JPPT

## Editorial

# The Balance Between Effective Opioid-Based Pain Management and Patient Safety: Can It Be Achieved?

*Michael D. Reed, PharmD*

*Director, Division of Clinical Pharmacology and Toxicology and Associate Chair, Department of Pediatrics, and Director, the Rebecca D. Considine Research Institute, Akron Children's Hospital, Akron, Ohio, and the College of Medicine, Northeast Ohio Medical University, Rootstown, Ohio*

**INDEX TERMS** analgesia, opioids, pain, respiratory depression

J Pediatr Pharmacol Ther 2013;18(4):264–268

*"Among the remedies which it has pleased Almighty God to give to man to relieve his sufferings, none is so universal and so efficacious as opium."*
*–Thomas Sydenham, 17th century physician*

The prompt and sustained relief of a patient's pain is the goal of all caregivers. Although laudable, this goal is often difficult to achieve as pain is such a highly variable and individualized subjective symptom. Complicating effective pain relief are the multiple factors that influence a patient's perception of pain, both presence and magnitude, including age, emotional state, previous pain episodes, cause of pain, and environment and culture, to mention a few. This variability in a patient's perception and experience of pain underscores the difficulty in attempting to define population-based optimal dosing strategies for analgesic drugs. This challenge is further complicated by the many and sometimes serious undesirable side effects associated with the use of virtually all medications and, particularly, the opioid analgesics. Despite intense ongoing debate as to the best medication, the best regimen, and the best holistic approach to treating a patient's pain, the opiate/opioid analgesics have for centuries remained a mainstay of effective pain treatment programs. The use of opium for medicinal purposes has been linked to as far back as the writings of Theophrastus in the third century BC.[1] The quote attributed to Thomas Sydenham in 1680 captures the essence of the value of the many natural and synthetic analgesic derivatives of opium used for pain relief. There is no question opiate/opioid drugs are the most effective analgesic medications available for the treatment of pain, regardless of cause. As noted above, the challenge is in designing the optimal, individualized, safe, and effective analgesic regimen that may or may not include or require an opioid.[2]

***see related article on page 269***

In this issue of the *Journal*, Whittaker[3] describes the findings of a review of the literature addressing opioid-induced respiratory depression and death in children who received opioid medications postoperatively or following trauma. Respiratory depression evolving to respiratory failure and death is the most feared opioid-induced adverse effect. Whittaker's review outlines 16 comparative trials, and when combined (opioid and comparator non-opioid), the trials provide data from a total of 1613 patients ranging in age from 0.5 to 18 years old; 827 of these subjects were enrolled in codeine-based comparator trials. Not surprisingly, there are very few published randomized controlled trials describing comparative assessments of an opioid versus a non-opioid analgesic in the author's targeted patient population, and there were no reported deaths or serious instances of morbidity in the studies reviewed. Considering the types of studies reviewed, the small numbers of patients involved, and the studies' strictly controlled safety-focused protocol constructs, the conclusion of this review is not surprising either: no increased morbidity or mortality was reported in the opioid-treated patients.[3] However, these conclusions counter well-described pharmacodynamic data, long-

term clinical experience,[4–6] and the more recent data and actions related specifically to codeine[7–10] (i.e., serious and sometimes fatal respiratory depression associated with "routine" and apparently "appropriately dosed" opioid therapy in the pediatric population).

An important finding of Whittaker's review[3] is what was not identified from the literature review and which highlights a profound discordance between clinical practice[4–6] and published clinical experience.[10,11] This clinical conundrum of the apparent lack of serious and even fatal opioid-induced side effects described in controlled trials versus what is observed, although fortunately rare in the clinical setting, underscores the importance of contemporary, active, post-market safety studies and drug-based registries. Adding to this serious conundrum is the lack of any defined epidemiologic data or even a solid consensus on what clinical characteristics may predispose a patient to opioid-induced respiratory depression.[10] The recent "codeine story," or more appropriately, codeine tragedy,[7-10] of conclusively linking codeine to respiratory-related deaths in children was not defined until after more than a century of the drug's prevalent clinical use,[1] reminding us of our responsibility to ensure safe and efficacious drug therapy for children of all ages, with not only new drugs but also old drugs, independent of market tenure. Not until August 2012 did the US Food and Drug Administration (FDA) issue a "boxed warning" and "contraindication" on codeine use, but it is important to note this warning focuses on tonsillectomy and/or adenoidectomy (FDA Drug Safety Communication August 15, 2012).

A number of clinically relevant adverse drug effects are associated with opioid drug administration,[11] with one of the most common resulting from opioid-induced decreases in intestinal motility. Despite our knowledge and understanding of this expected and nearly universal pharmacologic effect, especially with aggressive opioid dosing, we often neglect to institute cathartic therapies early in the treatment course to avoid the associated constipation and possibly even impaction. Polyethylene glycol solutions or mild stimulant cathartics, along with aggressively dosed stool softeners administered early in their treatment course, can often prevent the intestinal discomfort that can be substantial in patients receiving more than 1 day of aggressive opioid therapy. As with constipation, we council our patients about the other well-known and often encountered opioid-associated adverse effects of sedation, nausea, and vomiting. However, it is the fear of opioid-induced respiratory depression and its potential consequences that seems to paralyze care givers from every discipline, skill set, and spectrum of clinical experience and that unfortunately often leads to poorly treated patients and continued patient suffering. A landmark paper addressing this serious therapeutic mismatch appeared in 1973[12] and, unfortunately, more than 40 years later, opioid undertreatment continues. This practice of opioid undertreatment is prevalent and even has its own label, "opiophobia."[13]

Opiophobia is a clinical[2,13,14] and bioethical problem[15] that we can positively impact with our knowledge of molecular pharmacology, integrated with our expertise in opioid pharmacokinetics, pharmacodynamics, and pharmacogenomics. Optimal drug dosing for efficacy and safety and the definition of proper patient monitoring are central to our clinical responsibilities. Clinical pharmacists and clinical pharmacologists alike are those best prepared to determine the individualized analgesic dose regimen that effectively treats a patient's pain and allows the patient to be as awake and cognizant of their surroundings and environment as they desire, devoid of adverse effects. Whittaker's review[3] serves to remind us of the most serious of opioid-associated adverse effects, complementing the findings of other studies,[10,11,16–21] and emphasizing the need for continued vigilance in our patient monitoring for all opioid-induced adverse effects.

The exact molecular basis for opioid-induced respiratory depression in humans is unknown, and much of our knowledge of the probable mechanisms of this drug-induced effect is derived from animals, primarily mice. An abundance of data exists describing the primary endogenous opiate receptors including the mu (μ), kappa (κ), and delta (δ) receptors, which bind the endogenous opiate-like ligands beta-endorphins, enkephalins, and dynorphins.[20] These receptors are found in many locations other than the respiratory center within the central nervous system (CNS), including other CNS locations (i.e., thalamus, anterior cingulated cortex, and chemoreceptors in the brainstem), and relative to respiration, peripheral chemoreceptors linked to the carotid

and aortic bodies and receptors located in the epithelial, submucosal, and muscularis layers of the airways.[10,11,17–21] Binding to opiate receptors activates inhibitory intracellular pathways, closing voltage-gated calcium channels, augmenting potassium efflux, and reducing cyclic adenosine monophosphate (cAMP) production, culminating in reduced neuronal excitability.[17,20] Although still unresolved, it appears that most of the negative respiratory effects caused by opioids are a result of their binding to the μ receptor, the same receptor considered responsible for most of these drugs' desirable analgesic effects. Further complicating opioid drug effects on the respiratory system is the pain itself, as pain stimulates endogenous opiate-like compounds that bind to and modulate the same "opiate" receptors and, an often overlooked but commonly instituted concurrent therapy, supplemental oxygen. Hyperoxia appears to enhance opioid-induced respiratory depressant effects,[22] simply confirming the need for clinicians to carefully monitor the "dose" of all therapies their patient is receiving. The immense number of variables that directly influence safe and effective pain management unfortunately seriously complicate obtaining the much desired and needed data for optimal opioid use.

Following opioid administration, even after small doses, changes in a patient's breathing pattern will be observed. This will occur before and at smaller doses than are necessary to reduce a patient's tidal volume.[18] With increasing opioid dose, the patient's rate of respiration decreases, but, despite the opioid-induced effects on respiratory rate and rhythm, the patient will initially maintain adequate blood oxygen saturation. This maintenance of adequate blood oxygen saturation is probably a result of compensatory changes in the patient's tidal volume and minute ventilation, but once these compensatory processes begin to tire and/or fail, respiratory failure ensues.[11,17,18] Thus, a clinician's sole dependence upon the pulse oximeter as a primary safety measure for monitoring a patient's safety and tolerance of their opioid therapy is questionable. Clearly a multimodal monitoring approach is necessary. Respiratory rate is probably the best single parameter to clinically monitor for impending negative opioid-induced effects on a patient's respiratory status, as it probably provides the greatest predictability of impending respiratory depression and failure. However, waiting for the respiratory rate to achieve some artificially selected low respiratory rate (e.g., ≤8 breaths per minute [BPM]) before action is taken is extremely unwise. When the respiratory rate falls to ≤8 BPM, one should consider this a medical emergency. Close monitoring, including tracking the rhythm and intensity of a patient's breathing and clinical appearance (absence of any signs of cyanosis), and the routine measures of vital signs combined with tracking a patient's respiratory rate with their opioid dosing would appear to provide one approach to achieving a balance between effective opioid therapy and effective safety monitoring.

Whittaker's review[3] is complemented by a recent critique of case reports of opioid-treated pediatric patients ≤12 years of age who were considered to have experienced opioid-induced respiratory depression.[10] Those authors sought to define obvious risk factors for opioid-induced respiratory depression in pediatrics. Twenty-seven children, who either directly for medical purposes or indirectly from their mothers, were identified in 24 published reports. Seven of the 27 children died and 1 experienced ischemic brain injury.[10] As Whittaker does, the authors[10] underscore the paucity of available pediatric data and, in the later review, found their findings to "represent just the tip of the iceberg when estimating the prevalence of OIRD" (opioid-induced respiratory depression). The review by Niesters and colleagues[10] concludes that at a minimum, the presence of renal impairment, cytochrome (CYP) P450 2D6 polymorphisms, and recurrent hypoxic episodes, primarily from tonsillitis and obstructive sleep apnea, are important risk factors for the development of opioid-induced respiratory depression in the pediatric patient. Considering that many opioid drugs and/or their metabolites are substrates for blood–brain-barrier efflux transporters (e.g., P-glycoprotein [P-gP]) drug–drug interactions involving P-gP should also be considered a predisposing risk factor and be monitored and/or avoided whenever possible.[23,24] The publications by Whittaker[3] and Niesters and colleagues[10] highlight the need for controlled trials to address important knowledge gaps[17–21] including incidence rates for opioid-induced respiratory depression, specific opioid drug propensity for inducing adverse effects, comprehensive description of risk factors

predisposing a pediatric patient to developing opioid-induced respiratory depression, opioid-drug safety, and optimal monitoring strategies relative to age, to name a few.

Morton and colleagues[4] report an opioid-induced respiratory rate of 0.13%, captured from their prospective audit of neonates, infants, and children who received opioid infusions and who were managed by a pain team in 18 centers in the United Kingdom and Ireland. Data from 10,726 pediatric patients were collected, and, although their data provide some insight into an incidence of opioid-induced respiratory depression (0.13%), half of the respiratory depression events occurred within the immediate postoperative period, and most of the patients had risk factors often associated with opioid-induced respiratory depression,[4] (i.e., young age and neurodevelopmental and respiratory or cardiac comorbidities).[4–6] The publications by Whittaker[3] and these many others serve to remind us that only when active clinical observation is combined with a detailed understanding of a drug's integrated pharmacokinetic-pharmacodynamic-pharmacogenomic profiles can one determine that important balance between effective opioid therapy and patient safety.

**DISCLOSURE** The author declares no conflicts or financial interest in any product or service mentioned in the manuscript, including grants, equipment, medications, employment, gifts and honoraria.

**ABBREVIATIONS** BPM, breaths per minute; cAMP**,** cyclic adenosine monophosphate; CNS, central nervous system; CYP, cytochrome; OIRD, opioid-induced respiratory depression; P-gP, P-glycoprotein

**CORRESPONDENCE** Michael D. Reed, PharmD, Rebecca D. Considine Research Institute, Akron Children's Hospital, One Perkins Square, Akron, OH 44308-1062, email: mreed@chmca.org.

## REFERENCES

1. Gutstein HB, Akil H. Opioid analgesics. In: Hardman JG, Limbird LE, eds. *Goodman and Gilman's The Pharmacological Basis of Therapeutics*. 10th ed. New York: McGraw-Hill; 569.
2. Morton NS. The pain-free ward: Myth or reality. *Pediatr Anesth*. 2012;22(6):527-529.
3. Whittaker MR. Opioid use and the risk of respiratory depression and death in the pediatric population. *J Pediatr Pharmacol Ther*. 2013;18(4):269-276.
4. Morton NS, Errera A. APA national audit of pediatric opioid infusions. *Pediatr Anesth.* 2010;20(2):119-125.
5. Howard RF, Lloyd-Thomas A, Thomas M, et. el. Nurse-controlled analgesia (NCA) following major surgery in 10,000 patients in a children's hospital. *Pediatr Anesth*. 2010; 20(2):126-134.
6. Anand KJS. Pain panacea for opiophobia in infants? *JAMA.* 2013;309(2):183-184.
7. Koren G, Cairns J, Chtayat D, et al. Pharmacogenetics of morphine poisoning in a breastfed neonate of a codeine prescribed mother. *Lancet.* 2006;368(9536):704.
8. Madadi P, Shirazi F, Walter FG, Koren G. Establishing causality of CNS depression in breastfed infants following maternal codeine use. *Pediatr Drugs.* 2008;10(6):399-404.
9. Kelly LE, Rieder M, van den Anker J, et al. More codeine fatalities after tonsillectomy in North American children. *Pediatrics.* 2012;129(5):e1343-e1347.
10. Niesters M, Overdyk F, Smith T, et al. Opioid-induced respiratory depression in paediatrics: A review of case reports. *Br J Anesth.* 2013;110(2):175-182.
11. Boland J, Boland E, Brooks D. Importance of the correct diagnosis of opioid-induced respiratory depression in adult cancer patients and titration of naloxone. *Clin Med.* 2013;13(2):149-51.
12. Marks RM, Sachar EJ. Undertreatment of medical inpatients with narcotic analgesics. *Ann Intern Med.* 1973;78(2):173-181.
13. Morgan JP. American opiophobia: customary underutilization of opioid analgesics. *Adv Alcohol Subst Abuse.* 1985;5(1-2):163-173.
14. Rhodin A. The rise of opiophobia: is history a barrier to prescribing? *J Pain Palliat Care Pharmacother.* 2006;20(3)31-32.
15. Goldberg DS. On the erroneous conflation of opiophobia and the undertreatment of pain. *Am J Bioeth.* 2010;10(11):20-22.

16. McCrimmon DR, Alheid GF. On the opiate trail of respiratory depression. *Am J Physiol Regul Integr Comp Physiol.* 2003;285(6):R1274-R1275.
17. Dahan A. Respiratory depression with opioids. *J Pain Palliat Care Pharmacother.* 2007;21(1):63-66.
18. Pattinson KTS. Opioids and the control of respiration. *Br J Anesth.* 2008;100:747-58.
19. Dahan A, Aarts L, Smith TW. Incidence, reversal, and prevention of opioid-induced respiratory depression. *Anesthesiology.* 2010;112(1):226-238.
20. Yamanaka T, Sadikot RT. Opioid effect on lungs. *Respirology.* 2013;18(2):255-262.
21. Kimura S, Haji A. Pharmacological strategy for overcoming opioid-induced ventilatory disturbances. *Eur J Pharmacol.* In press.
22. Niesters M, Mahajan RP, Aarts, DahanA. High-inspired oxygen concentration further impairs opioid-induced respiratory depression. *Br J Anaesth.* 2013;110(5):837-841.
23. Tournier N, Decleves X, Saubamea B, et al. Opioid transport by ATP-binding cassette transporters at the blood-brain-barrier: Implications for neuropsychopharmacology. *Curr Pharm Des.* 2011;17(26):2829-2842.
24. Megarbane B, Alhaddad H. P-glycoprotein should be considered as an additional factor contributing to opioid-induced respiratory depression in paediatrics: The buprenorphine example (Letter). *Br J Anaesth.* 2013;110(5):842-843.