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From breathtaking to encapsulation: a novel approach to reverse respiratory depression from opioid overdosing

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This editorial accompanies: Calabadion 1 selectively reverses respiratory and central nervous system effects of fentanyl in a rat model by Thevathasan et al., *Br J Anaesth* 2020:125: e140–e147, doi: 10.1016/j.bja.2020.02.019

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The observation that opioids reduce the chemical drive to breathe is well documented in the scientific literature.[1] The reduced ventilatory drive is related to the slowing and eventually silencing of respiratory networks in the brainstem after opioid administration. The influence of drugs in general and opioids in particular on the ventilatory control system has been an understudied topic for a long time. In fact, in recent years we encountered many physicians who prescribed opioids but had no idea of the potentially life-threatening effects of these drugs. The surge in opioid fatalities that we witnessed in the last decade in the USA and other countries including the Netherlands has been a hard lesson learned.[2,3]

Given the problems that opioids cause (apart from slow breathing they induce sedation, muscle rigidity, constipation, hypotension, etc.) scientists have searched for possibilities to reverse the adverse effects of opioids for many years, preferably without reversing analgesia. While the latter is irrelevant when opioid-induced respiratory depression is life-threatening, early and also current studies focus(ed) on *non-opioid* antagonists and stimulants. For example, in 1945 Handley and Ensberg[4] compared amphetamine sulphate with other stimulants, such as ephedrine, caffeine, and coramine, in their ability to antagonise morphine-induced respiratory depression. They concluded that amphetamine was the most effective and fastest drug of all stimulants tested. About 20 yr later, 'pure' opioid antagonists were developed and were rapidly considered the treatment of choice in reversing opioid effects, such as counteracting heroin overdose, reversing the effect of opioids used during anaesthesia, and reversing the effects on the newly born when opioids were given to parturients during labour.[5] Currently several non-opioid respiratory stimulants are being researched to reverse opioid-induced respiratory depression, including drugs that excite the respiratory centres in the brainstem (e.g. ampakines, serotonin receptor agonists, D1 dopamine receptor agonists, phosphodiesterase inhibitors, thyrotropin-releasing hormone, ketamine), and agents that act at the carotid bodies in the bifurcation of the common carotid arteries and that mimic the effect of hypoxia at type 1 chemoreceptor cells (e.g. the BK-channel blocker GAL021, doxapram).[6–8]

In the current issue of the *British Journal of Anaesthesia*, Thevathasan and colleagues[9] present yet another approach to deal with opioid-induced depression. Their method is radically different from earlier methods: they describe a technique to lower the free (unbound) opioid concentration in plasma rather than targeting the opioid receptor with an antagonist or overcoming respiratory depression using a respiratory stimulant. Thevathasan and colleagues[9] studied the ability of calabadion 1 (CLB1) to restore breathing to acceptable levels after administration of fentanyl in a rat model of respiratory

depression. CLB1 is a container molecule that is able to selectively encapsulate ammonium cations such as fentanyl, a popular opioid in anaesthesia and chronic pain management. Container molecules are not new to our specialty. Another example is sugammadex, a modified gamma-cyclodextrin that selectively encapsulates steroidal neuromuscular blocking agents such as rocuronium, enabling rapid reversal of even deep neuromuscular relaxation.[10] Thevathasan and colleagues convincingly show that CLB1 reverses fentanyl-induced respiratory depression, reduces muscle rigidity, another possible cause of respiratory impairment, and accelerates motor function recovery after isoflurane anaesthesia.[9] Importantly, the affinity of CLB1 for morphine and hydromorphone is 100-fold less than its affinity for fentanyl. Consequently, CLB1 does not affect opioids from the 'morphine' class of opioid analgesics.[9] This is an important observation that is relevant to clinical practice. When patients at the end of surgery are antagonised with CLB1, just the fentanyl effect is reversed and the analgesic and respiratory effects of morphine, given during surgery or during recovery, will not be affected. Assuming a higher morphine than fentanyl respiratory safety factor, this indeed may be advantageous to the patient.[11]

The novel approach Thevathasan and colleagues used to reduce fentanyl concentrations in plasma is of great interest and may possibly be used in the near future in postoperative patients. The aim of such treatment would be to reduce unbound fentanyl concentrations at the opioid receptor to concentrations that ensure stable breathing while not concomitantly causing withdrawal symptoms, pain, stress, or agitation. While the opioid antagonist naloxone may be titrated to effect to restore rhythmic breathing activity, it often is associated with such unwanted effects.[1] Additionally, naloxone is short-acting and upon reversal of high-dose potent opioids, renarcotisation can occur. Further studies are evidently needed before CLB1 may be routinely used in humans.[12] Safety, selectivity, and long-term efficacy are just a few of the issues that need to be addressed. The authors previously presented data on another container molecule, calabadion 2 (CLB2). CLB2 was shown to encapsulate ketamine and etomidate.[13] CLB1 has a higher binding affinity for fentanyl than CLB2,[14] and because of its smaller cavity, does not bind ketamine.

Opioids are currently the most effective therapy in the management of moderate to severe acute pain. Any approach that reduces the ability of opioids to cause lethal respiratory instability and apnoea is welcome. Adjuvant therapies with high efficacy are not yet available to us. We therefore remind all of our colleagues that monitoring of ventilation is the best approach in detecting respiratory instability in patients on opioids.[15]

Authors' contributions

Writing of the editorial; commenting on the manuscript; approval of the final version: all authors.

Declaration of interest

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