

Magnitude of Acute Tolerance to Opioids Is Not Related to Their Potency

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It was suggested that for a given analgesic effect, more potent opioids may produce smaller degrees of tolerance than those with lower analgesic potency. The use of opioids with high analgesic potency to reduce the rate of tolerance development would be an important therapeutic consideration. This study tested the hypothesis that the degree of acute tolerance to the analgesic effect of opioids is inversely related to their potency. In the experiments on rats, the analgesic effects of morphine, alfentanil, and sufentanil given by a continuous 8-h infusion at a constant rate, were determined by measuring the threshold of motor response to noxious pressure on the tail. The comparative degree of acute tolerance was determined on the basis of the decline in the level of analgesia at the end of the infusion period. Morphine $4 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$, alfentanil $0.45 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$, and sufentanil $0.0085 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ caused approximately similar increases in the pain threshold. The peak of analgesia could not be maintained; it declined by $74 \pm 6\%$ ($P < 0.0001$) with morphine, $86 \pm 6\%$ ($P < 0.0001$) with alfentanil, and $92 \pm 2\%$ ($P < 0.0001$) with sufentanil. The results indicate that the infusion of alfentanil and sufentanil, which differ from morphine by higher analgesic potency (by 10-fold and more than 100-fold, respectively), results in a decline in the degree of analgesia during infusion similar to that of morphine. These data reject the hypothesis that the magnitude of acute tolerance to the analgesic action of opioid drugs following their systemic administration is inversely related to their potency. (Key words: Analgesics, opioid: alfentanil; morphine; sufentanil. Potency, analgesic: tolerance.)

A PREVIOUS STUDY¹ demonstrated that during a constant-rate infusion of morphine, its analgesic effect declines profoundly despite the absence of any decrease in morphine brain concentration. This suggests the development of acute tolerance, which is pharmacodynamic in nature. It has also been suggested that the degree of tolerance observed with long-term administration of morphine is inversely related to the reserve of spare opioid receptors in the tissue.^{2,3} Various opioids have different analgesic potency and require different degrees of the fractional receptor occupancy to produce equianalgesic effect.^{4,5} When tolerance to Tyr-D-Ala-Gly-MePhe-Glyol (DAGO) was compared to that of morphine, the administration of DAGO was found to result in a smaller

degree of tolerance with greater reserve of spare opioid receptors.⁶ Stevens and Yaksh⁷ reported that the use of agents believed to have high reserve of the spare receptors and high potency (*e.g.*, sufentanil and D-Ala-MePhe-Glyol) results in a lesser magnitude of tolerance for spinal antinociceptive action than the use of those with low receptor reserve and low potency (morphine). The authors suggested that for a given effect, more potent agents may produce smaller degrees of tolerance than those with lower analgesic potency.⁷

The use of opioids with high analgesic potency to reduce the rate of tolerance development would be an important therapeutic consideration. The aim of the present study was to test the hypothesis that the degree of acute tolerance to the analgesic effect of opioids is inversely related to their potency. Three opioid analgesics, morphine, alfentanil, and sufentanil, with wide differences in analgesic potency and opioid receptor occupancy, were selected for study.

Materials and Methods

Experiments were performed on 40 male Sprague-Dawley rats weighing 225–275 g. The protocol for this study was approved by the Institutional Panel on Laboratory Animal Care. Analgesia was determined by measuring the threshold of motor response to increasing noxious pressure applied to the tail⁸ with the use of an Analgesy-Meter (Ugo Basile, Milan, Italy). The rat's tail was positioned on a Teflon platform, and the pressure plate (0.7-mm edge) attached to this device was placed 4.5 cm from the tip of the tail while the rat was held in the experimenter's hand. Pressure was increased at a constant rate (cut-off pressure of 2.75 kg) until the animal attempted to escape. The pressure at that moment was recorded, and the mean of three measurements was taken as the reaction threshold. For each consecutive determination of the pain threshold (total of seven) the pressure plate was moved 2 mm cephalad.

A catheter for the drug infusion was chronically implanted into the jugular vein, and its free end was exteriorized through the skin at the back of the neck. The surgical procedure for implantation was performed under pentobarbital anesthesia ($50 \text{ mg} \cdot \text{kg}^{-1}$, intraperitoneal) several days before the experiment. The drugs were infused for 8 h at a constant rate (Harvard Apparatus Compact Infusion Pump, model 975, Harvard Apparatus Co., Natick, MA). The rates of infusion were selected on the

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basis of the data obtained in pilot experiments to provide maximal individual increases in the pain threshold that did not exceed the cut-off pressure. The infusion rates were: $4 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ for morphine, $0.45 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ for alfentanil, and $0.0085 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ for sufentanil. Doses of the drugs were expressed in terms of the salt. Morphine sulfate (Robins Co., Cherry Hill, NJ), alfentanil hydrochloride, or sufentanil citrate (Janssen Pharmaceutica, Piscataway, NJ) was dissolved in normal saline and infused at a rate of $0.6 \text{ ml} \cdot \text{h}^{-1}$. Four groups of ten rats received either saline $0.6 \text{ ml} \cdot \text{h}^{-1}$ (control), morphine, alfentanil, or sufentanil. Drug selection was made randomly with blocked allocation of animals, and the observer was blinded to the treatment. Each rat had seven determinations of pain threshold at the following time intervals: baseline, 0.5, 1, 2, 4, 6, and 8 h.

As in the previous publication,¹ the comparative degree of acute tolerance was determined on the basis of the decline in the level of analgesia at the end of the constant-rate opioid infusion. In addition, the time to 50% recovery during the infusion (a 50% reduction of the maximal increase in the pain threshold) was determined from a time course of the effect in each animal.

The pressure threshold measurements, the time to 50% recovery, and the degree of recovery during infusion were summarized as the mean plus or minus one standard error of the mean for each of the groups studied. Comparisons of the mean among the groups was performed with a one-way analysis of variance⁹; comparisons of mean threshold pressures among times from infusion with a repeated-measures analysis of variance⁹; and pairwise tests between any two means with Fisher's protected least significant difference test.⁹ Differences were declared statistically significant if $P < 0.05$.

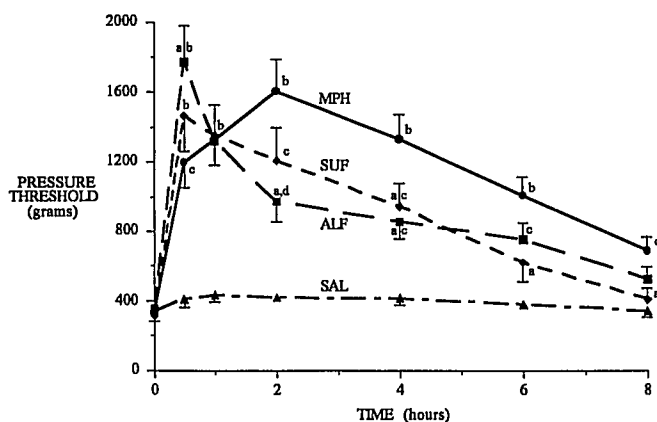


FIG. 1. Effect of constant-rate infusions of morphine, alfentanil, and sufentanil on pain threshold. MPH = morphine $4 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$; SUF = sufentanil $8.5 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$; ALF = alfentanil $450 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$; SAL = saline. Mean \pm SEM. * $P < 0.05$ versus morphine. ^b $P < 0.0001$, ^c $P < 0.01$, ^d $P < 0.05$ versus saline.

TABLE 1. Comparative Degrees of Acute Tolerance during Opioid Infusion

| Drug | Degree of Recovery* During Infusion (%) | |
|------------|---|-----------------------------|
| | At 6 h | At 8 h |
| Morphine | 51.1 \pm 6.7 | 73.6 \pm 5.9 |
| Alfentanil | 68.7 \pm 6.8 | 85.6 \pm 5.6 |
| Sufentanil | 76.5 \pm 6.4 [†] | 91.5 \pm 2.4 [†] |

Values are means \pm SEM.

* Reduction of the maximal increase in the threshold.

[†] $P < 0.05$ compared to morphine.

Results

Results of the experiments are presented in figure 1. The constant-rate infusion of the opioid drugs caused an increase in pain threshold that reached its peak at the 0.5–2-h interval depending on the drug. Degrees of the maximal increases in pain threshold with all three drugs were not significantly different from one another. After reaching its maximum, analgesia began to decline despite the continuing infusion. At 8 h the pain threshold increase was, on average, only one fourth of the peak value with morphine and was not significantly different from control animals receiving saline with alfentanil and sufentanil. In some animals (approximately 20%) the pain threshold completely returned to the baseline.

Comparative degrees of the reduction of the maximal increase in pain threshold are presented in table 1. The degree of recovery with sufentanil was greater than that with morphine at both 6 h (76.5 vs. 51.1%, $P < 0.05$) and at 8 h (91.5 vs. 73.6%, $P < 0.05$). Comparative rate in the development of acute tolerance measured in terms of time to 50% recovery (table 2) also indicated that with alfentanil and sufentanil, the decrease in analgesia is even faster than that with morphine (3.4 and 3.9 h vs. 5.8 h, $P < 0.05$, respectively, when measured from the beginning of infusion). Because the peak effect with morphine occurs later than with alfentanil and sufentanil (2 vs. 0.5 h), the difference between time to 50% recovery when measured from the beginning of infusion is greater than that measured from the peak effect. When time to 50% recovery was determined from the peak effect, it only tended to be longer with morphine compared to the two other opioids (table 2). We found no relationship between the magnitude of analgesia (peak effect) and the degree of acute tolerance. Figure 2 illustrates this with morphine. Similar results were obtained with alfentanil and sufentanil.

Discussion

Studies in which a constant rate of morphine was given by intravenous infusion for many hours demonstrated a

TABLE 2. Comparative Rate in Development of Acute Tolerance During Opioid Infusion.

| Drug | Time to 50% Recovery* During Infusion (h) | |
|------------|---|------------------|
| | From Beginning of Infusion | From Peak Effect |
| Morphine | 5.8 ± 0.6 | 3.8 ± 0.5 |
| Alfentanil | 3.4 ± 0.7† | 2.9 ± 0.7 |
| Sufentanil | 3.9 ± 0.5† | 3.1 ± 0.5 |

* Reduction of the maximal increase in the threshold.
† $P < 0.05$ compared to morphine.

profound decrease in analgesia both in dogs¹⁰ and in rats.^{1,11} The most important result of the present study is that the approximately equally pronounced analgesic effects of the three opioids resulted in the development of acute tolerance at rates that were not markedly different. At the same time, morphine:alfentanil and alfentanil:sufentanil potency ratios under our experimental conditions were approximately 1:10 and 1:500, respectively. This indicates that with both alfentanil and sufentanil, which differ from morphine by higher analgesic potency (by 10-fold and more than 100-fold, respectively), acute tolerance does not develop to a lesser degree. On the contrary, it was even somewhat greater with sufentanil. This does not support the hypothesis that the magnitude of acute tolerance to analgesic effect of opioids is inversely related to their potency, defined as the dose of a drug required to produce an effect.¹²

Acute tolerance is defined as a rapidly developed state of decreased whole-animal responsiveness to the pharmacologic effect of a drug.¹³ The mechanisms involved in the development of tolerance might be pharmacodynamic and/or pharmacokinetic.¹² The previous study¹ indicated that acute tolerance to the analgesic effect of morphine is pharmacodynamic in nature. Because of similarity in the analgesic effects of morphine, alfentanil, and sufentanil, it is possible to speculate that the mechanisms of acute tolerance to alfentanil and sufentanil is also pharmacodynamic. Because the present results do not indicate that more potent opioids—alfentanil and sufentanil—can produce lesser degrees of tolerance, possible differences in the mechanisms of acute tolerance between these opioids cannot be important to the hypothesis tested in this study.

Stevens and Yaksh⁷ reported data suggesting that the infusion of opioid agents with higher potency results in a decreased degree of tolerance. However, their study is different from the present study in at least three respects: spinal *versus* systemic administration of opioids, 7-day *versus* 8-h infusion, and thermal *versus* mechanical noxious stimuli. Each of these differences may result in involvement of the different mechanisms of tolerance, which are

suggested to be multiple.¹⁴⁻¹⁶ To underline the complexity of the possible mechanisms involved in the development of the tolerance, it is enough to mention that when Stevens and Yaksh¹⁷ compared the time course of loss of the effects of morphine, sufentanil, and DAGO they found them to be identical. Chavkin and Goldstein² and Porreca and Burks³ studied chronic tolerance and indicated that the degree of tolerance observed for the action of morphine was inversely related to the receptor reserve. It is quite possible that acute tolerance (developed on the order of hours) has a different nature from chronic tolerance and that the fractional receptor occupancy mechanism is not involved in the process that already becomes obvious several hours after the beginning of opioid infusion. One should also consider the differences between the uncoupling of a receptor from effector mechanism for a short-term effect and receptor internalization for a long-term effect.¹⁸

Koob and Bloom¹⁵ have suggested two groups of possible mechanisms for tolerance: a within-system adaptation and a between-system adaptation. In the within-system mechanism, the primary response element to the drug would itself adapt to neutralize the drug's effect. In the between-system mechanism, adaptation could derive from another system counter-balancing the initial effect. With all three opioids used in this study, no correlation was seen between the magnitude of peak analgesic effect and the degree of acute tolerance developed later (fig. 2). This fact may suggest that the between-system adaptation is a less likely mechanism for the observed acute tolerance than the within-system adaptation.

Differences among the agents used in this study regarding the rate of decrease of the analgesic effect are relatively small and probably dependent on their phar-

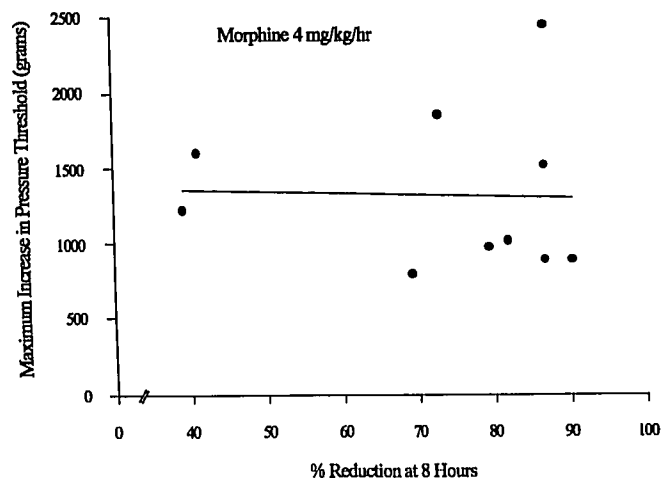


FIG. 2. Absence of relationship between magnitude of analgesic peak effect and degree of acute tolerance (percent reduction from peak effect during infusion).

macokinetic characteristics determining the timing of peak effect. Alfentanil has the shortest distribution and elimination half-lives and the fastest rate of equilibration between the plasma and the site of drug effect.^{19,20} These pharmacokinetic features are probably the main determinants for the difference between the degrees of alfentanil, sufentanil, and morphine analgesia at 0.5 and 2 h (fig. 1). It is interesting that the difference between the morphine and alfentanil pain threshold values at 8 h of the infusion (688 ± 87 vs. 524 ± 71 g, not significant) is less than that at 4 h (1332 ± 143 vs. 856 ± 96 g, $P < 0.05$). This fact is evidence against the possible role of a very active metabolite, morphine-6-glucuronide, in the somewhat slower rate of decrease in pain threshold with the infusion of morphine.

It has been reported that the administration of alfentanil for 2–3 h can induce complete tolerance to the depressant effect of the drug on somatosympathetic reflexes evoked by nociceptive stimulation.²¹ Tolerance to the cardiorespiratory effects of alfentanil has been reported to occur in as little as 1 h after subsequent bolus injection.²² Thus, the fast rate of the tolerance development obtained in the present study is not an unexpected finding.

By the 8th h of the infusion of the drugs used in the present study, differences in the degree of acute tolerance among the drugs were not very significant. This suggests that probably all morphine and meperidine congeners share relatively rapid development of tolerance to their analgesic effect. Although methadone is structurally different from the above two groups, it has such a profound discrepancy between serum half-life (13–58 h) and duration of the analgesic effect (4 h)²³ that the development of acute tolerance to the analgesic effect of methadone can be suggested.

In conclusion, the results of this study indicate that the magnitude of acute tolerance to the analgesic action of opioid drugs following their systemic administration is not inversely related to their potency. A continuous 8-h constant-rate infusion of alfentanil and sufentanil, which differ from morphine by higher analgesic potency (by 10-fold and more than 100-fold, respectively), resulted during the infusion in a profound decline in the degree of analgesia, similar to that seen with morphine.

References

- Kissin I, Brown PT, Robinson CA, Bradley EL Jr: Acute tolerance in morphine analgesia: continuous infusion and single injection in rats. *ANESTHESIOLOGY* 74:166–171, 1991
- Chavkin C, Goldstein A: Opioid receptor reserve in normal and morphine-tolerant guinea pig ileum myenteric plexus. *Proc Natl Acad Sci USA*. 81:7253–7257, 1984
- Porreca F, Burks TF: Affinity of normorphine for its pharmacologic receptor in the native and morphine-treated guinea pig ileum myenteric plexus. *J Pharmacol Exp Ther* 225:688–693, 1983
- Rosenbaum JS, Holford NJH, Sadee W: Opiate receptor binding-effect relationship: Sufentanil and etorphine produce analgesia at the mu-site with low fractional receptor occupancy. *Brain Res* 291:317–314, 1984
- Miller L, Shaw JS, Whiting EM: The contribution of intrinsic activity to the action of opioids in vitro. *Br J Pharmacol* 87:595–601, 1986
- Christie MJ, Williams JT, North RA: Cellular mechanisms of opioid tolerance: Studies in single brain neurons. *Mol Pharmacol* 32:633–638, 1987
- Stevens CW, Yaksh TL: Potency of infused spinal agents is inversely related to magnitude of tolerance after continuous infusion. *J Pharmacol Exp Ther* 250:1–8, 1989
- Green AF, Young PA: A comparison of heat and pressure analgesimetric methods in rats. *Br J Pharmacol* 6:572–585, 1951
- Snedecor GW, Cochran WG: *Statistical Methods*. 7th edition. Ames, The Iowa State University Press, 1980, pp 215–223, 227–233
- Martin WR, Eades CG: Demonstration of tolerance and physical dependence in the dog following a short-term infusion of morphine. *J Pharmacol Exp Ther* 133:262–270, 1961
- Cox BM, Ginsburg M, Osman OH: Acute tolerance to narcotic drugs in rats. *Br J Pharmacol* 33:245–256, 1968
- Nies AS: *Principles of therapeutics*, Goodman and Gilman's Pharmacological Basis of Therapeutics. Edited by Gilman AG, Rall TW, Nies AS, Taylor P. New York, Pergamon Press, 1990, pp 62–72
- Neubig RR: The time course of drug action, *Principles of Drug Action, The Basis of Pharmacology*. Edited by Pratt WB, Taylor P. New York, Churchill Livingstone, 1990, p 344
- Hug CC: Characteristics and theories related to acute and chronic tolerance development, *Clinical and Biological Aspects of Drug Dependence*. Edited by Wikler A. Cleveland, CRC Press, 1972, pp 307–358
- Koob GF, Bloom FE: Cellular and molecular mechanisms of drug dependence. *Science* 242:715–723, 1988
- Neil A: Tolerance and dependence, *Advances in Pain Research and Therapy*. Volume 14. Edited by Benedetti C. New York, Raven Press, 1990, pp 121–142
- Stevens GW, Yaksh TL: Time course characteristics of tolerance development to continuously infused antinociceptive agents in rat spinal cord. *J Pharmacol Exp Ther* 251:216–223, 1989
- Collins S, Bouvier M, Lohse MJ, Benovic JL, Caron MG, Lefkowitz RJ: Mechanisms involved in adrenergic receptor desensitization. *Biochem Soc Trans* 18:541–544, 1990
- Scott TC, Stanski DR: Decreased fentanyl and alfentanil dose requirements with age: A simultaneous pharmacokinetic and pharmacodynamic evaluation. *J Pharmacol Exp Ther* 240:159–166, 1987
- Scott JC, Pongranis KV, Stanski DR: EEG quantitation of narcotic effect: The comparative pharmacodynamics of fentanyl and alfentanil. *ANESTHESIOLOGY* 62:234–241, 1985
- Swenzen GO, Whitwam JG: Selective tolerance of group III and IV somatosympathetic reflexes to the effects of alfentanil. *Neuropharmacology* 25:1379–1385, 1986
- Doorley BM, Knight VV, Spaulding TC: Development of acute tolerance to the cardiorespiratory effects of alfentanil after subsequent bolus injection in conscious dogs. *Life Sci* 43:365–372, 1988
- Grochow L, Sheidler V, Grossman S, Green L, Enterline J: Does intravenous methadone provide longer lasting analgesia than intravenous morphine? A randomized, double-blind study. *Pain* 38:151–157, 1989