Antinociceptive Opioid Activity Ratio

To the Editor—Jacobson et al.1 recently reported that the parenteral dose-response relationship of methadone was one of their criteria for selecting the dose of intrathecal methadone. However, this and interpretations of their results ignore some of the older and newer findings on lipophilic opioids, especially methadone. As early as 1970, Cule et al.2 reported that the antinociceptive opioid activity ratio (AOAR) was lower the more polar the opioid. The AOAR was defined as the effective analgesic dose (µg per animal) following iv administration divided by the effective analgesic dose following intraventricular administration in rabbits and is designated AOAR iv/intraventricular. The AOAR of morphine, meperidine, methadone, and fentanyl were 0.00112, 0.117, 0.163, and 0.172, respectively,2 indicating that as lipophilicity increases, the difference between iv and intrathecal analgesic dose decreases. With respect to the lipophilic methadone, the intrathecal analgesic potency is even less than one-tenth of that of morphine as Jacobson et al.3 have recently published, thus confirming the experimental findings. It has to be considered, however, that opiate lipophilicity is only one of the factors that govern the opioid analgesic effectiveness, which in fact also depends on the opiate’s opioid affinity and opioid receptor specificity.4

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In Reply—It is reassuring that our clinical study corroborates prior animal investigations on the antinociceptive opioid activity ratio.1

The parenteral dose-response relationship of methadone was not one of the criteria for selecting the intrathecal methadone (ITMe) dose. As discussed and referenced in our paper, the main information was obtained from prior use of ITMe 2–5 mg in opioid-tolerant cancer patients. In addition, information on the dose-response relationship of intrathecal morphine (ITMS) and the equivalent analgesic dose tables for the systemic administration of morphine and methadone was used. Currently, except for morphine, the analgesic potency (AP) of intrathecal opioids relative to that of epidural opioids is unknown. The disposition of intrathecal and epidural opioids is governed by different factors. Intrathecal opioids do not have to cross the blood-brain barrier. The fate of opioids given epidurally is complicated because the desired direct transfer of opioid across the dura competes with uptake and removal by the epidural vasculature and with reversible uptake into epidural adipose tissue.5 Drug molecular weight and rate of absorption are important determinants of the efficiency of dural transfer.4 Consequently, morphine is well suited to epidural administration but buprenorphine is theoretically unsuitable.3 Extrapolations from epidural to intrathecal opioid administration are of little value in the absence of data that systematically compares and contrasts intrathecal dose-response data with epidural data for a variety of opioids with different physicochemical and pharmacologic properties. Until this is done we will be comparing apples with oranges. Laboratory investigations on the relationship between potency and lipophilicity for intrathecal opioids demonstrate that the most liposoluble drugs are the least potent.4 This supports our clinical observations using the µ-opioid receptor agonists morphine, methadone and diamorphine.1–7 Clinically, lipid solubility is pivotal in determining whether intrathecal analgesia of superior quality and longer duration is achieved. While factors other than lipophilicity (e.g., molecular structure, receptor affinity, rate of metabolism) may influence the potency, they are dwarfed by the lipid solubility consideration and are clinically irrelevant when the intrathecal opioids alluded to are administered.

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