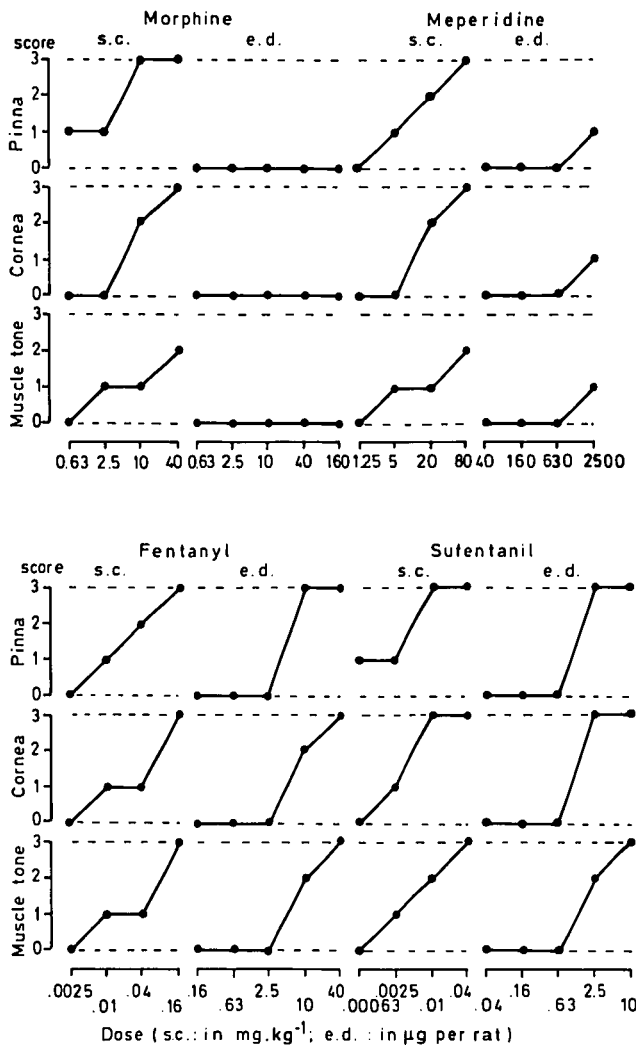


FIG. 2. Effects on pinna and cornea reflexes and on skeletal muscle tone of subcutaneous and epidural injections of morphine, meperidine (pethidine), fentanyl, and sufentanil in rats. Data points represent the median of the highest score that the animals were given at any point of time after injection. See also legend to figure 1.

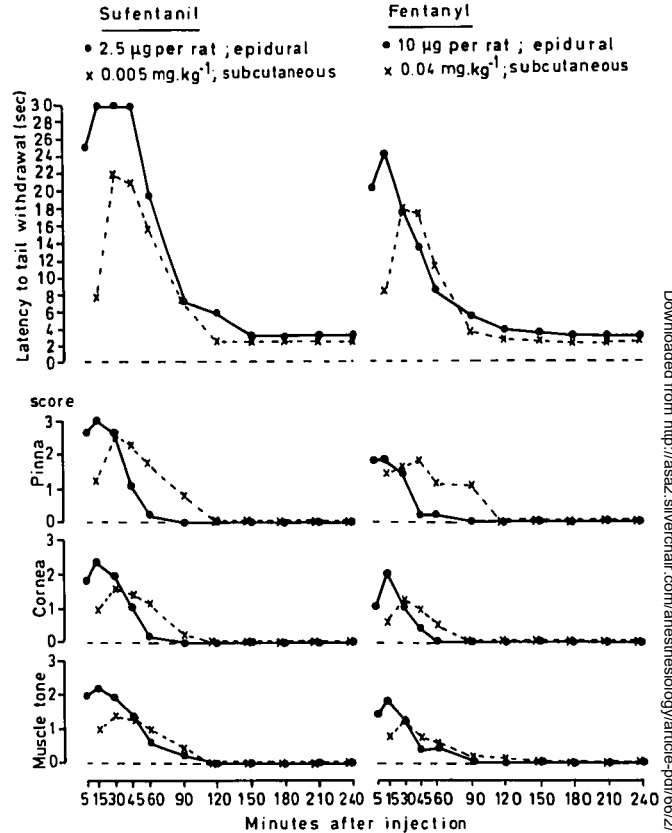


FIG. 3. Time course of analgesia, blockade of pinna and cornea reflexes, and increased muscle tone after epidural and subcutaneous injections of sufentanil and fentanyl. The data points represent mean values ($n = 7$ and 5 for subcutaneous and epidural administration, respectively) at each interval of time. Latencies >30 s were given the value 30 . See also legend to figures 1 and 2. Note that, unlike figures 1 and 2, means are used in this figure. This is because means better reflect graded changes in response than medians do, albeit that to compute means on ordinal data is a less than perfectly admissible operation.³⁷

the spinal cord constitutes a site at which opiates produce analgesia³ and can be reached relatively fast from the epidural space by penetration of the dura and/or through the posterior radicular spinal artery, which directly supplies the dorsal horn region of the spinal cord.²⁵ Also, having reached the spinal cord, lipid-soluble drugs can be expected³⁹ to penetrate this tissue more readily and thus to act faster. The shorter duration of action of epidural as opposed to subcutaneous opiates is more difficult to explain. One possibility is that the epidural but not the subcutaneous animals received a fentanyl injection for the purpose of anesthesia 1 week prior to the experiment, and were perhaps rendered at least partly tolerant to opiate analgesia. Also, after epidural injection, a relatively large portion of the drug is located in an area of CNS that is relevant to analgesia, and redistribution to organs

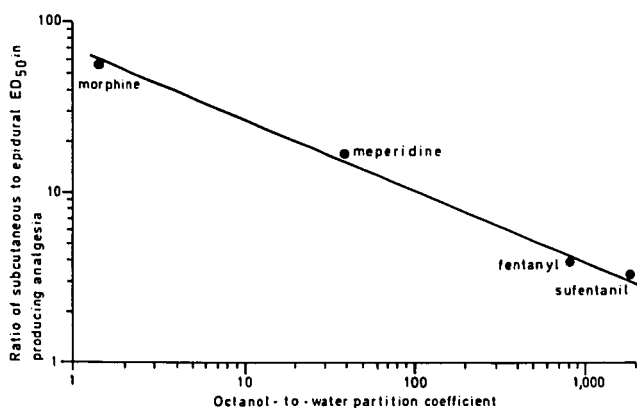


FIG. 4. Subcutaneous-to-epidural potency ratio of morphine, meperidine (pethidine), fentanyl, and sufentanil in producing analgesia in rats as a function of the octanol-to-water partition coefficient. Ordinate: ratio of the subcutaneous to the epidural ED₅₀ value in producing a latency of tail withdrawal greater than 6 s (table 1, row I). Abscissa: octanol-to-water partition coefficient.^{25,30} Spearman rank correlation coefficient $r_s = -1.0$; $P < 0.05$.³⁷

that are not relevant to analgesia is relatively fast because the concentration of the drug in these organs is relatively low. After subcutaneous injection, high drug concentrations in nonrelevant organs are reached as soon as analgesia occurs, and redistribution from relevant to nonrelevant sites is slower because of a smaller concentration

difference between those sites. Note, however, that these hypotheses cannot be substantiated at this point.

Data from patients (fig. 5) indicate that the rank order of potency of epidural sufentanil, fentanyl, morphine, and meperidine in producing analgesia in rats (table 1) is similar to their rank order of potency in producing analgesia in humans. In addition, the doses, in $\mu\text{g} \cdot \text{kg}^{-1}$, obtained in rats appear to be predictive of the $\mu\text{g} \cdot \text{kg}^{-1}$ doses at which these compounds produce analgesia in humans. This finding is significant for at least two reasons. First, it strongly supports the validity of the rat epidural preparation²⁷ as an animal model for the pharmacology of epidural opiates in humans. Second, it supports the hypothesis that the analgesic effects of epidural opiates are mediated to a significant extent by a spinal site of action. This is because such a relationship between rats and humans does not occur when species differences in pharmacokinetic variables contribute to the data, such as is the case with parenteral routes. For example, the analgesic potencies of intravenous opiates in rats, expressed in $\mu\text{g} \cdot \text{kg}^{-1}$, do not correspond with the $\mu\text{g} \cdot \text{kg}^{-1}$ doses used in humans (unpublished data).

In addition to this relationship (fig. 5), other findings support the validity of the rat epidural preparation. The greater specificity of epidural as compared with subcutaneous opiate analgesia (table 1, row L) is consistent with

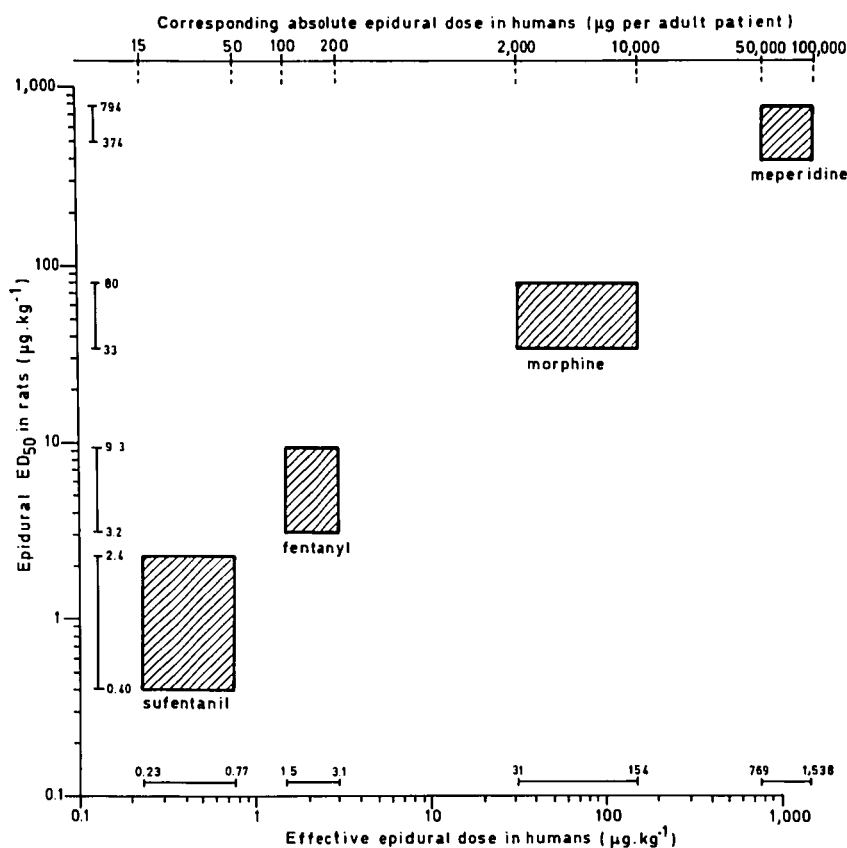


FIG. 5. Relationship between effective analgesic doses of morphine, meperidine (pethidine), fentanyl, and sufentanil on epidural injection in rats and humans. Ordinate: epidural ED₅₀ (in $\mu\text{g} \cdot \text{kg}^{-1}$) for prolonging tail withdrawal latency to >6.0 and ≥ 10 s in rats (see table 1). Upper abscissa: absolute epidural dose in humans (in $\mu\text{g}/\text{adult patient}$); corresponding doses in $\mu\text{g} \cdot \text{kg}^{-1}$ are given by the lower abscissa. Note that the rank orders of potency are the same in rats and humans ($r_s = 1.0$; $P \leq 0.05$) and that doses also correspond in terms of $\mu\text{g} \cdot \text{kg}^{-1}$ doses. Absolute epidural doses in humans were derived from dose-effect studies with morphine⁴⁰⁻⁴² and sufentanil.⁴³ Doses of meperidine and fentanyl indicate approximate ranges of dose at which these compounds have been demonstrated to produce analgesia in patients.⁴⁴⁻⁴⁶ In the conversion of $\mu\text{g}/\text{patient}$ to $\mu\text{g} \cdot \text{kg}^{-1}$ doses, patients were assumed to weight 65 kg.

data²⁵ showing that analgesia produced by epidural opiates in humans is associated with fewer side effects mediated by brain than that of parenteral opiates. There also appears to be a correspondence between animal and human data in terms of time of peak of analgesic action. The times of peak effect in rats were 14, 16, and 36 min for meperidine, fentanyl, and morphine, respectively (table 1), and have been estimated²⁵ as 12–30, 20, and 37 min, respectively, in patients. The present rat data may not correspond with patient data in terms of the duration of analgesia after epidural opiates. That is, there is a correspondence in relative duration of action (*i.e.*, morphine >> meperidine > fentanyl; table 1²⁵), but the absolute length of analgesia in the rat seems to be shorter than that in patients. For example, the 40 µg per rat dose of morphine (which would be approximately 10 mg for a 65-kg patient) had a duration of analgesic action of about 1 h in the rat (fig. 1). In contrast, the mean duration of analgesic action of 10 mg of epidural morphine in patients is approximately 12–18 h.^{13,17,49} Several explanations might account for this discrepancy. First, patients in whom epidural opiates are given are typically exposed to pain, and exposure to pain has been shown^{50,51} to enhance opiate analgesia. Second, duration of analgesic action was defined here (table 1) as the *rate* at which the duration of detectable analgesia progressed as a function of dose; this definition permits the effects of different compounds and different routes to be compared in a uniform manner. Clinical studies¹³ of intravenous *versus* epidural opiates have merely determined the length of time of apparent analgesia produced by a given dose of opiate. Perhaps the latter approach does not take into account that the specificity of opiate analgesia is greater with the epidural route (table 1) and that, therefore, relatively larger doses can be given by the epidural than by the intravenous route. Third, in addition to an epidural opiate, patients often receive other medications (*e.g.*, local anesthetics, epidural adrenaline, systemic opiates, muscle relaxants, and hypnotics²⁵) that may act to prolong apparent analgesia. Fourth, the apparent analgesic effects of intrathecal opiates vary with the pain test used,^{52,53} so that perhaps the differences between rat and patient data may also relate to differences in the methods or conditions by which pain is produced. Fifth, duration may perhaps be expected to relate inversely to metabolic rate and may thus be considerably shorter in rats than in humans. Consistent with this possibility is that the duration of analgesia produced by epidural opiates in cats⁵⁴ seems to be intermediate between that in rats and humans.

The present data add to earlier evidence^{23,25} that opiates with different lipid-to-water partition coefficients differ in terms of their effects on epidural injection. Lipid-soluble drugs (*e.g.*, sufentanil) have a rapid onset of analgesic action, and the greater specificity of epidural as

opposed to parenteral analgesia permits the analgesia to be produced with a relative absence of side effects that are mediated by the brain. Drugs that are less lipid soluble (*e.g.*, morphine) have a slower onset but a greater gain in specificity. This greater gain in specificity allows relatively higher doses to be administered. Because duration of analgesia increases with dose, less lipid-soluble drugs have the advantage that a longer duration of analgesia can be produced. However, less lipid-soluble compounds may more readily migrate throughout the CSF; the theoretical possibility thus emerges that, late after injection, the compound reaches the opiate-sensitive^{55,56} respiratory centers in the brain stem⁵⁷ and causes respiratory depression by this process.²³

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