Does Divergence Exist between Animal and Human Data on the Effect of Cebranopadol?

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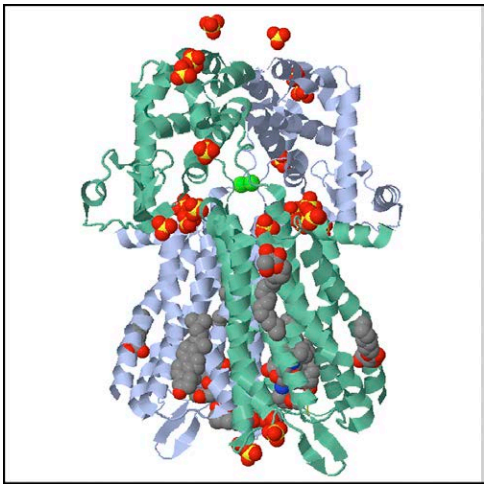
The opioid epidemic has made physicians painfully aware of the extensive and serious side-effect profile of opioids, including when used perioperatively, in the treatment of chronic pain and when abused outside of the realm of medical treatment. The variety of side effects is large, and the most devastating adverse effects include: (1) reward and liking, which may cause addiction; (2) lightheadedness, which may cause posture instability and falls; and (3) respiratory depression, which may be potentially life-threatening. Opioid-induced respiratory depression occurs when opioids are overdosed or combined with other drugs acting within the central nervous system, such as alcohol, sedatives, antidepressants and antipsychotics,[1] but may also occur at "normal doses" in vulnerable individuals. The cost of the opioid epidemic is large, both at the individual level and at the socio-(macro)-economic level. Hence, it is not surprising that there is renewed interest in the development of novel opioids with the promise of fewer side effects. One such novel and still experimental opioid is cebranopadol. Cebranopadol acts at the classical opioid receptor subtypes (μ-, κ-, and δ-opioid receptors) as well as at the fourth and atypical opioid receptor, the nociceptin/orphanin FQ or nociceptin opioid protein (NOP) receptor. It has a high affinity for the nociceptin opioid protein and μ-opioid receptors (inhibitory constant [Ki] = 0.7 and 0.9 nM, respectively) compared to the κ- and δ-opioid receptors (inhibitory constant = 2.6 and 18 nM, respectively).[2] The idea behind the development of drugs that act at the classical opioid receptors and the nociceptin opioid protein receptor is that nociceptin opioid protein receptor activation counteracts μ-opioid receptor–related side effects, most importantly respiratory depression, as well as drug liking.[3–5] Various animal studies provide direct evidence for such behavior.[3–5] Additionally, the nociceptin opioid protein receptor is implicated in various biologic functions including nociception, reward, cardiovascular control, and immunity.



"…opioids that act at the μ-opioid and nociceptin opioid protein receptors are promising novel drugs…"

In this issue of Anesthesiology, Ding *et al.*[4] describe the functional profile of cebranopadol in a nonhuman primate model. In 22 rhesus monkeys, subcutaneous cebranopadol was administered and compared to fentanyl. In contrast to fentanyl, cebranopadol, at doses that caused pain relief, did not cause any reduction of respiratory rate or minute volume during the first 60 min after administration. The study was well performed, and the data are exciting and are mirrored by earlier data in rats. Linz *et al.*[5] studied the effect of intravenous cebranopadol and fentanyl in a rat model. Similar to Ding *et al.*,[4] they observed that while cebranopadol and fentanyl produce potent analgesia, the respiratory effects of fentanyl were much greater than those of cebranopadol. Selective nociceptin opioid protein receptor antagonism potentiated the respiratory depressant effects of cebranopadol, an effect that was reversed by naloxone, the antagonist of the classical opioid receptors (but not of the nociceptin opioid protein receptor). Ding *et al.*[4] conclude that "[the] study demonstrates that cebranopadol displays analgesic efficacy with an improved side effect profile when compared with clinically used [μ-opioid receptor agonists]." Both animal studies give compelling evidence that opioids that act at the μ-opioid and nociceptin opioid protein receptors are promising novel drugs with an improved utility over the classical opioids such as morphine, oxycodone, and fentanyl. This regards respiratory depression but not its abuse potential, which requires further evaluation.[4] The question remains how these basic scientific data translate to the treatment of pain in humans.

In 2010, we tested the effect of a single dose of oral cebranopadol (0.6 mg) and intravenous fentanyl (280 μg/80 kg) in healthy volunteers using a crossover design and measured their effect on antinociception (using an electrical pain model), resting ventilation, isohypercapnic ventilation,

Image: Jmol: an open-source Java viewer for chemical structures in 3D. http://www.jmol.org/.

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and the hypercapnic ventilatory response.[6,7] As expected, fentanyl produced antinociception combined with respiratory depression.[6] Cebranopadol was analgesic but caused significant respiratory depression: a 30% depression of resting minute ventilation, a 50% depression of isohypercapnic ventilation, and an 80% depression of the slope of the hypercapnic ventilatory response (see figs. 1 and 7 in Dahan *et al.*[6]). Some respiratory protection was implied, however. Modeling of the isohypercapnic ventilatory response suggested that cebranopadol exhibits a "ceiling" in respiratory depression,[6] very similar to buprenorphine, another μ-opioid that acts at the nociceptin opioid protein receptor.[8] In other words, at a high dose, cessation of respiration had a relatively low probability.

One of many questions is, "Does cebranopadol behave differently in humans compared to the nonhuman primate and rat, and if so, why is that?" There may be evident mechanistic differences between species such as a possible a differential distribution of nociceptin opioid protein receptors, a lesser sensitivity of nociceptin opioid protein for cebranopadol in humans, or differences in transduction pathways after nociceptin opioid protein receptor activation. Alternatively, the differences may be related to differences in respiratory measurement techniques. Ding *et al.*[4] did not measure blood gasses, and possibly the respiratory effect was present in an increase in arterial partial pressure of carbon dioxide. This may have offset the effect on resting minute ventilation and respiratory rate. However, we contend that these differences seem not to be the cause of the divergence between species.

Our early human study has one important limitation that might explain the apparent discrepancies among studies, *i.e.,* just one oral dose was tested, and hence we remain uninformed about the dose–response relationship in the human experimental respiratory model. The human data are therefore best considered provisional. From the elaborate and elegantly performed animal studies that allow testing at a high dose, we learn and anticipate that particularly at high brain concentrations, cebranopadol has a limited side-effect profile. Hence, further human studies are needed in which multiple and higher cebranopadol doses are administered. Study endpoints should be analgesia, respiratory depression, and abuse potential. Only then can we decide whether a true divergence exists between animal and human studies in the effect of the experimental opioid cebranopadol on respiration and reward/liking. The study by Ding *et al.* shows the utility of nonhuman primate studies as a clear guide for human studies. The complete set of animal data on bifunctional nociceptin opioid protein and μ-opioid receptors shows that these drugs hold a promise that still needs to be substantiated in proper human studies.

Competing Interests

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References

1. van der Schrier R, Roozekrans M, Olofsen E, Aarts L, van Velzen M, de Jong M, Dahan A, Niesters M: Influence of ethanol on oxycodone-induced respiratory depression: A dose-escalating study in young and elderly individuals. Anesthesiology 2017; 126:534–42
2. Linz K, Christoph T, Tzschentke TM, Koch T, Schiene K, Gautrois M, Schröder W, Kögel BY, Beier H, Englberger W, Schunk S, De Vry J, Jahnel U, Frosch S: Cebranopadol: A novel potent analgesic nociceptin/orphanin FQ peptide and opioid receptor agonist. J Pharmacol Exp Ther 2014; 349:535–48
3. Ding H, Kiguchi N, Yasuda D, Daga PR, Polgar WE, Lu JJ, Czoty PW, Kishioka S, Zaveri NT, Ko MC: A bifunctional nociceptin and mu opioid receptor agonist is analgesic without opioid side effects in nonhuman primates. Sci Transl Med 2018; 10:eaar3483
4. Ding H, Trapella C, Kiguchi N, Hsu FC, Caló G, Ko MC: Functional profile of systematic and intrathecal cebranopadol in nonhuman primates. Anesthesiology 2021; 135:482–93
5. Linz K, Schröder W, Frosch S, Christoph T: Opioid-type respiratory depressant side effects of cebranopadol in rats are limited by its nociceptin/orphanin FQ peptide receptor agonist activity. Anesthesiology 2017; 126:708–15
6. Dahan A, Boom M, Sarton E, Hay J, Groeneveld GJ, Neukirchen M, Bothmer J, Aarts L, Olofsen E: Respiratory effects of the nociceptin/orphanin FQ peptide and opioid receptor agonist, cebranopadol, in healthy human volunteers. Anesthesiology 2017; 126:697–707
7. Boom M, Olofsen E, Neukirchen M, Fussen R, Hay J, Groeneveld GJ, Aarts L, Sarton E, Dahan A: Fentanyl utility function: A risk-benefit composite of pain relief and breathing responses. Anesthesiology 2013; 119:663–74
8. Dahan A, Yassen A, Bijl H, Romberg R, Sarton E, Teppema L, Olofsen E, Danhof M: Comparison of the respiratory effects of intravenous buprenorphine and fentanyl in humans and rats. Br J Anaesth 2005; 94:825–34