P-glycoprotein should be considered as an additional factor contributing to opioid-induced respiratory depression in paediatrics: the buprenorphine example

Editor—We read with interest the recent review on opioid-induced respiratory depression (OIRD) in paediatrics by Niesters and colleagues.1 We would like to comment on buprenorphine toxicity in children and suggest an additional OIRD pattern to those identified in this review. Buprenorphine is a partial agonist with high affinity and slow dissociation at the µ-opioid receptors. However, despite its ceiling respiratory effects, poisonings with typical opioid syndrome and asphyxia-related fatalities were attributed to intentional and accidental buprenorphine ingestions in children.2–5 The incidence of such overdoses is increasing in relation to increased prescriptions and availability and also to the similarity to candy of the current formulations. Although exposures to buprenorphine are generally well tolerated in children, significant OIRD may occur in 7–56% of the cases.2–4 Concerns about increased vulnerability of children in comparison with adults has been raised, when linking clinical severity to ingested doses.4–5 Consequently, referral to hospital for a minimum of 6 h observation was recommended for any child ingesting >2 mg buprenorphine and any <2-yr-old child ingesting more than a lick or taste.2–6

Several opioids are substrates of P-glycoprotein (P-gp), a well-known ATP-binding cassette transporter, that alters their pharmacokinetics and subsequently increase their toxicity. Regarding buprenorphine, P-gp plays a key-protective role against its toxicity by allowing the efflux at the blood–brain barrier of norbuprenorphine, its main metabolite that exhibits a potent respiratory depressant activity.6 Therefore, decreased P-gp expression or function may represent a risk factor of OIRD. Consistently, a developmental age-related increase in P-gp activity was reported in newborns and infants.7 Such a mechanism and additional P-gp gene polymorphism or inhibition related to drug–drug interactions may explain children’s vulnerability to opioids as suggested for buprenorphine4–5 and assessed for loperamide used to treat diarrhoea.8 In conclusion, we support Niesters and colleagues’ approach to describe patterns of opioid toxicity in paediatrics, in order to improve OIRD prevention. Based on increasing published data, P-gp’s role in opioid toxicity should be acknowledged and its altered activity considered as an additional pattern leading to OIRD in paediatrics, like for instance with buprenorphine.

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Buprenorphine-induced respiratory depression and involvement of ABCB1 SNPs in opioid-induced respiratory depression in paediatrics

Reply from the authors

Editor—We thank Drs Mégarbane and Alhaddad for their interest in our paper on the description of opioid toxicity in the paediatric patient population aimed at increasing awareness for this important problem and by doing so improving opioid-induced respiratory depression (OIRD) prevention.

Drs Megarbane and Alhaddad raise an important issue, buprenorphine-induced respiratory depression in paediatrics, that was not discussed in our paper. We chose to divide the cases that we retrieved from the literature into four distinct categories and focused in our paper on groups that received opioids for treatment of acute or chronic pain, sedation, or coughing and patients who received opioids via a transfer from their mother (via blood through the placenta or through their mouth from breast milk). Since buprenorphine

Declaration of interest

None declared.
is not an opioid that was prescribed in the retrieved cases, we did not report on buprenorphine-induced respiratory depression. Indeed, buprenorphine-induced respiratory depression was prominently apparent in the fourth category that we labelled ‘non-medical’, in which the opioid intake by the child was inadvertent without any role of a physician. This is a separate category and involves cases in which children are confronted with opioid medication in their home setting. Toxicity occurs when they mistakenly take the drugs for candy and playfully ingest these capsules or tablets. Also other cases are described such as the unintentional transfer of a transdermal patch from an adult to a child while playing together or when putting a child to bed, or the self-medication of the child by an adult without consultation of a physician.

Having said this, we would like to acknowledge that we believe that buprenorphine-induced respiratory depression-related toxicity and mortality is important as it is described more frequently in the literature over recent years. Buprenorphine is a partial μ-opioid receptor agonist that has very high affinity for this receptor. Reversal therefore requires a continuous infusion of high-dose naloxone. And although a ceiling for respiratory depression has been demonstrated for buprenorphine, this has only been studied in adults and possibly may not occur in the (very young) paediatric population. Worldwide, buprenorphine is used in increasing frequency not only for the treatment of pain through a transdermal patch but also for the treatment of opioid dependence. This increased use certainly increases the probability of exposure to children. Hence, awareness of buprenorphine-induced respiratory depression in paediatrics seems therefore warranted.

Another important issue raised by Drs Megarbane and Alhaddad is the involvement of polymorphisms of the gene ABCB1 in OIRD. The product of ABCB1, ABCB1, or P-glycoprotein is one of a series of polymorphic efflux pumps acting at the level of the blood–brain barrier and already present and active in neonates. ABCB1 has several opioids as substrate. For example, Park and colleagues studied three polymorphisms of the ABCB1 gene on fentanyl-induced respiratory depression in a Korean adult population and showed enhanced probability of respiratory depression in some polymorphisms, possibly related to a lesser ability to clear fentanyl from the brain compartment. A similar mechanism may be playing a role in buprenorphine-induced respiratory depression when the active metabolite of buprenorphine accumulates in the brain compartment due to a lesser activity of the efflux pump at the blood–brain barrier. We acknowledge that a lesser function of the efflux pump systems may be associated with an increased probability of OIRD.

We are happy to see that our review of case reports in OIRD in paediatrics leads to awareness and discussion of this very important problem. OIRD should be on our minds, not only when treating infants and children with opioids but also when we are confronted with signs of toxicity in a child that may inadvertently have been exposed to these potent modifiers of the respiratory control system.

### Codeine: the ‘safe’ analgesic?

Editor—We enjoyed reading the article by Niesters and colleagues about opioid-induced respiratory depression (OIRD) in children, and felt that it highlighted an important issue regarding the safety of codeine in this patient population.

It is concerning that within the paediatric category, not only were eight of the 14 case reports related to codeine use, but more importantly four of the six fatalities. Concerns surrounding the use of codeine are not new, but recent fatalities prompted the FDA to issue a caution and a new investigation about its safety.

Interpretation of the data could lead to the assumption that the mortality associated with codeine is a direct result of its frequent prescription. However, the most up-to-date information on hospital opioid prescribing from North America demonstrates morphine use far outweighs that of codeine, and the majority of case reports in Niesters and colleagues’ review in the paediatric category originated from North America and Canada. If the frequency of prescribing was the only cause for these results, the number of morphine-associated OIRD cases should predominate.

Niesters and colleagues succinctly present the safety issue regarding ultra-rapid metabolizers, who are at increased risk of OIRD. Conversely, the large inter-individual variation in codeine metabolism also greatly affects efficacy, with around

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