Pharmacology of Clonidine

To the Editor—The case report by Burney1 describes clonidine as a "centrally acting α blocker" and guanfacine as "a drug related to clonidine." Though later in the text this description is clarified somewhat by reference to guanfacine as "an α2 adrenergic agonist with pharmacologic properties similar to those of clonidine," this does not clarify the error in the original sentence.

As reviewed by Berthelsen and Pettinger,6 clonidine is both a central and a peripheral acting α2 agonist at clinically relevant concentrations. At both sites this agonist property is exerted at pre- and postsynaptic sites.

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References


In Reply—Jones is quite correct that pharmacologically, clonidine and guanfacine are central α2 agonists. Clonidine was originally developed as a vasoconstrictor nasal drops, and intravenous administration results in a transient rise in blood pressure. Their clinical usefulness as antihypertensive drugs rests on actions in the central nervous system that produce a decrease in sympathetic tone and a slowing of the pulse. Interestingly, these effects can be blocked by α blockers such as phentolamine.7 It is easy to think of a drug that acts in the brain to reduce sympathetic tone as a "centrally acting α blocker." However, this is not correct, and I regret any confusion created by this imprecise terminology.

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Reference


Preoperative Epidural Fentanyl, Neuroplasticity, and Postoperative Pain

To the Editor—Recently Katz et al.,3 in a study of patients undergoing thoracotomy, demonstrated that a significantly lower pain score at 6 h but not at 2, 4, 12, 24, and 48 h postoperatively and a significantly reduced morphine consumption at 12–24 h but not at 0–2, 2–4, 4–6, 6–12, and 24–48 h postoperatively was achieved by giving preemptive epidural fentanyl compared with the same fentanyl dose administered 15 min after skin incision. They conclude that these results suggest preemptive analgesia to reduce central

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consequences of surgical incision and rib retraction, and as mentioned in the title, that these results represent "clinical evidence of neuroplasticty contributing to postoperative pain."

Although we agree that the concept of preemptive analgesia is extremely interesting for the understanding and potential improvement of postoperative pain treatment, we find the paper and conclusion of Katz et al. to be an overinterpretation of their rather minimal findings.

First, Katz et al. accidentally were unlucky in their randomization, since the preemptive group was significantly older than the postincisional fentanyl group. This is a problem because it is well known that pain and postoperative opioid requirements decrease in old age. Katz et al. tried to remove the two youngest patients from their data set in the postincisional fentanyl group and mentioned that this did not alter the outcome of the statistical analyses, although they did not show exact date. This does not change the fact that the preemptive group was elderly compared to the control group (significant or not significant).

Second, the preemptive group was overrepresented by female patients: 9 of 15 versus 3 of 15 in the control group. Katz et al. mention this difference to be nonsignificant, but the actual P value is 0.06, which may be of potential clinical significance, since postoperative opioid consumption is less in females than males. Thus, the composition of the patient material in the preemptive group with both more old patients and more females may result in less pain and opioid requirements, thereby hindering interpretation of the study (or, in fact, explaining their results).

Third, Katz et al. used 5–10 ml 2% lidocaine as a test dose but did not provide information about the magnitude of this dose in the two groups. We will postulate that the test dose in fact may provide "preemptive analgesia" and that the exact dose given either should have been similar or at least should have been presented in their results.

Finally, the results on pain and opioid consumption are quantitatively of such a small magnitude that the conclusions, in our opinion, represent an overinterpretation of the data regarding the potential clinical value of their efforts. In this context, other double-blind studies on the potential effects of preemptive analgesia on postoperative pain or need for analgesics have mostly been negative, or only slightly positive.

Therefore, more well designed studies on effective preemptive analgesic regimens, which may really prevent noxious neural impulses from getting into the central nervous system, should be performed. Furthermore, the role of the continuous afferent input during the postoperative period, as long as the inflammatory response in the wound exists, needs to be evaluated. Also, interpretation of the existing literature of preemptive analgesia should be less biased than in the past, thereby clarifying the exact role of and potential for preemptive analgesia to improve postoperative pain treatment.

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References


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In Reply—Dahl and Kehlet raise four points concerning the results and interpretation of our study. We will address each of these points in turn. First, Dahl and Kehlet suggest that the difference in postoperative pain 6 h after surgery may have been due to the age difference between the groups since pain and opioid consumption have been shown to decrease with age. They make this argument notwithstanding our statement that removing the two patients in group 2, whose ages (22 and 24 yr, respectively) were each more than 2 standard deviations below the mean age of the entire sample of 30 patients, produced a nonsignificant age difference without altering the significant difference in pain or morphine consumption. To correct any misunderstanding surrounding our results, we pro-

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