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Some Mechanistic Insights into Opioid Tolerance

THE REPORT by Sosnowski and Yaksh[1] in this issue is important for two reasons. First, it illustrates some important principles of pharmacologic analysis of drug–receptor interactions, and second, it suggests that the rates at which analgesic tolerance to opioids develop are functions of the efficacies of the drugs. Thus, the results have obvious, potentially important clinical implications.

We teach that opioid agonists such as morphine, methadone, fentanyl, and sufentanil have equal analgesic efficacy but differ in relative potency.[2] In other words, all are capable of producing an identical, maximum analgesic effect and differ only in the dose required. This concept is basically correct since differences in the efficacy of opioids as analgesics may not be discernible with the methods available to determine maximum analgesic effect. An important principle that often is not appreciated is that maximum drug effect can be produced by a drug that is occupying only a proportion of the total finite number of receptors available. It follows then that different drugs can produce equivalent effects (*e.g.*, identical pain relief) while occupying different proportions of the available receptors.[3] Thus, drugs in the same class can have very different intrinsic efficacies. The fraction of the total receptor pool *not* required for maximal effect is the receptor reserve (or "spare" receptors).[3] In a sense, then, many drugs are more "powerful" than necessary since maximum effects can be produced with only fractional occupancy of the receptors available. In the examples provided in the report by Sosnowski and Yaksh,[1] animals given morphine and sufentanil at dosages that initially produced an equivalent, maximal effect were observed to develop tolerance of different magnitudes to their antinociceptive effects. That is, the tolerance that developed to chronic spinal infusions of these two agents was "nonsymmetric," even though both morphine and sufentanil acted at the same mu opioid receptor.

The important implications of these results are twofold. First, more efficacious opioids, because they require occupancy of fewer receptors to produce analgesia, should provide pain relief for a significantly longer period of time before tolerance to their analgesic effects begins to develop. Second, because fewer receptors need to be occupied to produce an effect, switching from less efficacious to a more efficacious opioid as tolerance develops should provide an improved degree of pain relief. This second point is emphasized by the data in table 1 of the report by Sosnowski and Yaksh.[1] In the absence of any prior exposure to opioids, sufentanil was about 9 times more potent an antinociceptive drug than morphine. After 7 days of continuous sufentanil infusion, the potency ratio was 29; sufentanil became 44 times more potent than morphine after 7 days of chronic morphine infusion. Thus, the relative potency of sufentanil to morphine increased as tolerance developed and was greater in the presence of tolerance associated with a low efficacy agonist such as morphine.

There are, however, some issues other than efficacy and tolerance that merit consideration. As pointed out in the paper, high efficacy opioids such as etorphine and fentanyl generally are more lipophylic than are lower efficacy opioids such as morphine. In situations other than chronic infusion of opioids, this generally means a faster onset of analgesia but a shorter duration of action. In circumstances of chronic infusion, greater lipophylicity likely means more ready redistribution of drug to sites other than the spinal cord. Also, it is not apparent how

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the current results apply to administration of opioids for relief of pain by routes other than infusion. In such circumstances, pharmacokinetic considerations are likely to be more important.

Despite the apparent clinical implications of this work, a few words of caution are in order. Tolerance simply is not a problem with short-term postoperative epidural or intrathecal opioids, and extensive study has been unable to demonstrate convincingly a difference between drugs such as morphine and fentanyl in terms of the quality of pain relief (although side effects may differ). In contrast, chronic epidural or intrathecal opioids are used almost exclusively in patients with terminal malignancies. The development of tolerance in such patients is a much more gradual process than that seen in the animals studied by Sosnowski and Yaksh.[1] Furthermore, it is sometimes difficult in these patients to determine whether increasing analgesic requirements represents tolerance or represents the progression of their disease.

Therefore, while the results presented in the current study are tantalizing (and certainly provide important insights into the mechanism of drug action), it remains to be proven whether the distinctions between opioids of different efficacies will persist over a time course of many months, particularly when given against a background of constant pain and a worsening disease. Nevertheless, the findings presented by Sosnowski and Yaksh seem readily testable in humans, and we eagerly await an appropriate prospective, blinded comparative trial.

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