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ANESTHESIOLOGY® 2020

Make the Most of This Year's Virtual Annual Meeting

ANESTHESIOLOGY 2020 Offers Opportunities for Scientific Discovery

Research continues to be an essential force driving the evolution of the specialty. To advance the practice of medicine in anesthesiology and patient care, ANESTHESIOLOGY 2020 offers a robust research track program to keep you informed of the latest research and scientific breakthroughs.

Here is an overview of the scientific sessions delivered by leading researchers, subject matter experts, and industry partners. All sessions listed in the program are in Central Time.

Saturday Sessions: Keynote Address and FAER-Helrich Research Lecture October 3

9-10 a.m. Francis S. Collins, MD, PhD, the current director of the National Institutes of Health, the largest supporter of biomedical research in the world, will open the meeting with our keynote address: "Exceptional Opportunities in Biomedical Research." Previously, Dr. Collins served as director of the National Human Genome Research Institute, where he led the completion

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Mieke Soens, MD, FAER 2020 Mentored Research Training Grant Recipient.

Residents and Medical Students Sessions You Won't Want to Miss

Residents engage with their peers at the 2019 Residents Reception. ANESTHESIOLOGY 2020 will offer several virtual opportunities to foster engagement.

As a medical student or resident at ANESTHESIOLOGY 2020, you will have access to a wide range of educational sessions guaranteed to ignite your interest and excitement for the specialty.

ANESTHESIOLOGY 2020 will be an amazing experience that maintains the quality and variety of education sessions residents and medical students need and expect from the annual meeting. But you won't have to head to the airport, find your way to the convention center, or arrive early to a meeting room to get the perfect seat. Instead, through an interactive virtual

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Novel Approaches in Opioid Therapy for Treatment of Postoperative Pain

Albert Dahan, MD, PhD

In our anesthesiology practice, opioids are the standard of care for treatment of moderate to severe acute pain. This is particularly true for treatment of postoperative pain when we decide against the use of regional anesthesia – such as a local anesthetic nerve block or epidural analgesia – for postoperative pain relief. Remarkably, for postoperative pain relief, we still mostly rely on older opioids such as morphine (first extracted from opium in 1804), hydromorphone (1923), oxycodone (1916),

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Opioid Therapy

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methadone (1938), and fentanyl (1960), to name a few. These opioids, all full agonists at the mu-opioid receptor and very effective in treating acute pain, became part of our current armamentarium, often without proper examination of their safety.

Apart from producing analgesia, activation of this receptor induces a series of adverse effects due to the ubiquitous presence of mu-opioid receptors in the brainstem. Adverse effects range from nausea and vomiting that, although not life-threatening, are major nuisances to the patient, to more severe effects, including sedation and life-threatening respiratory depression (*Anesthesiology* 2010; 112:226-38). Although deaths from perioperative opioids are uncommon (*Anesthesiology* 2010; 112:226-38), opioid-induced respiratory events do occur in almost 50% of postoperative patients (*Anesth Analg* April 16, 2020), and fatalities do happen (*Pain Manage* 2014;4:317-25). Additionally, long-term opioid use is associated with loss of analgesic efficacy (tolerance) and addictive behavior, which is related to opioid likability and the avoidance of withdrawal symptoms.

Signaling pathways

Following mu-opioid receptor activation, two separate intracellular signaling pathways are engaged – the G-protein-coupled pathway and the b-arrestin pathway. Animal data suggest these pathways have distinct pharmacological effects (*J Pharmacol Exp Ther* 2013;344:708-17). The G-protein pathway is primarily involved in pain relief and euphoria, while b-arrestin involvement causes respiratory depression and gastrointestinal side effects as well as inhibition of the G-protein pathway (*Nature* 2015; 525:315-21; *Trends Pharmacol Sci* 2007;28:416-22). Initial studies in mice that lack b-arrestin (so called b-arrestin 2 knockout mice) show that these animals have more pronounced and longer morphine analgesia (reduced tolerance) combined with reduced morphine-induced respiratory depression and less constipation (*J Pharmacol Exp Ther* 2005;314:1195-2001).

Given the seemingly distinct pharmacological pathways that separate analgesia from respiratory depression, interest rose in the design and development of opioids that selectively activate the G-coupled pathway, so-called biased ligands, for clinical use (*Nature* 2016;537:185-190; *Cell* 2017;171:1165-71). One such biased opioid under consideration by the FDA is oliceridine (*Pain* 2014;155:1829-35; *J Pain Res* 2019;12:927-43; *Pain Pract* 2019;19:715-31). In healthy volunteers, oliceridine produces less depression of the respiratory drive than morphine, while analgesic responses are greater (*Pain* 2014;155:1829-35). Still, in clinical studies, the separation between analgesic and respiratory depression is so far less evident (*J Pain Res* 2019;12:927-43; *Pain Pract* 2019;19:715-31).

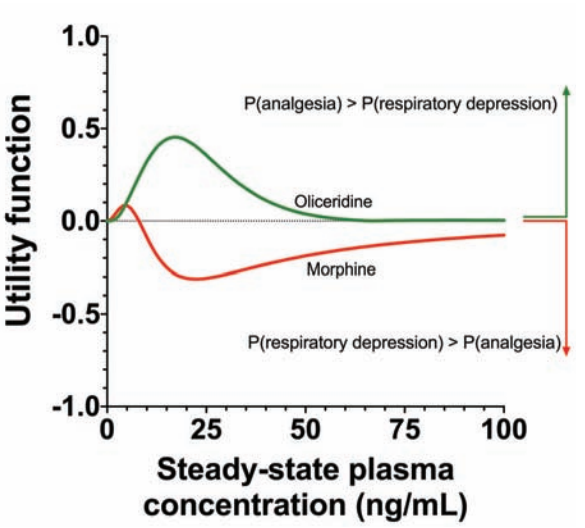

Figure 1: Utility function, the probability of analgesia minus the probability of respiratory depression, P (analgesia) – P (respiratory depression), of morphine (red) and biased ligand oliceridine (green).

Comparisons and effects

As earlier stated by Kharasch and Rosow, and recently reiterated, it is not clear how to compare the analgesic and respiratory effects of two (or more) opioids in clinical studies, as not only do concentration-effect relationships differ between endpoints, but also these differences may vary among different opioids (*Anesthesiology* 2013;119:504-6; *Anesthesiology*, in press).

One way to solve this issue is to construct so-called utility or safety functions (*Anesthesiology*, in press; *Anesthesiology* 2018;128:932-42; *Ann Palliat Med* 2020;9:528-36). These functions quantify the difference in the probability of a beneficial and an adverse effect, i.e., opioid analgesia and respiratory depression.

To compare oliceridine and morphine, we constructed their utilities based on the previously mentioned volunteer study, which attempts to control for a number of potential confounding concomitant conditions (*Anesthesiology*, in press). The results depict the clear separation between morphine and oliceridine, with a negative utility function for morphine (i.e., the probability of respiratory depression exceeds the probability of analgesia) and a positive one for oliceridine (i.e., the probability of analgesia exceeds the probability of respiratory depression), at least over the clinical concentration range (*Anesthesiology*, in press) (see Figure 1). At higher concentration (e.g., when overdosed), the two drugs behave similarly, and their probability of respiratory depression becomes comparable. These data suggest the advantage of oliceridine over morphine in clinical practice when simultaneously considering analgesia and respiratory depression. Whether this is related to the difference in bias toward the G-coupled protein or to other properties – such as low intrinsic efficacy, as has recently been suggested (*Sci Signal* 2020;13:eaaz3140) – needs further study, but is less relevant. Overall, oliceridine seems a realistic alternative to commonly used opioids in the treatment of postoperative pain, particularly in high-risk patients such as the elderly.

Bifunctional and multifunctional opioids

Apart from the discovery of biased ligands, some other initiatives aimed to curb the occurrences of respiratory depression events are worth mentioning. Much effort is being put in the development of bi- and multifunctional opioids. By activation of multiple specific opioid (and non-opioid) receptor systems, these opioids may reinforce their analgesic activity while they potentially produce fewer adverse effects. For example, various drugs have been developed that activate the mu-opioid receptor and the nociceptin/orphanin FQ peptide (NOP) receptor (*Anesthesiology* 2017;126:697-707; *Sci Transl Med* 2018;10:eaar3483). The NOP receptor is the fourth opioid receptor and was formerly known as the opioid-receptor like receptor. Opioids that act at these receptors are analgesic but produce less respiratory depression. Cebranopadol is such a bifunctional opioid. In humans, cebranopadol is analgesic and has a reduced but certainly not absent respiratory effect (*Anesthesiology* 2017;126:697-707).

Another bifunctional mu-opioid/NOP receptor agonist under investigation, AT-121, produces analgesia without detectable respiratory effects in nonhuman primates (*Sci Transl Med* 2018;10:eaar3483). A bifunctional opioid approved in the U.S. and EU is tapentadol. Tapentadol activates the mu-opioid receptor and simultaneously inhibits the neuronal reuptake of norepinephrine. When in pain, the release of norepinephrine activates postsynaptic 2-adrenergic receptors that subsequently inhibit trafficking of afferent nociceptive input to the brainstem. This phenomenon is part of the endogenous pain modulatory system (*Br J Anaesth* 2014;113:148-56). Tapentadol further enhances the adrenergic component of pain relief and produces less respiratory depression in humans compared to an equi-analgesic dose of oxycodone (*Br J Anaesth* 2017;119:1169-77).

Finally, a recent study focused on the enhancement of the endogenous opioid peptide system by reducing the breakdown of enkephalin. STR-324, an opiorphin analog, inhibits the degradation of met-enkephalin and produces long-term and naloxone-reversible analgesia in a rodent model of postoperative pain, without causing any changes in respiratory rate or oxygen saturation (*Anesthesiology* 2016;125:1017-29). STR-324 showed no safety issues in phase 1 and will soon be tested in a human phase 2 study (https://clinicaltrials.gov/ct2/show/NCT03430232).

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Respiratory stimulants

Since opioids remain important instruments in the treatment of acute pain, and the design and development of an opioid devoid of any respiratory effects is unlikely, another approach seems prudent. The administration of (non-opioid) respiratory stimulants may prevent and overcome respiratory depression during postoperative opioid therapy, without compromising analgesia.

Over the last few years, various stimulants have been tested and many reduce opioid-induced respiratory depression in experimental studies (*Anesthesiology* 2018;128:1027-37; *F1000Res* 2020;9:91).

Examples of stimulants shown to be effective in humans are the ampakines, which activate AMPA receptors in brainstem respiratory centers, and drugs that block potassium channels in the carotid bodies. Both mechanisms produce respiratory stimulation in experimental human studies, but more studies are needed to assess the efficacy of these stimulants in clinical practice. So far, clinical data are sparse.

A radical new approach is the use of a container molecule that reduces respiratory depression by lowering the free bound opioid concentration in plasma following encapsulation of the opioid. In a rodent model of fentanyl-induced respiratory depression, the container molecule calabadion 1 rapidly improved ventilation (*Br J Anaesth* 2020;125(1):e140-e147). This process is similar to the encapsulation of rocuronium by the modified gamma cyclodextrin (sugar ring) sugammadex.

The search for an opioid that produces potent analgesia with limited respiratory effect continues. The first novel opioid with an improved safety profile that could be admitted to the market is oliceridine. Although respiratory events are less likely to occur following treatment with oliceridine, they cannot be eliminated, especially when the drug is overdosed. Hence, continuous monitoring of ventilation is our best approach in detection and prevention of respiratory depression in postoperative patients on opioids (*Br J Anaesth* 2020;125(1):e16-e17). ■