

# Primum Non Nocere or How to Resolve Drug-induced Respiratory Depression

## Drug-induced Respiratory Depression and Ampakines

MANY of the drugs used currently by anesthesiologists produce serious side effects, of which respiratory depression is one that is potentially fatal. Although we know that anesthetics and opioids are relatively safe in the hands of anesthesiologists and other well-trained anesthesia specialists (although there are always potential problems), the risks from the use of these drugs are potentially increasing with the growing trend of their use by nonanesthesia caregivers. Consequently, with the increased use and prescription of potent drugs that depress the ventilatory control system and/or increase the probability of an upper airway patency problem, one may expect to see an increase in morbidity and mortality, especially when monitoring is insufficient and/or the caregiver is insufficiently able to diagnose or treat respiratory depression. In the current issue of *ANESTHESIOLOGY*, Ren *et al.*<sup>1</sup> report a study on the effect of an ampakine on propofol-induced respiratory depression and fatal apneas in rodents. They demonstrate elegantly that coadministration of the ampakine CX717 attenuates respiratory depression induced by propofol. This group previously demonstrated in rats that the same ampakine also alleviates opioid-induced respiratory depression (OIRD) and suppression of hypoglossal motoneuron activity that suggest the ability of this drug



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to overcome opioid-induced impairment of airway patency.<sup>2,3</sup> One important feature of the attenuation by CX717 of OIRD is that this effect was not accompanied by a significant reduction in analgesia.<sup>4</sup> Ampakines act at AMPA (amino-3-hydroxy-5-methyl-D-aspartate) receptors. Glutamatergic transmission through AMPA receptors within the brainstem respiratory centers, most importantly the pre-Bötzinger complex, is essential for rhythmogenesis and induction of increased respiratory frequency. Various ampakines that interact with the AMPA receptor have been studied in respiratory systems; the most studied agent is CX717. A major advantage of CX717 is that it is available for human use and has been tested for safety and efficacy in the treatment of human attention deficit hyperactivity disorders and Alzheimer disease. Indeed, a proof of concept study with CX717 in human volunteers demonstrated that a single oral dose of CX717 (1500 mg) reduced

low-dose (plasma concentration 100 ng/ml) alfentanil-induced respiratory depression without significant effects on analgesia.<sup>4</sup> These data suggest that, in patients, the coadministration of an ampakine during exposure to potent opioids and anesthetics such as propofol will be a major step forward in the *prevention* of drug-induced respiratory depression without negating their analgesic (and possibly hypnotic) effects. Evidently, further clinical studies are required showing that CX717 works in patients as well and is not associated with serious side effects.

*Photo: J. P. Rathmell.*

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## Ampakines versus Other Respiratory Stimulants

Apart from ampakines, there are various other nonopioid respiratory stimulants clinically available or under investigation to combat the risks of respiratory depression including potassium channel modulators (such as doxapram), serotonin receptor agonists, and phosphodiesterase inhibitors.<sup>5,6</sup> Although most of these agents are effective in animal models, there is little evidence that, in contrast to the ampakine CX717, the coadministration of these respiratory stimulants provides sufficient reduction of drug-induced respiratory depression in a clinical setting. Hence, we should be cautious to dismiss other approaches to reverse OIRD (including naloxone-reversal). An exception might be GAL-021 an agent that selectively inhibits a sub-type of potassium channel in the carotid bodies and that is currently under investigation and seems able to effectively reverse OIRD in humans.\*

## Who Do We Treat with the Coadministration of Respiratory Stimulants?

An important question is which patients or patient groups are best served by coadministration of a respiratory stimulant? As indicated earlier, we believe that foremost among patients who will benefit from these agents are those being treated with potent anesthetics or opioids by nonanesthesia personnel. Certainly, there is also a group of patients in the postanesthesia care unit or in the ward after surgery that may benefit from these stimulants and possibly even patients being treated in the intensive care unit. Whether these agents are suitable for symptomatic treatment of patients with sleep-related obstructive breathing disorders requires study. Another question is whether these respiratory stimulants are of any use in patients treated at home with potent opioids for chronic (cancer and noncancer) pain? Possibly, but as these patients are often prone to polypharmacy, illicit drug use, and/or alcohol (ab)use, this is an uncertain group. However, taken the high incidence of fatalities in this population from their drug use,<sup>7</sup> further studies on coadministration of a respiratory stimulant such as CX717 are strongly indicated.

## Prevention versus Reversal of Drug-induced Respiratory Depression

A final question is whether these agents will eventually replace the potent opioid-antagonist naloxone in case of established severe OIRD? This is not easily answered, but in some specific circumstances a nonopioid antagonist may be preferable over naloxone, such as in case of opioids with a much greater

affinity for the  $\mu$ -opioid receptor than naloxone (buprenorphine is such an opioid).<sup>5,6</sup> Otherwise, our familiarity with naloxone and its safety make it the primary agent for reversal of acute opioid toxicity and life-threatening respiratory depression.<sup>8</sup> One further note of caution may be illustrated by CX717 in the recent study by Ren *et al.*<sup>1</sup> is that this agent failed to reverse established propofol-induced respiratory depression, although it had been previously shown to reverse established OIRD. Hence, it is likely that an agent required for the reversal of an established drug-induced respiratory depression may have different pharmacological (including specific pharmacokinetic and pharmacodynamic) properties than those required for the prevention of respiratory depression by prior or coadministration.

## Monitoring Remains Key

The list of respiratory stimulants aforementioned is large and possibly a novel agent, such as CX717, will soon be clinically available for the prevention of respiratory depression in our patients. However, before we start comedicated our patients with ampakines or any of the other respiratory stimulants, we will need further evidence that these positive effects are maintained under a variety of circumstances (at high drug dose, in polypharmacy, in patients with obstructive sleep apnea, in the elderly, and so on) and that patient safety is guaranteed. If so, we can begin to envision our ideals for these respiratory stimulants to increase the safety of potent anesthetics and opioids. However, as an ideal world does not exist, coadministration of respiratory stimulants will never relieve us from the obligation to apply optimal patient monitoring during and after the administration of potent modulators of the ventilatory control system and educate nonanesthesia care givers involved in the prescription and administration of opioids, sedatives, and anesthetics. Only then we can state that our intents were to *primum non nocere* (above all, do no harm).

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\* Available at: <http://www.trialregister.nl/trialreg/admin/rctview.asp?TC=3718>. Accessed January 28, 2013.

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## ANESTHESIOLOGY REFLECTIONS FROM THE WOOD LIBRARY-MUSEUM

### From Fish Poison to Merck Picrotoxin



For countless centuries, many fishermen in South and Southeast Asia used a stupefying fish poison derived from the seeds of the fishberry shrub (*Anamirta cocculus*). Picrotoxin, the active ingredient of fishberry seeds, acts as a noncompetitive GABA<sub>A</sub> receptor antagonist. A neurostimulant and occasional convulsant, picrotoxin can block chloride conductance enhanced by GABA<sub>A</sub> receptor agonists such as propofol and barbiturates. Thus, picrotoxin has been employed to investigate anesthetic mechanisms of action at the GABA<sub>A</sub> receptor, as well as used as an antidote for barbiturate toxicity. Manufactured by Merck in Germany, the bottle of picrotoxin (above) is now part of the collection of the Wood Library-Museum. (Copyright © the American Society of Anesthesiologists, Inc.)

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