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Received: 9 December 2020 | Revised: 20 December 2020 | Accepted: 26 December 2020

DOI: 10.1111/jcpt.13362

COMMENTARY

Journal of Clinical Pharmacy and Therapeutics WILEY

The conundrum of polysubstance overdose

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Abstract

What is known and objective: Treating an opioid overdose using an opioid receptor antagonist (such as naloxone) makes mechanistic sense and can be effective. Unfortunately, the majority of current drug overdose deaths involve polysubstance use (i.e., an opioid plus a non-opioid).

Comment: Respiratory depression induced by opioids results from excessive opioid molecules binding to opioid receptors. This effect can be reversed by an opioid receptor antagonist. However, the respiratory depression induced by non-opioid drugs is not due to action at opioid receptors; thus, an opioid receptor antagonist is ineffective in many of these cases. For respiratory depression induced by non-opioids, receptor antagonists are either not available (e.g., for propofol overdose) or there may be attendant risks with their use (e.g., seizures with flumazenil). This gives rise to a need for more effective ways to treat polysubstance overdose.

What is new and conclusion: A new approach to treating opioid-induced respiratory depression due to drug overdose focuses on agents that stimulate respiratory drive rather than competing for opioid receptors. Such an approach is "agnostic" to the cause of the respiratory depression, so might be a potential way to treat polysubstance overdose.

KEYWORDS
overdose, polysubstance use, respiratory depression, respiratory stimulant

1 | WHAT IS KNOWN AND OBJECTIVE

Opioid-induced respiratory depression (OIRD) can occur in or out of the hospital setting and in the right circumstances can be reversed using an opioid receptor antagonist such as naloxone. But receptor antagonists will reverse analgesia as well, limiting their role in peri- and postoperative settings. While naloxone is often advocated by harms-reduction programs to help fight illicit and prescription opioid overdose deaths, this approach is less effective in victims who overdose on high-potency opioids such as fentanyl and fentanyl analogs (e.g., alfentanil, carfentanil, sufentenil, etc.), and it is generally ineffective against non-opioid substances. Furthermore, the American Heart Association recommends using naloxone at the lowest effective doses possible, as it may precipitate withdrawal symptoms, increase blood pressure and raise heart rate. Naloxone can be used against a high dose of a fentanoid, but high doses are required and for a long time.

As an alternative approach to treating respiratory depression, in any setting, are drugs that stimulate respiration. Rather than blocking specific receptors, such drugs should reverse respiratory depression independent of the precipitating cause. We review historical attempts to design such agents, their positive and negative attributes and summarize the newest, ENA-001 (formerly GAL-021). ENA-001 inhibits a special type of potassium channel outside the central nervous system—on the glomus cells of the carotid body. In clinical studies, ENA-001 stimulated respiration,

increased minute ventilation and decreased end-tidal carbon dioxide, at doses that were well tolerated. Thus, it might be an agent capable of restoring respiration in polysubstance overdoses ("agnostic" to the cause).

2 | COMMENT

2.1 | The rising incidence of polysubstance abuse

Polysubstance abuse occurs when illicit drugs, prescription drugs, alcohol or other substances (e.g., opioids, benzodiazepines, marijuana, cocaine, amphetamine, alcohol, etc.), are abused concurrently, and it increases the risk of overdose morbidity and mortality.[1] Polydrug selection may be determined by preference, or dictated by availability of substances.[2] From 2018 to 2019 in the United States, overdoses involving both opioids and amphetamines increased, and in 2019, 23.6% of cocaine, 17.1% of amphetamine, and 18.7% of benzodiazepine overdose involved concurrent opioid use.[3] While most polydrug abusers regularly take two or three substances, a study in the state of Tennessee in the US found that little over 3% use as many as four to nine drugs regularly.[2] An excellent review on the topic has very recently been published by Compton et al. (2020).[4]

About 35 million people worldwide have some form of substance use disorder; more than 19 million in the United States alone.[5] Unfortunately, having substance use disorder for one substance increases the risk of developing a use disorders for other substances.[5] For example, people with cocaine use disorder have a 15-fold increased risk of developing heroin use disorder, and alcohol or nicotine use increases the risk of other substance use disorders.[5] As a result of thinking that use disorders are specific to a certain drug or drug class, polydrug abuse is often overlooked, and often undertreated or inappropriately treated. Emergency medical personnel may not be able to ascertain what substance(s) the overdose victim has taken, even if bystanders are available, because drug users themselves do not always know what they have ingested.

Compounding the problem, not all substances have reversal agents. The widespread use of naloxone to reverse OIRD has saved lives,[6] but naloxone is not without its limitations.[7] In some cases, emergency personnel will administer large amounts of naloxone if the patient is unresponsive, even though naloxone may not be the appropriate agent. While naloxone is generally considered a safe drug, high doses may be associated with dizziness and elevated systolic blood pressure and in some cases is simply not effective in treating the respiratory depression.[6]

Despite the prevalence, there is a paucity of evidence about polysubstance abuse. Many studies actually exclude individuals who take multiple drugs, despite the fact that the practice is so common: 30%–80% of people who use heroin also sometimes use cocaine at the same time[8]; most people who use hydromorphone or oxycodone for recreational purposes also use alcohol, marijuana, cocaine or other drugs if available and affordable, even if they do not take them at the same time; and in a treatment centre in Tennessee, about half of all admissions (48.7%) were for polydrug abuse.[2] The risk factors for polydrug abuse are not thoroughly defined,[2] and the costs are hard to assess, but include emergency medical services (rescue and resuscitation), hospitalization, medical care, rehabilitation services, lost productivity, criminal activity, law enforcement and incarceration, and costs to the foster-care system. It has also been identified as a risk factor in preterm birth.[9] The concurrent use of synthetic cathiones (monoamine alkaloids with effects similar to amphetamines) and other drugs may enhance dependence, neurotoxicity, impaired cognition and emotional responses.[10]

2.2 | Patterns of polydrug abuse

The motivations behind polydrug abuse are many and varied. Some take multiple drugs for an enhanced effect, to reduce withdrawal, or for the sake of experimentation. In general, those who use cocaine and/or amphetamines are more likely to misuse other substances.[11]

Polydrug abuse can exhibit a variety of patterns. In a study of 729 people in five cities in Canada who used illicit opioids and cocaine, 57% said they had taken them concomitantly in the week before the interview. Those who used illicit opioid intravenously had a relatively stable pattern of either co-injecting cocaine (n = 119) or insufflating cocaine (n = 111) at the same time as they took heroin. About 30% of this population used the drugs individually, but sequentially, 35% took them together or within an hour of each other, and 35% took what was available at a given time.[12] In a database study of 356 subjects with diagnosed opioid use disorder, 57.3% were polydrug users (n = 204).[13]

Using the short-form Personality Inventory established by the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5-SF), a sample of 289 subjects who had entered treatment for substance use disorder was evaluated, with the result that four distinct personality types emerged: POLY (for polydrug abusers), COC-HER (for those who used exclusively the combination of cocaine-heroin), ALC (alcoholics) and CAN (cannabis; marijuana). The POLY subjects showed the greatest tendency towards a pathological personality, while CAN subjects had more normalized personality attributes.[14] The most common substances added to opioids by polydrug users are as follows: alcohol, cocaine, benzodiazepines and marijuana. The most common three-drug combinations using opioids include the following: alcohol/cocaine, alcohol/benzodiazepines, cocaine/marijuana, marijuana/benzodiazepines, and cocaine/benzodiazepines.[2] Since those who overdose on opioids may likely have taken other drugs, only reversing the opioid may or may not rescue them.[15]

2.3 | The perioperative setting

OIRD can also occur in the perioperative and postoperative settings, in some cases even days after surgery. When it occurs, naloxone may

be used, but it also reverses the analgesic effect of opioids, leaving the person in pain.[16] Approximately 2% of the surgical population requires some sort of intervention to restore proper respiration.[17] Risk factors for such perioperative respiratory complications include age, sex, body mass index (BMI), comorbidities and concomitantly administered medications.[16] Bariatric surgery patients are at a particularly high risk for breathing complications.[17] Morbidly obese and patients older than 65 are at greater risk for oxygen desaturation.[17] In a comparative study of 178 surgical patients, 12% had at least one episode of oxygen desaturation (defined as SpO_2 < 90%) and 41% had bradypnea (defined as respiratory rate <10) lasting at least 3 min.[17] Even under close clinical supervision, the challenge in these cases is that OIRD may begin precipitously and occur in patients without known risks. When respiratory depression cannot be corrected by verbal stimulation, oxygen therapy, or positive airway pressure, pharmacological intervention in the form of a selective antagonist may be used, such as naloxone (for opioids) or flumazenil (with caution) for benzodiazepines, with concomitant reduction in analgesia or sedation.[16]

Sleep-disordered breathing can also occur in the perioperative period, but since it is often not diagnosed, it often goes untreated.[18] Sedation and anaesthesia can make the airways more susceptible to collapse, and patients with undiagnosed sleep apnoea are at particular risk.[18,19]

2.4 | Carotid bodies and respiratory drive

The carotid bodies in humans are extremely sensitive to even subtle changes in PO_2.[20] It is believed that within the carotid body, an initial transduction step is followed by activation of afferent nerve endings (sensory transmission).[20] Chemoreceptors in the carotid body are categorized as Type I or II. Type I, also known as glomus cells, are neural and express several different types of neurotransmitters. Type II, or sustentacular cells, resemble glial cells. The prevailing theory is that Type I are the initial sites of oxygen sensing and trigger the opposing afferent nerve endings. The neurotransmitters can signal both excitatory and inhibitory effects.[20] If hypoxia is detected, respiration is stimulated and blood pressure increases. While the brainstem controls respiration, input from higher brain structures and the periphery also play roles, as do chemoreceptors in the central nervous system (in nucleus tractus solitarius) that function together with the peripheral carotid bodies.[21]

The carotid bodies respond within seconds to even a small changes by way of specialized potassium channels.[21] BK (big potassium) channels, also known as BK_{Ca}, Maxi-K, slo1 or Kca1.1 respond to the various gases associated with human respiration, namely carbon dioxide, oxygen and carbon monoxide, and decrease in pH. When the BK channels are inhibited, carotid body signalling is stimulated, phrenic nerve activity increases, and respiratory drive is activated. Hypoxia inhibits the potassium channels of the type I glomus cells, which depolarize the cell membranes and allows an influx of calcium ions to enter the cell through voltage-gated calcium channels. This inflow of calcium triggers exocytosis of the excitatory neurotransmitters and produces action potentials that work to stimulate the afferent carotid sinus nerves. When drugs inhibit these calcium channels, both action potentials and the excitability of the channels increase.[22]

Thus, if a respiratory stimulant was added to an opioid or was available for rescue, it might circumvent OIRD by facilitating respiration without reversing analgesia.[23] An interesting historical appraisal of early analeptic use is presented by Wax (1997).[24]

2.5 | Other agents to counteract OIRD by driving respiration

2.5.1 | Doxapram

Doxapram (1-Ethyl-4-(2-morpholinoethyl)-3,3-diphenylpyrrolidin-2-one monohydrochloride) is indicated for induction of respiration in a postoperative patient or to restore respiration in a patient with some form of drug-induced respiratory depression. Doxapram decreases OIRD, and because it does not interact with opioid receptors, does not reduce opioid-associated analgesia.[20] But it is infrequently used because of its side effects, which include dyspnoea, anxiety and elevated blood pressure.

2.5.2 | Almitrine

Almitrine (6-[4-[Bis(4-fluorophenyl)methyl]piperazin-1-yl]-2-*N*,4-*N*-bis(prop-2-enyl)-1,3,5-triazine-2,4-diamine) is a respiratory stimulant that was sometimes used to treat chronic obstructive pulmonary disorder (COPD), although it was never approved for this or any other indication in the United States.[25] By stimulating peripheral chemoreceptors, almitrine has been shown to be effective in reducing OIRD.[25] However, the European Medicines Association, which originally approved almitrine, has withdrawn approval because of side effects of weight loss and neuropathy, and because better treatments for COPD are available.[26]

2.5.3 | AMPAkines

AMPAkines are positive modulators of the α-Amino-3-hydroxy-5-methyl-4-isocazolepropionic acid (AMPA) receptors and act to enhance excitatory glutamatergic neurotransmission. AMPAkines are the first class of peripherally administered drugs that can increase the excitatory monosynaptic brain responses, that is, they facilitate neurotransmission over complex networks.[27] Since rhythmic respiration is thought to be controlled in the pre-Bötzinger complex in the medulla of the brainstem, facilitated by glutamate at AMPA receptors,[28,29] it is speculated that AMPAkines could treat depressed respiration by allosteric modulation of AMPA receptors. In preclinical studies, the AMPAkine CX546 (Cortex Pharmaceuticals, Inc.)

reversed respiratory depression induced by a combination of fentanyl and phenobarbital.[30] Another AMPAkine, CX717, has been reported to be effective in treating fentanyl-, alcohol- and pentobarbital respiratory depression in rats.[31,32] Hypoglossal motoneurons, which maintain upper-airway patency during breathing, are suppressed by opioids; CX717 reverses that.[33] In a human study, CX717 preserved respiration rate to a greater extent than did placebo,[34] but the drug interacted with alfentanil and created feelings of fatigue.

2.5.4 | Serotonin receptor agonists

In preclinical studies, serotonin agonists working at the 5HT1A, 5HT17 and 5HT4a receptors were shown to increase respiratory drive, but studies in humans did not produce the same results.[35]

2.5.5 | Other drugs

Buspirone and mosapride showed effectiveness in preclinical studies, but were not effective in humans.[36,37]

2.6 | ENA-001 (formerly GAL-021)

The adverse effects of almitrine are believed associated with the difluoro-benzhydryl-piperidine that is released during metabolism. Elimination of these groups resulted in ENA-001 (2-[(*N*-Methyl-*N*-methoxy)amino]-4,6-bis(propylamino)-1,3,5-triazine).[15] ENA-001 attenuates OIRD and reverses respiratory depression caused by other agents, such as isoflurane, propofol and midazolam. It has thus been termed a "pharmacologic ventilator".[15] It has a peripheral effect on the BK channels in the carotid bodies. Inhibited potassium conductance causes the carotid bodies to sense hypoxia and acidemia (decrease in pH). ENA-001 acts as a BK potassium channel blocker. In this way, ENA-001 can stimulate respiration without reversing opioid-induced analgesia.[15] The mechanism of ENA-001 is different from that of doxapram and almitrine, which act at a different type of potassium channel (TASK-1 and TASK-3). ENA-001, in contrast, blocks BK_{Ca}-mediated currents in the glomus cells of the carotid body and, in that way, stimulates respiratory drive.[21] In a nine-period, randomized, double-blind, placebo-controlled crossover ascending first-in-human clinical study, 30 volunteers were administered intravenous (IV) infusions of 0.1 to 0.96 mg/kg/h of ENA-001 (GAL-021) and intermediate doses up to 4 h. There were significant differences with ENA-001 versus placebo in increased minute ventilation and decreased end-tidal carbon dioxide. ENA-001 was well tolerated and the adverse events were similar to placebo, except for injection-site irritation.[21]

In two companion studies, IV low-dose and IV high-dose ENA-001 or placebo was administered to treat alfentanil-induced respiratory depression in 12 healthy men. The second of the two studies evaluated the effect of the active agent versus placebo on poikilocapnic ventilation as well as analgesic effect and sedation. In both studies, ENA-001 significantly stimulated respiration compared to placebo, and preserved opioid-induced analgesia, without further increasing sedation levels.[38]

3 | WHAT IS NEW AND CONCLUSION

OIRD occurs in post-surgical patients, among those who take prescription opioids under clinical supervision, and it is a leading driver of opioid-associated mortality among those with opioid use disorder. Among those who depend on opioids for their analgesic benefits, the role of an agnostic respiratory stimulant offers the possibility of treatment of OIRD without the reversal or abrupt cessation of analgesic benefit. Among those who are at risk of illicit opioid overdose, an agnostic respiratory stimulant may be protective even in individuals with polysubstance use disorder.

CONFLICT OF INTEREST

Enalare Therapeutics is developing novel therapies for patients suffering from acute respiratory conditions.

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How to cite this article: Pergolizzi JV, Dahan A, LeQuang JA, Raffa RB. The conundrum of polysubstance overdose. *J Clin Pharm Ther*. 2021;46:1189–1193. https://doi.org/10.1111/jcpt.13362