



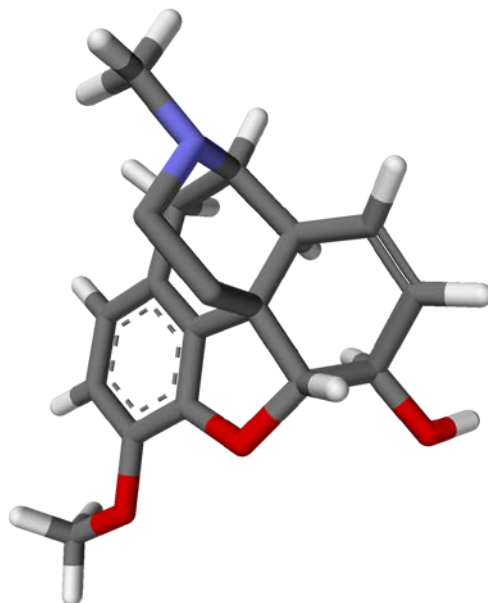
Australian Government
Department of Health
Therapeutic Goods Administration

Codeine use in children and ultra-rapid metabolisers

Pharmacovigilance and Special Access Branch
Safety Review

Version 1.0, October 2015

TGA Health Safety
Regulation



About the Therapeutic Goods Administration (TGA)

The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health, and is responsible for regulating medicines and medical devices.

The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.

The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.

The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.

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Executive summary

This review concerns the safety of use of all codeine-containing products in children and breast-feeding mothers, in the context of genetically determined ultra-rapid metabolism of codeine to morphine. Children who metabolise codeine to morphine rapidly are at a higher risk of accidental morphine overdose, which can lead to respiratory compromise and death. Children are more susceptible to respiratory problems than adults due to their immature airway anatomy. Children who have had a tonsillectomy/adenoidectomy (referred to as adenotonsillectomy throughout this review) for obstructive sleep apnoea may be particularly susceptible to opioid-induced respiratory depression in the post-operative period. Codeine that has been metabolised to morphine can also be ingested by infants through breast milk, causing risk of respiratory depression to infants of ultra-rapid metaboliser mothers who take codeine.

Internationally, deaths have been reported in children with ultra-rapid metabolism who were given codeine for analgesia post adenotonsillectomy, and for other indications. Deaths have also been reported in the breast-fed infants of mothers who are ultra-rapid metabolisers of codeine.

Australian post-market and coronial data do not suggest that cases of respiratory compromise leading to deaths with paediatric codeine use in ultra-rapid metabolisers have occurred in the Australian setting to date. However, the risk to Australians, whilst hard to quantify, is certainly present.

Currently there are inconsistencies in the way the risks associated with ultra-rapid codeine metabolism are addressed across over-the-counter (OTC) and prescription-only codeine products in Australia. This is in contrast to other major jurisdictions including the United States, European Union and Canada. Codeine is a commonly used medication that may be perceived by the Australian public to be very safe, especially in light of its availability in OTC preparations. Therefore the warnings with regard to the potential risks associated with ultra-rapid metabolism of codeine, particularly in children, should be standardised across all codeine products, regardless of schedule.

Evidence from this safety review shows that codeine should not be used in children under the age of 12 for any reason, or in children younger than 18 years of age who have undergone adenotonsillectomy for obstructive sleep apnoea. Additionally, existing warnings contraindicating codeine use by breastfeeding mothers should be made consistent across all codeine-containing products.

TGA recommendations

After reviewing Australian and international data, the TGA recommends the following:

1. Use of codeine in children younger than 12 years of age for any indication should be contraindicated.
2. Use of codeine in children aged 12-18 years should be contraindicated post adenotonsillectomy for obstructive sleep apnoea.
3. Existing warnings contraindicating codeine use by breastfeeding mothers should be made consistent across all codeine-containing products, and warnings should be added to advise against using codeine if known to be an ultra-rapid metaboliser.
4. Health professionals, patients and caregivers should be educated regarding the variability of codeine efficacy, the possibility of ultra-rapid metabolism-related morphine overdose and the signs of such, including respiratory depression.

1 Introduction

This review concerns the safety of use of all codeine-containing products in children (under 18 years of age) and breastfeeding mothers, in the context of genetically determined ultra-rapid metabolism of codeine to morphine.

People who metabolise codeine to morphine ultra-rapidly are at a higher risk of accidental morphine overdose. In people with underlying respiratory compromise and in children (whose airways are more vulnerable than adults) there may be a greater risk of resulting respiratory depression and death.

There are two principal situations in which ultra-rapid metabolism of codeine to morphine may be of concern: where a child is an ultra-rapid metaboliser of codeine and ingests a codeine-containing product, or where the mother of a child is an ultra-rapid metaboliser of codeine and the resulting metabolite (morphine) is ingested by an infant through breast milk. One of the most common scenarios in which the former situation might arise is codeine being given to children for post-operative pain after adenoidectomy and/or tonsillectomy (referred to throughout this review as 'adenotonsillectomy').

The recognition of a series of deaths in children who were given codeine for analgesia post adenotonsillectomy in the United States (US) led to contraindication of its use for analgesia in children aged less than 18 post adenotonsillectomy in the US and subsequently in Europe. Europe additionally recommends against its use in children younger than 18 for analgesia unless not relieved by other medicines or in children younger than 12 for analgesia at all. Canada recommends against the use of codeine in children younger than 12 whether for pain or cough.

This safety review was commenced by the TGA after the publication of a Drug Safety Communication by the United States of America (USA) Food and Drug Administration (FDA) entitled *Safety review update of codeine use in children; new Boxed Warning and Contraindication on use after tonsillectomy and/or adenoidectomy* in February 2013.¹ It includes discussion of international safety review findings and related regulatory activity, consideration of the current regulation of codeine in Australia, assessment of the risk within the Australian context and recommendations for regulatory action in Australia.

2 Background

2.1 Codeine metabolism and CYP2D6 genotype

Since codeine has a very low affinity for opioid receptors, its analgesic effect is dependent on its conversion to morphine through the cytochrome P-450 enzyme 2D6 (CYP2D6), which catalyses the conversion of codeine into morphine. Morphine is then conjugated with glucuronic acid by glucuronidases to form two main morphine metabolites, the inactive morphine-3-glucuronide (M3G) and the active morphine-6-glucuronide (M6G). The gene that encodes the CYP2D6 enzyme is highly polymorphic, and the resultant variability in inter-individual response to codeine analgesia has been well described in both the medical literature and clinical experience.²

CYP2D6 allele haplotypes are named as CYP2D6*X, following a system devised in the mid-1990s³ where X is an alphanumeric tag specific to each allele. CYP2D6 diplotypes are described with a forward slash dividing the two alphanumeric haplotype tags, so that CYP2D6*1/*1 describes a genotype where both chromosomes carry the CYP2D6*1 allele. Also known as wild-type, or WT, this is the most common variant of CYP2D6, and is considered fully functional.⁴ Allele CYP2D6*2 also has normal function, however increased enzyme activity is seen in

CYP2D6*1XN and CYP2D6*2XN variants, where “N” represents the multiplication of the allele. The remainder of the known alleles are partial or non-functioning variants.

Genetic polymorphism of CYP2D6 can also be described in terms of four different categories of phenotype; ultra-rapid metabolism (UM), extensive metabolism (EM), intermediate metabolism (IM) and poor metabolism (PM). The phenotypes are determined from the efficiency of metabolism observed in pharmacokinetic studies. Multiple different genotypes/diplotypes can result in the same phenotype (Table 1).⁵ Due to the genetic polymorphism of CYP2D6, UM individuals can metabolise codeine to morphine much faster, resulting in higher than expected morphine blood levels after a codeine dose.²

Table 1. Recommended dosing of codeine by CYP2D6 phenotype

Likely phenotype (prevalence estimates)	Activity score	Genotypes	Examples of diplotypes	Implications for codeine metabolism	Recommendations for codeine therapy
Ultra-rapid metabolism (~1-2% of patients)	>2.0	An individual carrying more than two copies of functional alleles	*1/*1xN, *1/*2xN	Increased formation of morphine leading to higher risk of toxicity	Avoid codeine use due to potential for toxicity.
Extensive metabolism (~77-92% of patients)	1.0-2.0	An individual carrying two alleles encoding full or reduced function, or one full function allele and one non-functional or reduced-function allele	*1/*1, *1/*2, *2/*2, *1/*41, *1/*4, *2/*5, *10/*10	Normal morphine formation	Use label recommended age or weight-specific dosing.
Intermediate metabolism (~2-11% of patients)	0.5	An individual carrying one reduced and one non-functional allele	*4/*10, *5/*41	Reduced morphine formation	Use label recommended age or weight-specific dosing. If no response, consider alternative analgesics such as morphine or non-opioid.
Poor metabolism (~5-10% of patients)	0	An individual carrying no functional alleles	*4/*4, *4/*5, *5/*5, *4/*6	Greatly reduced morphine formation leading to insufficient pain relief	Avoid codeine use due to lack of efficacy.

Table 1 has been adapted from Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines for cytochrome P450 2D6 (CYP2D6) genotype and codeine therapy: 2014 Update.⁵

It is difficult to predict the phenotypic expression of ultra-rapid CYP2D6 metabolism from genotype alone: people with genotypes that are expected to express an EM phenotype may, in

some cases, convert codeine to morphine at levels similar to those seen in an UM phenotype. Genetic tests for codeine metabolism are therefore of limited value in predicting ultra-rapid metabolism, and such tests are not widely accessible outside of the research setting.² For these reasons, routine genotyping prior to receiving codeine has not been recommended (as discussed below), and no suitable test is currently included in the Medicare Benefits Schedule.

The prevalence of codeine ultra-rapid metabolism by CYP2D6 in children is not known, but is assumed to be similar to that reported in adults. The prevalence of UM is estimated to be 1% in those of Chinese, Japanese and Hispanic descent, 3% in African Americans and 1%–10% in Caucasians. The highest prevalence (16%–28%) occurs in the North African, Ethiopian and Arab populations.²

2.2 Adenotonsillectomy for obstructive sleep apnoea in paediatrics

Adenotonsillectomy is commonly performed in children as a treatment for obstructive sleep apnoea (OSA).⁶ Whilst generally, symptoms and signs including oxygen saturation improve dramatically post-surgery, some children experience persistent sleep disordered breathing, most consistently associated with severity of pre-operative OSA.⁷ The failure of oxygen saturation rates to improve the day after surgery in paediatric patients undergoing adenotonsillectomy for obstructive sleep apnoea (OSA) may be explained by a number of possible causes, including residual anaesthetic effects, post-surgical oedema/inflammation, and the increased airway compliance and decreased airway neuromuscular function seen in paediatric OSA patients. However, studies have reported cases in which apnoea rates rose dramatically the night after surgery and it is possible that prescribed opioids may have contributed to respiratory depression in the observed cases.⁸ It has been previously shown that the recurrent hypoxemia seen in OSA is associated with increased sensitivity to morphine,⁹ and a recent study by the American Academy of Pediatrics in 91 children demonstrated a dramatic difference between oxygen desaturation on the first postoperative night in children assigned to morphine analgesia compared to ibuprofen.¹⁰ Of the children assigned to morphine, 14 per cent showed improvement, whilst 68 per cent of the children assigned to ibuprofen showed improvement. The number of desaturation events in the morphine group increased substantially, with an average increase of 11.17 ± 15.02 desaturation events per hour ($P < .01$). No differences were seen in efficacy of analgesia, bleeding or adverse drug reactions.

3 International regulatory action

3.1 FDA

3.1.1 FDA actions relating to ultra-rapid metabolism of codeine in the context of breast feeding

In the USA, concerns over ultra-rapid metabolism of codeine to morphine and safety for children have arisen on two separate occasions: firstly in the context of breastfeeding infants, followed by the more recent concern with respect to children being given codeine post-adenotonsillectomy.¹¹

In August 2007, the FDA published a press release and public health advisory *Use of Codeine By Some Breastfeeding Mothers May Lead To Life-Threatening Side Effects In Nursing Babies* and the labelling of codeine-containing products was updated to describe this risk.¹²

3.1.2 FDA safety review of the use of codeine in children post-adenotonsillectomy

In August 2012, the FDA began a comprehensive safety review of the use of codeine in children post-adenotonsillectomy due to growing concerns and recognition of a trend in reports of cases of deaths and serious adverse events in this setting where there was evidence to suggest ultra-rapid metabolism of codeine.¹³ Review was also undertaken to identify any additional cases of overdose or death in children taking codeine in other treatment settings.

The review found 13 paediatric cases in the FDA's Adverse Event Reporting System (AERS) database between 1969 and mid-2012 of overdose and/or death associated with codeine.¹¹ Six cases were not literature cases, and did not report CYP2D6 status. The information available for these six cases is summarised in Table 2.

Table 2. Characteristics of six paediatric cases of death identified in the FDA Adverse Event Reporting System involving codeine but where CYP2D6 status was not reported

Characteristic	Statistics
Age	Mean: 7.5 years. Median: 3 years. Range: 2-9 years
Sex	Male: 2 cases. Female: 3 cases. Unknown: 1 case
Report year	2003: 1 case. 2005: 1 case. 2006: 1 case. 2010: 2 cases. Unknown: 1 case
Country of occurrence	United States: 4 cases. Foreign: 1 case. Unknown: 1 case
Report type	Expedited: all 6 cases
Indication for use	Pain post adenotonsillectomy: 3 cases. Oral aphthae: 1 case. Cough: 1 case. Unknown: 1 case
Dose (reported in 3/6 cases)	Mean: 0.6 mg/kg/dose. Range: 0.4-1 mg/kg/dose
Time to onset (reported in 5/6 cases)	Mean: 39 hours. Median: 48 hours. Range: 1-48 hours

Table 2 has been adapted from an FDA Pediatric Advisory Committee briefing document titled *Death and respiratory arrest related to ultra-rapid metabolism of codeine to morphine*.¹¹

The remaining seven of the 13 cases identified in the FDA's AERS database were also described in the medical literature (across four articles)^{14,15,16,17} and the details of these cases are described in Appendix 1. CYP2D6 metaboliser status (based on genotype) in four of the seven children was found to be UM, whilst the other three were EM. The presence of patients with genotypes expected to be associated with EM in this group of cases of deaths illustrates that the CYP2D6 phenotypes can't be fully predicted from CYP2D6 genotypes. Overlap of the EM-predictive genotype with the UM phenotype may result in underestimation of the true prevalence of ultra-rapid metabolism in the community.

Overall, the patients described in the cases identified in the FDA's AERS database search ranged in age from 21 months to nine years. Eleven of the 13 cases occurred in the setting of adenotonsillectomy (8 cases) or respiratory tract infection (3 cases), and most of them also appeared to involve appropriate doses of codeine. The FDA review of the AERS database did not identify robust cases of unexplainable or non-confounded death or opioid toxicity following use of oxycodone, hydrocodone, or morphine in paediatric patients.¹¹

In late 2011, the Patient Safety and Quality Improvement Committee of the American Academy of Otolaryngology – Head and Neck Surgery (AAO-HNS) was also becoming concerned about adverse events, particularly respiratory depression, after adenotonsillectomy.¹⁸ Their Patient Safety and Quality Improvement Committee conducted its own study of mortality and major morbidity following tonsillectomy and/or adenoidectomy, the findings of which were also considered by the FDA in their safety review.¹⁹ Limited information was available from these AAO-HNS cases; however, one 3-year-old patient with obstructive sleep apnoea who died after adenotonsillectomy was confirmed as being an ultra-rapid metaboliser, and one 12-year-old patient with OSA who died after adenotonsillectomy was suspected of being an ultra-rapid metaboliser after high blood morphine levels were identified on autopsy.

The AAO-HNS study consisted of a survey of their physician membership regarding negative outcomes following tonsillectomy, such as death or permanent disability. Eight paediatric cases were identified as being related to narcotic medications.¹¹ These cases had the following characteristics recorded:

- Indication (8 of 8): OSA (7), chronic tonsillitis (1)
- Underlying condition (4 of 8): Down's syndrome (3), neurologic disorder (1)
- Outcome (8 of 8): deaths (7), anoxic brain injury (1)
- UM status (2 of 8): suspected due to high morphine levels (1), confirmed in post-mortem exam (1)

Dispensing patterns were considered by the FDA in order to consider the size of the patient group who may be affected by the risk. Using data extracted in September of 2012 from the Total Patient Tracker (health software made by information technology company IMS Health), the FDA estimated the number of paediatric patients receiving dispensed opioids in 2011.¹¹ The estimates for codeine usage in conjunction with paracetamol were:

- 0-1 year olds approx. 100,000 patients
- 2-5 year olds approx. 350,000 patients
- 6-10 year olds approx. 500,000 patients
- 11-17 year olds approx. 800,000 patients

The most common code associated with the use of codeine/acetaminophen in all age groups was "Surgery Follow-Up" (ICD-9 code V67.0). The most clearly documented cases of death or respiratory arrest after codeine treatment in children with ultra-rapid metabolism involved patients who had just undergone adenotonsillectomy.

3.1.3 FDA decision and regulatory action

As a result of the FDA safety review, extensive labelling changes for all codeine-containing products in the USA were undertaken, with additional labelling changes to reinforce the previously noted FDA concerns over codeine use in breastfeeding mothers. The changes were

applied to all codeine-containing products regardless of indication (pain, cough/cold), and can be summarised as follows.

- The addition of a Boxed Warning regarding ultra-rapid metabolism:

“WARNING: Death Related to Ultra-Rapid Metabolism of Codeine to Morphine: Respiratory depression and death have occurred in children who received codeine following tonsillectomy and/or adenoidectomy and had evidence of being ultra-rapid metabolisers of codeine due to a CYP2D6 polymorphism.”
- A new contraindication for codeine use in children post- tonsillectomy and/or adenoidectomy:

“Codeine-containing products are contraindicated for postoperative pain management in children who have undergone tonsillectomy and/or adenoidectomy.”
- Modifications to Warnings, Pediatric Use, Patient Counselling Information sections of the labelling documents. These sections discuss rapid metabolisers, the above mentioned warnings in children for tonsillectomy and/or adenoidectomy and the risks of use in breastfeeding mothers.

Routine genotyping prior to receiving codeine was considered but not recommended by the FDA review for several reasons.

- Extensive metabolisers (EM) may, in some cases, convert codeine to morphine at levels similar to ultra-rapid metabolisers (UM).
- The positive predictive value of the test is likely low, thus the number needed to screen in order to prevent one event is very high.
- Genotyping may be difficult to implement because preoperative lab tests are not routinely obtained before adenotonsillectomy.

Following notification from the FDA, other international medicine safety regulators have carried out reviews of this issue, and taken action as outlined below.

3.2 European Medicines Agency

On 14 June 2013, the Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicines Agency (EMA) published the Committee’s recommended risk minimisation measures to ensure that the risk:benefit ratio for children taking codeine is upheld.

3.2.1 PRAC safety review

An extensive review of the literature and post-market data had been conducted by the PRAC regarding codeine use both in children and in breastfeeding mothers.²⁰ The PRAC noted the lack of pharmacokinetic and pharmacodynamic data for children amongst the body of evidence, particularly in relation to the effect of CYP2D6 polymorphism on efficacy.

The data considered in the PRAC review included:

- The cases considered by the FDA from the international literature.
- An additional 14 fatal adverse event cases that were identified in the EMA’s EudraVigilance adverse event report system where codeine was used for analgesia in paediatric patients (though most of these are poorly documented).
 - Seven of the 14 cases were between two and six years old.

- Five of the 14 cases were not relevant due to improper dosing or alternative cause of death. In the remaining nine cases, age ranged from 2-17 years. Of the same nine cases, four recorded toxic morphine levels, and in two cases children “appeared to receive codeine in the range of the recommended dose”. It is not clear from the EMA report document whether these two cases were also cases in which toxic morphine levels were recorded.
- Genotype/phenotype was not available for any of the cases, and indications for use were adenotonsillectomy (2 cases), headache (1 case), sporting injury (1 case), aphthous stomatitis (1 case) and unknown (4 cases).
- Cases associated with codeine exposure through breastfeeding:
 - Koren G et al (2006)²¹, in which oral codeine 30mg and paracetamol 500mg used twice daily for episiotomy pain by a mother later found to be an UM resulted in respiratory depression and death of a 13-day-old infant. Assayed breast milk morphine levels were about four times higher than the expected range for a higher and more frequent codeine dose.
 - Madadi P et al (2009)²² conducted a review of 72 mother-child pairs which showed that 17 (24%) breastfed infants exhibited CNS depression while their mothers used codeine. Three of the cases (11.8%) were found to be UMs. One was asymptomatic, and the second was already described above (Koren G et al 2006). In the third UM case, 120 mg/day codeine was taken for severe muscle pain after childbirth by the mother. The breastfed infant was described as “extremely drowsy and feeding poorly”. A complete switch to formula feeding was undertaken over the first 7 days post-delivery (due to maternal exhaustion and poor feeding), and a complete reversal of the infant’s symptoms was noted in the following days.
 - Lam et al (2012) counted a total of 44 cases reported in the literature of neonatal respiratory depression in breastfed infants of mothers who were using codeine.²³
 - Davis et al (1985)²⁴ noted neonatal apnoea attacks occurring in four near-term breastfed infants 4–6 days after the mothers commenced taking 60 mg codeine every 4-6 hours.
 - Naumburg et al (1987)²⁵ reported that, of a series of 12 full term infants between age 0.5 and 7 days who had unexplained episodes of apnoea, bradycardia and/or cyanosis in hospital, 10 of them had been exposed to opioids through breast milk. In six cases the opioid was codeine.
 - Willmann A et al (2009)²⁶ conducted a quantitative mechanistic modelling study to study risk to the breast-fed neonate from maternal codeine use. Their physiologically-based PK simulations showed accumulation of morphine in the neonate was determined critically by maternal codeine and morphine clearances, and neonatal morphine clearance. They also showed that toxic morphine levels could be reached within four days after repeated codeine dosing to the mother, given the low neonatal capacity for morphine elimination. Both EM and UM genotypes conferred comparable risk of opioid poisoning to the neonate.
 - Nezvalová-Henriksen K et al (2011)²⁷ examined risk of transplacental morphine transfer in a large population-based cohort study of 2,666 women who used codeine during pregnancy versus 65,316 who used no opioids during pregnancy. Neither infant survival nor congenital malformation rate were affected by maternal codeine intake during pregnancy.

- Neisters et al (2012)²⁸ conducted a case report review and identified 27 cases described in 24 reports of opioid-induced respiratory depression (OIRD) in children aged 12 years or younger receiving opioids, either directly for medical reasons or indirectly via their mother. They all required naloxone, with or without tracheal intubation and/or resuscitation. Seven of the cases were fatal. Four patterns were identified in the dataset: iatrogenic overdose (8 cases), morphine administration to patients with renal impairment (3 cases), codeine use in UMs (7 cases) and opioid use post adenotonsillectomy for OSA/recurrent tonsillitis (5 cases).

In the last of the studies listed above, the authors (Neisters et al) noted that publication bias probably causes underestimation of the true number of cases that occurs:

“The retrieved cases describe only very serious cases of OIRD that without an intervention would have resulted in the death of all 28 (sic) children. Clearly, this is related to the fact that case reports are published based on the policy of the editorial team, and consequently, the majority of cases do not reach the medical literature. Bias of the editorial team towards the more severe cases but also the lack of will of the physician to publish their ‘failures’ and ‘complications’ of opioid therapy will restrict publication.”

3.2.2 PRAC decision and regulatory action

Having assessed all the available data, the PRAC concluded that the reported cases of respiratory depression with codeine indicate that children below 12 years of age may be at increased risk of morphine side effects. In addition, they concluded that the limited data on the effectiveness of codeine for pain relief in children suggest that the effect of codeine on pain is not significantly better than non-opioid painkillers such as paracetamol or ibuprofen.

The recommendations were endorsed by the Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh) on 28 June 2013 for direct implementation by Member States.²⁹ The recommendations were:

- Codeine-containing medicines should only be used to treat acute (short lived) moderate pain in children above 12 years of age, and only if it cannot be relieved by other painkillers such as paracetamol or ibuprofen, because of the risk of respiratory depression associated with codeine use.
- Codeine should not be used at all in children (aged below 18 years) who undergo surgery for the removal of the tonsils or adenoids to treat obstructive sleep apnoea (OSA), as these patients are more susceptible to respiratory problems.
- The prescribing information should carry a warning that children with conditions associated with breathing problems should not use codeine.
- The PRAC further recommended that, as the risk of side effects with codeine may also apply to adults, codeine should not be used in people of any age who are known to be ultra-rapid metabolisers nor in breastfeeding mothers, because codeine can pass to the baby through breast milk. The prescribing information for codeine should also include general information for healthcare professionals, patients and carers on the risk of morphine side effects with codeine, and how to recognise their symptoms.

The EMA restrictions have only been applied to codeine-containing products and do not apply to dihydrocodeine because dihydrocodeine was not included in the PRAC review. In the US the FDA boxed warning and label changes were imposed on all codeine-containing products and to a dihydrocodeine bitartrate, aspirin and caffeine product (SynalgosDC) and generics. However, CYP2D6 phenotype has been previously shown to have no major impact on opioid receptor-mediated effects of a single 60 mg dihydrocodeine dose.³⁰

In March 2015, the EMA also recommended restrictions on the use of codeine-containing medicines for cough and cold in children, including contraindication in children under 12, and caution in children 12-18 years old with breathing problems.³¹

3.3 Health Canada

Health Canada released a warning on its website (June 6th, 2013) stating that they have reviewed the safety of prescription pain and cough medications containing codeine and are no longer recommending their use in children less than 12 years of age. They stated that the use of codeine by UMs can lead to unexpected morphine overdose, and that healthcare professionals and consumers should seek alternatives to codeine for the management of mild to moderate pain or cough in children less than 12 years of age.³²

3.4 Medsafe (New Zealand)

Medsafe also released a web statement (revised 31st May, 2013) warning of the risk to rapid metabolisers.³³ Recently, the Medicines Adverse Reactions Committee (MARC) reviewed the results of Medsafe's review of codeine use in cough and cold medicines, and agreed that "the use of codeine-containing medicines for cough and cold in children should be restricted to those aged 12 years and over."³⁴

4 Codeine in Australia

Codeine is an ingredient in a wide variety of therapeutic products in Australia and is used as an antitussive or as an analgesic.

4.1 Regulation under the Poisons Standard 2015

Regulation of codeine-containing products in Australia is complex as the products fall under four different schedules under the most recent Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP) – SUSMP 6, also known as the Poisons Standard 2015.³⁵ As at 29 January 2015, there were 317 entries in the Australian Register of Therapeutic Goods (ARTG) for products that contain codeine: 70 listings for Schedule 2 (S2) products, 223 listings for Schedule (S3) products, 13 listings for Schedule (S4) products and 11 listings for Schedule (S8) products.³⁶

4.1.1 Scheduling of codeine

The entries relevant to codeine under the schedules are as follows.

Schedule 2

"CODEINE in preparations for the treatment of coughs and colds when:

- a) not combined with any other opiate substance;
- b) compounded with one or more other therapeutically active substances, of which at least one is phenylephrine and not more than one is an analgesic substance:
 - i) in divided preparations containing 10 mg or less of codeine per dosage unit;
or
 - ii) in undivided preparations containing 0.25 per cent or less of codeine;

- c) labelled with a recommended daily dose not exceeding 60 mg of codeine; and
- d) in packs containing not more than 6 days' supply at the maximum dose recommended on the label."

Schedule 3

"CODEINE when:

- a) not combined with any other opiate substance;
- b) compounded with one or more other therapeutically active substances, of which not more than one is an analgesic substance:
 - i) in divided preparations containing 12 mg or less of codeine per dosage unit;
 - or
 - ii) in undivided preparations containing 0.25 per cent or less of codeine;
- c) labelled with a recommended daily dose not exceeding 100 mg of codeine; and
- d) in packs containing not more than 5 days' of supply at the maximum dose recommended on the label,
except when included in Schedule 2."

Schedule 4

"CODEINE when compounded with one or more other therapeutically active substances:

- a) in divided preparations containing 30 mg or less of codeine per dosage unit; or
- b) in undivided preparations containing 1 per cent or less of codeine,
except when included in Schedule 2 or 3."

Schedule 8

"CODEINE except when included in Schedule 2, 3 or 4."

4.1.2 Mandatory label sedation warning

Additional information in the appendices to the SUSMP (Appendix K) mandates that codeine-containing products are to be labelled with a sedation warning. Any of three statements can be chosen for use as the label sedation warning, and these are specified in Appendix F Part 1 as follows.

Statement 39: This medication may cause drowsiness. If affected do not drive a vehicle or operate machinery. Avoid alcohol.

Statement 40: This medication may cause drowsiness and may increase the effects of alcohol. If affected do not drive a motor vehicle or operate machinery.

Statement 90: This preparation is to aid sleep. Drowsiness may continue the following day. If affected do not drive or operate machinery. Avoid alcohol.

4.2 Over the counter (S2 and S3) codeine-containing products

As laid out by the Poisons Standard, antitussive products containing codeine fall under S2, whilst all analgesic codeine-containing products are S3 or above. This section discusses the mechanisms of regulation that over-the-counter (OTC; S3 or below) codeine-containing products are subject to.

4.2.1 Required Advisory Statements for Medicine Labels

The labels of over-the-counter medicines are often required to contain particular advisory statements about specific risks related to use of the medicines. These advisory statements are compiled into the Required Advisory Statements for Medicine Labels (RASML).³⁷

The RASML is registered as a Specification titled *Medicines Advisory Statements Specification 2014* on the Federal Register of Legislative Instruments.³⁸ The Specification is a legislative instrument under section 3(5A) of the *Therapeutic Goods Act 1989* ('the Act'). Therapeutic Goods Order No. 69D [TGO 69], an Order under section 10 of the Act, is the amendment to the Labelling order that makes it mandatory for medicine labels to include any requirements as specified in the Medicines Advisory Statements Specification that are relevant to the medicine from time to time. The Specification and TGO 69D commenced on 12 June 2014. To allow for a transition period for sponsors to comply with the updated requirements, the Specification includes two versions of the RASML ('RASML No. 1' and 'RASML No. 2') as Schedule 1 and Schedule 2 to the Specifications, respectively. RASML No. 2 is the most up to date version, and will come into effect on 12 December 2015.

RASML No. 2 contains a number of labelling requirements pertaining to codeine (and dihydrocodeine), as outlined in Table 3.

Table 3. Labelling requirements in RASML 2 that pertain to codeine (and dihydrocodeine)

Entry	Circumstances	Label statements required
Codeine (Entry 1 of 2)	In oral preparations indicated for cough, cold or flu which DO NOT include dosage instructions for children aged under 12 years	<ul style="list-style-type: none"> • Do not give to children under 12 years of age.
Codeine (Entry 2 of 2)	In oral preparations indicated for cough, cold or flu which include dosage instructions for children aged from 'x' to 11 years (where 'x' is 6, 7, 8, 9, 10 or 11)	<ul style="list-style-type: none"> • Do not give to children under 'x' years of age. <ul style="list-style-type: none"> - either (if 'x' is 11) <ul style="list-style-type: none"> ▪ Do not give to children aged 11 years, except on the advice of a doctor, pharmacist or nurse practitioner. - or (if 'x' is 6, 7, 8, 9 or 10) <ul style="list-style-type: none"> ▪ Do not give to children aged between 'x' and 11 years of age, except on the advice of a doctor, pharmacist or nurse practitioner.

These entries in RASML were brought about due to a review of the risk-benefit ratio of cough and cold preparations for children that was completed by the TGA in 2012.³⁹ Similar international reviews had raised concerns that efficacy data was not strong enough to justify risk for a number of ingredients seen in these medicines, including codeine and antihistamines. The TGA review recommended that children under the age of 6 should not be treated with

codeine for cough. As a result, sponsors of all cough and cold products containing codeine were mandated to remove any dosing instructions that allowed administration to children under the age of 6 years and the above entries regarding codeine were added to the RASML. The result of these actions was that codeine-containing OTC medicines indicated for cough and cold (i.e. S2 medicines) are not recommended for use in children under 6, and are to be used in children aged 6-11 years only on the advice of a doctor, pharmacist or nurse practitioner.

The RASML does not, however, contain any requirements for specific labelling of codeine-containing products for any other indication, and so these restrictions only affect S2 and S3 codeine-containing products indicated for coughs and colds.

4.2.2 Australian regulatory guidelines for over-the-counter medicines

To ensure that future registration applications for OTC products also adhere to the recommendations regarding codeine-containing cough and cold medicines in children made by the 2012 review, text was added to Appendix 5 of the Australian regulatory guidelines for over-the-counter medicines (ARGOM) document: *Guidelines on OTC application for specific substances*.⁴⁰ The ARGOM guidelines have been prepared to guide sponsors in the preparation of applications that are in keeping with the TGA's stance on particular issues, encouraging a more efficient registration process.

The added text regarding codeine is as follows.

"A review by the TGA of OTC cough and cold medicines for children aged 2-12 years has concluded that, in light of the current lack of evidence of efficacy and the historical profile of adverse drug reactions (ADRs) in Australia and overseas, it is likely that the risks associated with the use of cough and cold preparations in children outweigh the benefits for children below the age of 6 years. There is currently a lack of evidence of efficacy for cough and cold medicines in children aged 6 to 12 years of age. Additionally, the historical profile of adverse drug reactions indicates that there are potential risks involved in use of these medicines in that age group.

"Following this review, the TGA has agreed that OTC cough and cold products containing any of the following ingredients should not be used for the treatment of children under 6 years of age, and should only be administered to children aged 6-11 years on the advice of a doctor, pharmacist or nurse practitioner."

The list of ingredients following that section of text includes codeine, dihydrocodeine and pholcodine. Again, however, these guidelines specify that the risk outweighs the potential benefit when used as an antitussive, and so these restrictions do not provide protection to children who may be given codeine as an analgesic.

4.2.3 Product Information and Consumer Medicine Information

Product Information (PI) and Consumer Medicine Information (CMI) documents are used by the TGA to provide safety information to pharmacists/prescribers and consumers of medicines respectively. S2 products are not required to have these documents, but S3 products are required to have both.

In 2010, codeine products for analgesia were rescheduled from S2 to S3. Some of these products did not have a PI, being S2 previously, and some were originally introduced into the ARTG by the "grandfather" process, meaning they had not been fully evaluated previously by the TGA. As a result, there were a large number of products which needed to introduce new PI documents at the same time. In order to assist sponsors and to encourage consistency between products, the TGA and Australian Self Medication Industry (ASMI) developed a set of basic template information documents ("core" PI and CMI documents)⁴¹ for codeine in combination with aspirin, paracetamol and ibuprofen. By conforming to the wording in these documents, sponsors

could introduce their PI in a streamlined way via a notification application at that time. PI applications not conforming to the required information had to undergo individual evaluation.

The core PI documents do not contain warnings regarding ultra-rapid metabolisers or children post adenotonsillectomy but do advise caution in pre-existing respiratory depression or decreased respiratory reserve. Use during lactation is not recommended unless the risk to the infant is outweighed by the benefit of the medicine to the mother. There are no specific warnings regarding use in children for the paracetamol-codeine or the ibuprofen-codeine analgesic products. The aspirin-codeine combination core PI states that it should only be given to children under 12 on medical advice due to the aspirin content. There are no consistent PI requirements for Schedule 3 products in terms of codeine dosing recommendations for children, or inclusion of safety information regarding ultra-rapid metabolisers.

Thorough review of all of the PIs for codeine-containing schedule 3 products has not been performed as there are around 300 such products on the ARTG (as at June 2015), a number of which may be vestigial registrations/non-marketed products, products indicated for cough or products for which electronic PI documents are not readily available. However, for the purposes of this review the PIs (current as at January 1, 2013) for two codeine-containing products indicated for use in children were reviewed.

The following safety information was included in both PIs:

- Contraindications for use in children under the age of six years post tonsillectomy and/or adenoidectomy for OSA.
- Not recommended for breastfeeding mothers unless the potential benefits to the patient outweigh the possible risk to the infant.

The CMI's for the same products were identified and contain similar warnings. There was no mention of UM in either of the PI documents.

4.3 Prescribed (S4 and S8) codeine-containing products

The PIs for all Schedule 4 and Schedule 8 codeine-containing products were reviewed. Areas of concern were noted throughout the PIs, which were also inconsistent with each other in the safety information provided in a number of areas. The areas of concern included:

- Dosing information regarding suitability in children is not consistent.
- Contraindications regarding use in children post-adenotonsillectomy are not consistently present.
- Contraindications regarding UM are not consistently present and existing warnings are not consistent. In some PIs, UM is mentioned only in context of breastfeeding, and in some PIs there was no text at all regarding the possibility of UM.
- Some PIs contained outdated text regarding use in breastfeeding, including statements such as that codeine use in breastfeeding mothers "should be avoided" rather than contraindicated. Also missing, from some PIs, was the advice that alternative arrangements should be made for feeding a breastfed infant whilst their mother was exposed to codeine.
- A lack of specific instruction regarding use in children, often only including an adult dose but not specifying any advice for use in children. Some products did not include a minimum age recommendation at all.
- One product does not specify a minimum time between doses.

4.4 Other Australian prescribing guidelines

Sources of prescribing information other than the PI are often used in a clinical setting by practitioners in making treatment decisions. Three such resources are the MIMS guide,⁴² the Australian Medicines Handbook⁴³ and the Australian Therapeutic Guidelines (TG).⁴⁴

The *Therapeutic Guidelines: Analgesia* currently recommends that codeine dosing in children be restricted to:

“0.5 to 1 mg/kg orally, 4- to 6-hourly
maximum 3 mg/kg/day up to 240 mg/day”

The TG also states: (underlining added for emphasis)

“Many children’s hospitals internationally have removed codeine from their formularies due to its risk in ultrarapid metabolisers. However, until the utility and safety of alternatives to codeine have been investigated in the community setting, codeine is likely to have a continued role for some years.

During loading and titration, regularly assess pain severity, the analgesic response, and the incidence of adverse effects (particularly sedation, nausea and vomiting).

Monitor for sedation, which is the earliest sign of opioid-induced respiratory depression.

Codeine efficacy in children is variable, particularly in poor metabolisers (neonates and 10% to 46% of children may have low cytochrome P450 2D6 activity). If ineffective, consider alternatives.

Ultrarapid metabolisers may experience morphine-related adverse effects.”

The Australian Medicines Handbook monograph for codeine in analgesic preparations contains the following information:

“Precautions – Breastfeeding – Avoid use as an infant death has occurred.

Dosage – Codeine – Child >1 year – Oral, 0.5–1 mg/kg every 4–6 hours if needed; maximum 240 mg in 24 hours.

Practice points

- codeine is not recommended; if an opioid is required, it may be more appropriate to use morphine
- regulatory authorities overseas state that all codeine-containing products are:
 - contraindicated in children <18 years undergoing tonsillectomy and/or adenoidectomy (all children in USA; if surgery is for sleep apnoea in Europe) as deaths have occurred
 - not be taken by children <12 years for the treatment of pain (Europe, Canada)
 - not be taken while breastfeeding (Europe)
 - contraindicated in all patients who are ultra-rapid metabolisers (Europe)
- codeine (a prodrug) is metabolised to morphine; people with normal codeine metabolism metabolise 30 mg of codeine to approximately 4.5 mg of morphine
- codeine is metabolised by CYP2D6:
 - some people are unlikely to obtain analgesia with codeine due to a genetic lack of CYP2D6, eg 6–10% of Caucasians and 1–2% of Asians
 - some people are ultra-rapid metabolisers, eg up to 10% of Caucasians, 1–2% of Asians and 29% of Ethiopians, and may achieve higher morphine concentrations, increasing their risk of toxicity
- beware of potential for misuse leading to dependence and over-use of OTC codeine fixed-dose combinations; this has resulted in toxicity from the non-opioid analgesic, eg acute renal failure and GI perforation from ibuprofen

- there is no conclusive evidence that products containing 8–15 mg of codeine per tablet with paracetamol, aspirin or ibuprofen have any benefits over these non-opioids alone.”

4.5 Adverse Events in Australia

4.5.1 ADRS database

The TGA Adverse Drug Reactions System (ADRS) database was searched for cases in which index patients were aged between 0 and 18 years old and where codeine was included in a suspected medication. 102 such reports were identified.⁴⁵

There were no reports of paediatric deaths with codeine as a sole suspected drug.

The case line listing was then reviewed to identify any cases suggesting exaggerated effect of codeine, possibly secondary to ultra-rapid metabolism, or for features suggestive of respiratory depression. Twelve cases were identified, with report dates between 1990 and 2013. The ages of the children range from less than one year of age to 17 years old, and five of the reports are confounded by the concurrent administration of other sedating medication.

Although none of these cases reported fatalities and most are confounded or do not provide enough information for adequate assessment, it is clear that there have been occasions when Australian children have been exposed to codeine and exhibited signs consistent with morphine overdose.

4.5.2 Coronial data

4.5.2.1 Child deaths involving codeine

Data was sought from the National Coronial Information System (NCIS) regarding child deaths and codeine. There were 17 deaths identified as notified to an Australian Coroner between 01/07/2000 and 31/12/2012 which involved persons under the age of 18 and which were at least partly attributed to the administration of codeine (codeine related). All these cases had undergone coronial investigation that had been formally concluded and closed.

Five of the deaths involved hospital or medicinal use of codeine, but none one of these were associated with tonsillectomy or adenoidectomy.

4.5.2.2 Child deaths post adenotonsillectomy

Data regarding child deaths within 14 days (two weeks) of adenotonsillectomy was also sought from the NCIS. There were three (3) closed cases identified as reported to an Australian Coroner between July 2000 and May 2013 that involved a child (a person under 18 years of age) and occurred within two weeks of a procedure to remove tonsils and/or adenoids. All deaths reported were closed cases that had been formally concluded by coronial investigation. None of these cases of deaths in children after adenotonsillectomy in Australia related to the use of codeine in the post-surgical period.

5 Alternatives to codeine for paediatric analgesia

5.1 World Health Organisation guidelines on paediatric analgesia

The most recent World Health Organisation (WHO) guidelines on the pharmacological treatment of persisting pain in children with medical illnesses reflects the way paediatric analgesia recommendations from the pre-eminent medical authorities have changed in recent years.⁴⁶

The WHO guidelines describe the previously recommended three step approach, in which a middle step of using “milder” opioid analgesics such as tramadol and codeine sat between the first step (simple analgesia such as paracetamol or ibuprofen) and the third step (stronger opioids such as morphine). However, codeine is now considered an “excluded medicine for pain relief” and the middle step has been removed, reducing the method to a two-step approach.

The concerns around codeine and tramadol are summarised on page 39 of the document:

“Codeine is a “weak” opioid that is widely available and has been previously recommended to control moderate pain. However, it presents well-known safety and efficacy problems related to genetic variability in biotransformation. Codeine is a prodrug that is converted into its active metabolite morphine by the enzyme CYP2D6. The efficacy of a prodrug depends on the amount of active metabolite formed. Variable expressions of the enzymes involved in the biotransformation of prodrugs can lead to substantial inter-individual and inter-ethnic differences in the conversion rate and the plasma concentration of the active metabolite. In the fetus, CYP2D6 activity is absent or less than 1% of adult values. It increases after birth, but it is estimated to be no higher than 25% of the adult values in children below five years. As a consequence, the analgesic effect is (very) low or absent in neonates and young children.

Furthermore, the percentage of poor metabolizers can vary in ethnic groups from 1% to 30%, resulting in ineffectiveness in large numbers of patients, including children. Conversely, individuals who metabolize codeine quickly and extensively are at risk of severe opioid toxicity, given the high and uncontrolled conversion of codeine into morphine.

Tramadol is another analgesic with opioid effects that has been considered for the control of moderate pain. However, there is currently no available evidence for its comparative effectiveness and safety in children. Furthermore, tramadol is not licensed for paediatric use in several countries. More research on tramadol and other intermediate potency opioids is needed.”

The WHO guidelines conclude that the risks associated with strong opioids are acceptable when compared with the uncertainty associated with the response to codeine and tramadol in children. Therefore, the benefits of using an effective strong opioid analgesic are believed to outweigh the benefits of intermediate potency opioids in the paediatric population and these are preferred in a situation where simple analgesia is not controlling pain.

5.2 Post-adenotonsillectomy analgesia in Australia and internationally

Acute pain management is a complex discipline and multiple non-pharmacological methods of post-operative pain management are involved. These include parental ability to recognise and assess a child's pain, parental misconceptions about analgesics, child refusal to take medication,

poor discharge instructions, difficulty obtaining medication and lack of information provision to caregivers.⁴⁷

Pharmacological pain management in Australian paediatric surgery has commonly included codeine in the past.⁴⁸ However, since the concerns over risk to ultra-rapid metabolisers have been raised, the use of codeine in this setting (particularly post-adenotonsillectomy) has come into question. There have been concerns in the past over the use of non-steroidal anti-inflammatories (NSAIDs) in the treatment of pain in children, particularly in the setting of post-adenotonsillectomy, when the risk of life threatening post-operative bleeding is already a concern. A Cochrane review on the topic, published in 2005, found that NSAIDs did not cause any increase in bleeding requiring a return to theatre. However, the review was updated in 2013 with the conclusion that NSAIDs did not significantly alter the number of perioperative bleeding events requiring non-surgical intervention (Peto odds ratio 0.99 and 95% CI 0.41 to 2.40) but the confidence intervals did not exclude an increased risk.⁴⁹

In contrast, another systematic review, published in *Clinical Otolaryngology* in 2013, concluded that “NSAIDs can be considered as a safe method of analgesia among children undergoing tonsillectomy”.⁵⁰ The AAO-HNS also takes a similar stance, and specifies that “ibuprofen can be used safely for pain control after surgery.” This is one of several suggested education points for caregivers that the AAOHNS suggests. In the body of the guideline text they explain, “Clinicians should advocate for pain management by establishing strategies to control pain after tonsillectomy. The panel avoided a recommendation to prescribe specific drugs, since pain can often be managed with over-the-counter analgesics and hydration.”

A 2010 clinical care guideline from the John Hunter Children’s Hospital Australia, published on children’s health website kaleidoscope.org.au, states that regular paracetamol is the mainstay of effective analgesia, that ibuprofen and other NSAIDs should be avoided due to risk of bleeding, and that some children will benefit from oxycodone to provide adequate analgesia.

A presentation document published by the Children’s Pain Management Service at the Australian Royal Children’s Hospital indicates that apart from paracetamol, it is unclear what analgesia is safe or effective in this setting.⁵¹ The recommendations for analgesia in the inpatient setting according to this document are:

“Lignocaine viscous 4% gargle to facilitate eating

Paracetamol 15mg/kg qid

Celecoxib 4mg/kg bd

Oxycodone 0.1- 0.2mg/kg q 4h

Tramadol 2 mg/kg q 6h”

Recommendations vary between centres in Australia and internationally, however the consensus appears to be that non-pharmaceutical strategies and regular dosing of paracetamol are central. The use of NSAIDs is not universally recommended due to continuing concerns and inconclusive evidence over bleeding risk. The use of additional measures such as non-CYP2D6-metabolised opioids for breakthrough pain (such as liquid hydromorphone or morphine) in the acute inpatient setting and local anaesthetic gargles are also suggested. The use of codeine for paediatric analgesia post-adenotonsillectomy does not appear to be generally recommended.

6 Discussion

The concerns over the safety of codeine use with regard to unintentional morphine overdose secondary to ultra-rapid metabolism of codeine can be considered to apply to all of the following groups:

- All children undergoing adenotonsillectomy for OSA
- All children undergoing adenotonsillectomy
- All children (under the age of 18)
- All infants who are breastfed
- All people who are ultra-rapid metabolisers.

What is not clear is the difference in the magnitude of risk within each and between each of these groups.

The over-representation noted by the FDA of deaths in children post-adenotonsillectomy for OSA (as opposed to any other analgesic indication) has been interpreted to mean that this setting carries a higher risk of respiratory difficulties, however this may simply represent that this is the most common setting in which codeine is used to treat pain in children. In more general terms, children are likely to be at higher risk of complications associated with the ultra-rapid metabolism of codeine due to a reduced ability to recognise drug effects and communicate them, and their different airway anatomy to adults, conferring higher susceptibility to breathing obstruction.

Another issue with quantifying risk associated with codeine use post-operatively is the way the risk will vary according to whether the products are available over-the-counter (OTC) or via prescription only. In theory, the prescription products should be higher risk as they contain higher doses of codeine, however medical supervision should be closer than for OTC medicines, which should mitigate the risk to some extent.

The international regulatory community has made various changes to the regulation of codeine to address the risk of morphine overdose and death in ultra-rapid metabolisers. In the USA, use has been restricted in children below the age of 18. However, the restrictions in the USA only apply to a particular setting – that of post-adenotonsillectomy for any reason. The FDA states that the indication for surgery has not been specified as they can't be sure whether underlying respiratory compromise related to OSA is a contributing factor or not.

By contrast, the EMA has taken the approach that the risk is present for any child who may be a ultra-rapid metaboliser, regardless of the indication for use. The age of 12 has been chosen for this restriction, consistent with the evidence considered in the EMA's review. They have then additionally contraindicated codeine use post adenotonsillectomy in children under 18, but only if the indication for surgery is OSA, due to the additional risk that appears to be present in this setting from the cases considered by the FDA in their initial safety action.

Thus, a selection of actions available to the TGA might be considered to be any or a combination of these:

1. No action
2. Contraindication of codeine use below 12 years of age
 - a. in any setting

- b. for analgesia
 - c. for analgesia in the setting of adenotonsillectomy for any indication
 - d. in the setting of adenotonsillectomy for obstructive sleep apnoea
3. Contraindication of codeine use below 18 years of age
- a. in any setting
 - b. for analgesia
 - c. for analgesia in the setting of adenotonsillectomy for any indication
 - d. for analgesia in the setting of adenotonsillectomy for obstructive sleep apnoea
4. Introduction of warning text in keeping with the recommendations of the PRAC
5. Introduction of warning text and a black box warning similar to the FDA.

According to this categorisation, the FDA has taken action 3c, contraindicating codeine use for children under the age of 18 post adenotonsillectomy for any indication, and introducing a boxed warning on all codeine-containing products, regardless of indication, and for a product containing only dihydrocodeine (combined with aspirin and caffeine). The FDA has also taken action 5, adding extensive warning text to the labelling under headings “Warning” “Precautions” and “Pediatric Use”. The FDA has not, however, made any general lower age limit contraindication, and liquid paracetamol-codeine medications remain available with doses specified for children as young as 3 years.⁵²

By contrast, the EMA has taken action 2a, contraindicating use of codeine in children under the age of 12 for any reason, in addition to action 3d, contraindicating codeine use for analgesia in children under the age of 18 post adenotonsillectomy, but specifying that the contraindication only applies when the indication for surgery is OSA.

There is no reason to believe that the risk of morphine overdose in ultra-rapid metabolisers is restricted to the post-operative setting. Additionally, the efficacy of codeine for analgesia in children younger than five is questionable as described by the WHO guidelines on the pharmacological treatment of persisting pain in children with medical illnesses. It is, therefore, appropriate to restrict the use of codeine in children based on a minimum age after which a child is more likely to derive benefit, the respiratory anatomy is likely to be reasonably resilient and a child is likely to be able to communicate the onset of possible adverse events to the caregiver. The European PRAC committee review concluded that the enzymatic system responsible for the metabolism of codeine can be considered fully matured by the age of 12, and that a majority of European products specified a minimum treatment age of 12 years based on a lack of established safety and efficacy below 12.²⁰ On this basis, the age of 12 years as a minimum treatment age recommendation is considered appropriate.

As demonstrated by the case series recognised in the literature, codeine use in the post-adenotonsillectomy for OSA setting carries additional risk in terms of respiratory compromise, and it is appropriate to impose an additional restriction on codeine use in children under 18 in this setting.

Additionally, the presence of an Australian case of a less than one-year-old child exposed via breast milk who displayed somnolence and hypotonia emphasises that the contraindication of codeine use in breastfeeding mothers should be established across all codeine-containing products, and advice given to suspend breastfeeding for any period during which a breastfeeding mother requires codeine therapy.

7 Conclusions

Morphine overdose in ultra-rapid metaboliser individuals leading to respiratory depression in a setting of relative airway obstruction is a potential lethal side effect of codeine. No matter what the dose, the indication or the age, ultra-rapid metabolisers (or their breastfeeding infants) may be at risk, and children aged less than 12 may be at particular risk.

From post-market and coronial data, there is no evidence that cases of respiratory compromise leading to deaths with paediatric codeine use in ultra-rapid metabolisers have occurred in the Australian setting to date. However, documented deaths have occurred overseas, and the risk to Australians, whilst hard to quantify, is certainly present. It must also be recognised that the lack of clearly recorded Australian cases may simply represent the fact that testing for ultra-rapid metabolisers is not specific or widely available, and that post-market data is likely to represent only a small, reported subset of true cases in a population.

Currently there are inconsistencies in the way the risks associated with ultra-rapid metabolism of codeine are addressed across OTC and prescription-only codeine products in Australia. This is inconsistent with other major jurisdictions including the US, EU and Canada. Codeine is a commonly used medication that may be perceived by the Australian public to be relatively safe, especially in light of its availability in OTC preparations. Therefore the warnings with regard to this potential risk should be standardised across all codeine products, regardless of schedule.

Evidence shows that codeine should not be used in children under the age of 12 for any reason, or in children younger than 18 years of age who have undergone adenotonsillectomy for obstructive sleep apnoea. Additionally, existing warnings contraindicating codeine use by breastfeeding mothers should be made consistent across all codeine-containing products.

TGA recommendations

1. Use of codeine in children younger than 12 years of age for any indication should be contraindicated.
2. Use of codeine in children aged 12-18 years should be contraindicated post adenotonsillectomy for obstructive sleep apnoea.
3. Existing warnings contraindicating codeine use by breastfeeding mothers should be made consistent across all codeine-containing products, and warnings should be added to advise against using codeine if known to be an ultra-rapid metaboliser.
4. Health professionals, patients and caregivers should be educated regarding the variability of codeine efficacy, the possibility of ultra-rapid metabolism-related morphine overdose and the signs of such, including respiratory depression.

8 References

- ¹ TRIM document R13/241323: Drug Information Update - FDA Drug Safety Communication: Safety Review Update of Codeine use in Children - new Boxed Warning and Contraindication on use after Tonsillectomy and/or Adenoidectomy.
- ² Wong C, Lau E, Palozzi L, Campbell F. Pain management in children: Part 2 - A transition from codeine to morphine for moderate to severe pain in children. *Can Pharm J (Ott)*. 2012 Nov;145(6):276-279.e1. doi: 10.3821/145.6.cpj276.
- ³ TRIM document R15/177061: Daly AK, Brockmöller J, Broly F, et al. "Nomenclature for human CYP2D6 alleles." *Pharmacogenetics*. 1996 Jun;6(3):193-201.
- ⁴ The Human Cytochrome P450 (CYP) Allele Nomenclature Database: CYP2D6 allele nomenclature. Determined by the CYP Allele Nomenclature Committee. Available at <http://www.cypalleles.ki.se/cyp2d6.htm>
- ⁵ Recommended dosing of codeine by CYP2D6 Phenotype. Adapted from the Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines for cytochrome P450 2D6 (CYP2D6) genotype and codeine therapy: 2014 Update. Available at: <http://www.pharmgkb.org/guideline/PA166104996>
- ⁶ Marcus CL1, Moore RH, Rosen CL, Giordani B, Garetz SL, Taylor HG, Mitchell RB, Amin R, Katz ES, Arens R, Paruthi S, Muzumdar H, Gozal D, Thomas NH, Ware J, Beebe D, Snyder K, Elden L, Sprecher RC, Willging P, Jones D, Bent JP, Hoban T, Chervin RD, Ellenberg SS, Redline S; Childhood Adenotonsillectomy Trial (CHAT). (2013) A randomized trial of adenotonsillectomy for childhood sleep apnea. *N Engl J Med*. Jun 20;368(25):2366-76. doi: 10.1056/NEJMoa1215881. Epub 2013 May 21
- ⁷ Nath A, Emani J, Suskind DL, Baroody FM. Predictors of persistent sleep apnea after surgery in children younger than 3 years. *JAMA Otolaryngol Head Neck Surg*. 2013 Oct;139(10):1002-8.
- ⁸ Khetani JD, Madadi P, Sommer DD, Reddy D, Sistonen J, Ross CJ, Carleton BC, Hayden MR, Koren G. (2012) Apnea and oxygen desaturations in children treated with opioids after adenotonsillectomy for obstructive sleep apnea syndrome: a prospective pilot study. *Paediatr Drugs*. Dec 1;14(6):411-5. doi: 10.2165/11633570-000000000-00000.
- ⁹ Brown KA1, Laferrière A, Lakheeram I, Moss IR. (2006) Recurrent hypoxemia in children is associated with increased analgesic sensitivity to opiates. *Anesthesiology*. Oct;105(4):665-9.
- ¹⁰ Kelly LE, Sommer DD, Ramakrishna J, Hoffbauer S, Arbab-Tafti S, Reid D, Maclean J, Koren G. (2015) Morphine or Ibuprofen for post-tonsillectomy analgesia: a randomized trial. *Pediatrics*. Feb;135(2):307-13. doi: 10.1542/peds.2014-1906.
- ¹¹ Racoosin JA. Slide presentation Pediatric Advisory Committee briefing document: "Death and respiratory arrest related to ultra-rapid metabolism of codeine to morphine." Division of Anesthesia, Analgesia, and Addiction Products, CDER, FDA. Available at: <http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/PediatricAdvisoryCommittee/UCM343601.pdf>
- ¹² FDA Public Health Advisory: Use of Codeine By Some Breastfeeding Mothers May Lead To Life-Threatening Side Effects In Nursing Babies. Available at: <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm054717.htm>
- ¹³ FDA Drug Safety Communication: Codeine use in certain children after tonsillectomy and/or adenoidectomy may lead to rare, but life-threatening adverse events or death. Available at: <http://www.fda.gov/Drugs/DrugSafety/ucm313631.htm>
- ¹⁴ Voronov P, Przybylo HJ, Jagannathan N. Apnea in a child after oral codeine: a genetic variant - an ultra-rapid metabolizer. *Paediatr Anaesth*. 2007 Jul;17(7):684-7.
- ¹⁵ Ciszkowski C, Madadi P, Phillips MS, Lauwers AE, Koren G. Codeine, ultrarapid-metabolism genotype, and postoperative death. *N Engl J Med*. 2009 Aug 20;361(8):827-8. doi: 10.1056/NEJMc0904266.
- ¹⁶ Kelly LE, Rieder M, van den Anker J, Malkin B, Ross C, Neely MN, Carleton B, Hayden MR, Madadi P, Koren G. More codeine fatalities after tonsillectomy in North American children. *Pediatrics*. 2012 May;129(5):e1343-7. doi: 10.1542/peds.2011-2538. Epub 2012 Apr 9.
- ¹⁷ Hermanns-Clausen M, Weinmann W, Auwärter V, Ferreirós N, Trittler R, Müller C, Pahl A, Superti-Furga A, Hentschel R. Drug dosing error with drops: severe clinical course of codeine intoxication in twins. *Eur J Pediatr*. 2009 Jul;168(7):819-24. doi: 10.1007/s00431-008-0842-7. Epub 2008 Oct 21.

- ¹⁸ Racoosin JA, Roberson DW, Pacanowski MA, Nielsen DR. New evidence about an old drug--risk with codeine after adenotonsillectomy. *N Engl J Med*. 2013 Jun 6;368(23):2155-7. doi: 10.1056/NEJMp1302454. Epub 2013 Apr 24. PubMed PMID: 23614474.
- ¹⁹ Goldman JL, Baugh RF, Davies L, et al. Mortality and major morbidity after tonsillectomy: etiologic factors and strategies for prevention. *Laryngoscope* 2013.
- ²⁰ Assessment report for codeine-containing medicinal products indicated in the management of pain in children. Procedure under Article 31 of Directive 2001/83/EC resulting from pharmacovigilance data. Procedure number: EMEA/H/A-31/1342. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/Codeine_containing_medicinal_products/Recommendation_provided_by_Pharmacovigilance_Risk_Assessment_Committee/WC500147065.pdf
- ²¹ Koren G, Cairns J, Chitayat D. Pharmacogenetics of morphine poisoning in a breastfed neonate of a codeineprescribed mother. *Lancet*. 2006;368:704. et al. doi:10.1016/S0140-6736(06)69255-6
- ²² Madadi, P., et al. "Pharmacogenetics of neonatal opioid toxicity following maternal use of codeine during breastfeeding: a case-control study." *Clinical Pharmacology & Therapeutics* 85.1 (2009): 31-35. DOI: 10.1038/clpt.2008.157
- ²³ Lam J, Matlow JN, Ross CJ, Hayden MR, Carleton BC, Madadi P. Postpartum maternal codeine therapy and the risk of adverse neonatal outcomes: the devil is in the details. *Ther Drug Monit*. 2012 Aug;34(4):378-80
- ²⁴ Davis JM, Bhutani VK. Neonatal apnea and maternal codeine use. *Pediatr Res*. 1985;19(4 pt 2):170A. Abstract. Available at: <http://www.nature.com/pr/journal/v19/n4/abs/pr1985467a.html>
- ²⁵ Naumburg EG, Meny RG, Findlay J et al. Codeine and morphine levels in breast milk and neonatal plasma. *Pediatr Res*. 1987;21(#4, Pt 2):240A. Abstract. Available at: <http://www.nature.com/pr/journal/v21/n4s/abs/pr1987523a.html>
- ²⁶ Willman S, Edginton AN, Coboeken K, Ahr G and Lippert J. (2009) Risk to the Breast-Fed Neonate From Codeine Treatment to the Mother: A Quantitative Mechanistic Modeling Study. *Clinical Pharmacology and Therapeutics*. 86(6):634-43. Available at: http://www.isdbweb.org/documents/file/1790_14.pdf
- ²⁷ Nezvalová-Henriksen et al. (2011) Effects of codeine on pregnancy outcome: results from a large population-based cohort study. *European Journal of Clinical Pharmacology* 67(12):1253-1261. doi:10.1007/s00228-011-1069-5. Available at: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3214255/>
- ²⁸ Niesters M, Overdyk F, Smith T, Aarts L, Dahan A. Opioid-induced respiratory depression in paediatrics: a review of case reports. *Br J Anaesth*. 2013 Feb;110(2):175-82. doi: 10.1093/bja/aes447. Epub 2012 Dec 17. Review. PubMed PMID: 23248093.
- ²⁹ Announcement regarding CMDh Position on EMA website. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2013/06/WC500144851.pdf
- ³⁰ Schmidt H, Vormfelde SV, Walchner-Bonjean M, Klinder K, Freudenthaler S, Gleiter CH, Gundert-Remy U, Skopp G, Aderjan R and Fuhr U. The role of active metabolites in dihydrocodeine effects. *Int J Clin Pharmacol Ther*. 2003 Mar;41(3):95-106.
- ³¹ Codeine-containing medicinal products for the treatment of cough or cold in paediatric patients: summary page. "PRAC recommends restrictions on the use of codeine for cough and cold in children." Available at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/referrals/Codeine_containing_medicinal_products_for_the_treatment_of_cough_and_cold_in_paediatric_patients/human_referral_prac_000039.jsp&mid=WC0b01ac05805c516f
- ³² Health Canada website statement. Available at: <http://www.healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2013/33915a-eng.php>
- ³³ Medsafe (New Zealand) website statement. Available at: <http://www.medsafe.govt.nz/profs/puarticles/mar2013codeine.htm>
- ³⁴ Medsafe advisory committee (MARC) minutes regarding codeine in cough and cold medicines for paediatric patients. Available at: <http://www.medsafe.govt.nz/profs/adverse/Minutes160.htm#3.2.4>
- ³⁵ SUSMP Number 6. Available at: <http://www.comlaw.gov.au/Details/F2015L00128>
- ³⁶ TRIM document R15/55993: Codeine containing products from Reporter search of the ARTG.
- ³⁷ TRIM document R14/375537: Required advisory statements for medicine labels (RASML).
- ³⁸ Medicines Advisory Statements Specification: source of Required advisory statements for medicine labels. Available at: <http://www.comlaw.gov.au/Details/F2014L00693>

- ³⁹ OTC cough and cold medicines for children – Final outcomes of TGA review. Available at: <https://www.tga.gov.au/otc-cough-and-cold-medicines-children-final-outcomes-tga-review>
- ⁴⁰ ARGOM Appendix 5: Guidelines on OTC application for specific substances, p22. V1.0 October 2012. Available at: <https://www.tga.gov.au/publication/argom-appendix-5-guidelines-otc-applications-specific-substances>
- ⁴¹ Codeine rescheduling - information for sponsors (24 Feb 2010) including Core PI and CMI document templates. Available at: <https://www.tga.gov.au/codeine-rescheduling-information-sponsors>
- ⁴² Monthly Index of Medical Specialties (MIMS) online pharmaceutical products guide. Available at: <https://www.mimsonline.com.au/Search/Search.aspx>
- ⁴³ The Australian Medicines Handbook. Available via TGA library services at: <https://amhonline.amh.net.au/>
- ⁴⁴ The Therapeutic Guidelines website. Available via TGA library services at: <http://online.tg.org.au/ip/desktop/index.htm>
- ⁴⁵ TRIM document R15/88205: ADRS search (CLL output) for respiratory effects of codeine in children
- ⁴⁶ WHO guidelines on the pharmacological treatment of persisting pain in children with medical illnesses. Available at: http://whqlibdoc.who.int/publications/2012/9789241548120_Guidelines.pdf
- ⁴⁷ TRIM document R15/109765: Dorkham et al. (2014) *Effective postoperative pain management in children after ambulatory surgery, with a focus on tonsillectomy: barriers and possible solutions*. Paediatric Anesthesia; 24: 239-248.
- ⁴⁸ Nierengarten MB. *Post-Operative Pain in Children Undergoing Tonsillectomy*. ENT Today, Sept 2012. Saved at R14/374467.
- ⁴⁹ Lewis SR, Nicholson A, Cardwell ME, Siviter G and Smith AF (2013) *Nonsteroidal anti-inflammatory drugs and perioperative bleeding in paediatric tonsillectomy*. Cochrane Database Syst Rev. 2013 Jul 18;7:CD003591. doi: 10.1002/14651858.CD003591.pub3.
- ⁵⁰ Riffin L, Ramakrishna J, Sommer DD, Koren G. (2013) A 2013 updated systematic review & meta-analysis of 36 randomized controlled trials; no apparent effects of non-steroidal anti-inflammatory agents on the risk of bleeding after tonsillectomy. Clin Otolaryngol. 2013 Apr;38(2):115-29. doi: 10.1111/coa.12106. Review. PubMed PMID: 23448586.
- ⁵¹ TRIM document R15/107671: Postoperative Analgesia for Children After Tonsillectomy (Royal Childrens Hospital presentation). Downloaded on 06/02/2015 from: <http://www.rch.org.au/uploadedFiles/Main/Content/anaes/Analgesia%20post%20tonsillectomy%202014.pdf>
- ⁵² FDA label for acetaminophen and codeine phosphate solution accessed via FDA Daily Med website. Available at: <http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=e1da6cd0-97fb-4dc4-b754-485ff364e35f>

Appendix 1

Literature cases identified by the FDA safety review

First case: Voronov et al (Ped Anesthesia, 2007)

A 29 months old previously healthy child who experienced apnoea resulting in brain injury following a dose of acetaminophen and codeine 2 days after an uneventful anaesthetic for tonsillectomy. A genetic polymorphism leading to ultra-rapid metabolism of codeine into morphine resulted in narcosis and apnoea. This paper discusses the use of codeine for pain relief, obstructive sleep apnoea, the alteration of the CYP2D6 gene and the resulting effect on drug metabolism.

Second case: Ciszkowski et al (NEJM, 2009)

A healthy 2-year-old boy weighing 13 kg, with a history of snoring and sleep-study-confirmed sleep apnoea, who underwent elective adenotonsillectomy. The outpatient surgery was uncomplicated, and 6 hours after surgery the boy received 10 mg of meperidine and 12.5 mg of dimenhydrinate intramuscularly and was sent home with instructions for 10 to 12.5 mg of codeine and 120 mg of acetaminophen syrup to be administered orally every 4 to 6 hours as needed. On the second evening after surgery, fever and wheezing developed in the child. At 9 a.m. the next day, the child's vital signs were absent, and resuscitation efforts failed. Postmortem examination showed evidence of chronic tracheitis, aspiration of food particles, and bilateral consolidation in the lungs that was consistent with bronchopneumonia. Codeine (0.70 mg per litre) and morphine (32 ng per millilitre) were detected in the femoral blood by means of gas chromatography-mass spectrometry; there was no evidence of other drugs or metabolites. Cytochrome P-450 2D6 (CYP2D6) genotyping revealed functional duplication of the CYP2D6 allele, resulting in the UM phenotype.

Third, fourth and fifth cases: Kelly et al (Pediatrics, 2012)

At a regional hospital in northern Ontario, Canada, a 4-year-old (27.6 kg) First Nations' boy underwent AT for OSAS and recurrent tonsillitis. He was discharged from the hospital after an uneventful overnight stay on liquid codeine at an age-appropriate dose (8 mg per dose, up to 5 doses a day as needed). His parents reported him to be sedated and lethargic the day after hospital discharge. The next afternoon, after a total of 4 codeine doses, he was brought to hospital without vital signs. His postmortem morphine serum concentration was 17.6 ng/mL (therapeutic morphine range 4.5 ± 2.1 ng/mL). His toxicology screen revealed a blood codeine level in the expected range after therapeutic use, and there were no other medications detected. Genotyping revealed a gene duplication and a CYP2D6 UM phenotype (CYP2D6 *1/*2AxN). His UM CYP2D6 status resulted in an increased level of morphine leading to respiratory arrest. Postmortem analysis revealed the cause of death to be bilateral acute bronchopneumonia as a consequence of codeine and morphine toxicity after adenotonsillectomy.

A 3-year-old girl (14.4 kg) of Middle Eastern descent underwent tonsillectomy for obstructive sleep apnoea (OSA) and was discharged after a 24-hour hospital stay at a Canadian Children's Hospital. In the hospital, she received 2 doses of codeine syrup (15 mg each). Upon discharge she was given a combination of codeine and acetaminophen (15 mg codeine/150 mg acetaminophen) every 4 to 6 hours as needed. More than 6 hours after her final codeine dose (total 60 mg codeine), she was found unresponsive with a fever of 100°F as measured at home. On admission to the hospital, she presented with minimal respirations and an oxygen saturation of 65%. She experienced 1 bout of vomiting with mild-dark blood observed. Her blood morphine concentration measured 17 ng/mL. After successful resuscitation, mechanical ventilation and naloxone dosing (1.5 mg), she showed a prompt improvement in her symptoms. The next day,

she was extubated and recovered fully. Her genotype was determined to be an EM (CYP2D6 *1/*1). In this case, her morphine levels suggested ultra-rapid metabolism, which was not consistent with her genotype. However, the EM genotype often overlaps with the UM phenotype.

A 5-year-old boy (29 kg) underwent bilateral myringotomy tube placement, and AT for recurrent tonsillitis and snoring in the Southern US. After surgery, he was prescribed acetaminophen and codeine (12 mg codeine) every 4 hours. This total 72 mg/day is within the recommended range of 6 mg/kg per day. The child was released home but was found without vital signs by his mother 24 hours after his surgery. The autopsy did not reveal a cause of death. This child's postmortem codeine concentration was 79 ng/mL, and morphine concentration was 30 ng/mL. A pharmacokinetic model using Pmetrics software (Los Angeles, CA) was constructed on the basis of published pediatric pharmacokinetic characteristics to simulate expected time concentration profiles for codeine and morphine based on his age, weight, and dosing schedule. Finally, the investigators compared his measured codeine and morphine concentrations to the expected ranges. The measured codeine concentration of 79 ng/mL ~8 hours after his last dose is at the 56th percentile of predicted pediatric codeine concentrations. In contrast, the measured morphine concentration of 30ng/mL is at the 99th percentile of predicted concentrations at the normal pediatric rate of conversion. The codeine levels are consistent with his prescription of 0.41 mg/kg every 4 hours as needed, which is within the recommended dose according to the published prescribing recommendations. It is highly likely that the child was a CYP2D6 UM given his exceedingly high morphine concentration relative to codeine.

Sixth and seventh cases: Hermanns-Clausen et al (Eur J Peds, 2008)

A 3-year-old boy (twin 1) was found lying in vomit and apnoeic at night; he was resuscitated and immediately transferred to the paediatric intensive care unit (PICU). Two and a half hours later, his twin brother (twin 2) was found dead in his bed at home. Twin 1 required mechanical ventilation for 3 days, but he eventually made a full recovery; autopsy in twin 2 showed massive aspiration of gastric content. History revealed that the monozygotic twins had an upper respiratory tract infection for several days and had both been given codeine at a dose of "10 drops per day" by their mother. The blood of both twins was found to contain high levels of codeine and its metabolites. The weight of "10 drops" was determined experimentally and was found to range from 494 to 940 mg. Thus, the highest possible dose given by mother was 23.5 mg of codeine instead of the recommended 10 mg. The twins had identical CYP2D6 gene polymorphisms corresponding to the "extensive metaboliser" type. Conclusions: Because of the variability of drop size drug dosage, dosage "by drops" is imprecise and may result in accidental overdose. The combination of repeated overdosing and extensive metabolism to morphine is likely to have caused apnoea in these twins. These cases illustrate the danger of codeine as an antitussive in young children.

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