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.1 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.

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