Int J Legal Med (2009) 123:387–394
DOI 10.1007/s00414-009-0340-0

ORIGINAL ARTICLE

Fatal and severe codeine intoxication in 3-year-old twins—interpretation of drug and metabolite concentrations

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Received: 12 September 2008 / Accepted: 6 March 2009 / Published online: 7 April 2009
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Abstract This work presents two cases of codeine intoxication in 3-year-old monozygotic twin brothers while treated with a codeine slow-release formulation. One child had to be admitted to the hospital, whereas the other one died at home after aspiration of gastric content. The concentrations of codeine and major metabolites including morphine and corresponding glucuronide conjugates were measured by liquid chromatography–tandem mass spectrometry in serum, urine, cerebrospinal fluid, and brain tissue, respectively. A genetic polymorphism study was carried out in order to determine the ability of the children to metabolize codeine by O-demethylation. A pharmacokinetic calculation was also performed to estimate the administered dose of codeine in question. High concentrations of all substances were found in samples of both children. The pharmacokinetic estimate suggests an overdose of codeine, and the possible reasons for the high opiate concentrations are discussed. Furthermore, the postmortem distribution—during and after resuscitation—might play a major role in the interpretation of postmortem concentration levels.

Keywords Fatal codeine intoxication · Dosing errors · Extensive metabolizer · Long-release medication

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Introduction

Codeine has been widely prescribed as an antitussive agent and analgesic for relief of moderate pain. The analgesic action is due to conversion to morphine by CYP2D6, which is a polymorphically controlled pathway [1]. Codeine is widely recommended for pediatric use due to its lower incidence of opioid-related side effects, especially in situations where airway management and neurological assessment are critical [2]. In spite of the use of codeine in children, there is insufficient evidence to support the safety or efficacy of codeine as an antitussive agent in this population group [3].

This work presents a fatal case of codeine intoxication in twin brothers at the age of 3 years and 4 months. The children had been suffering from a cold with fever for 6 days when the mother found one child lying breathless in vomit at about 2.40 a.m., but the other son showed no symptoms. The mother immediately started resuscitation. On admission to the university pediatric hospital, the child was comatose and had to be mechanically ventilated. The

boy was ventilated for 3 days because of radiologically confirmed aspiration pneumonia but recovered fully.

The other child was found dead by his father approximately 2.5 h after admission of the brother to hospital. The child was also lying in vomit and resuscitation was unsuccessful. Massive gastric aspiration and a diffuse cerebral edema were found at autopsy.

The parents reported that the two boys had been administered ten drops of a slow-release codeine cough medicine once a day for the last 6 days. The last administration had been at around 10.00 p.m. the same night.

Codeine, morphine, and their major metabolites were determined in serum, cerebrospinal fluid (CSF), urine, and brain by liquid chromatography–tandem mass spectrometry (LC–MS/MS). In addition, a genotype study of the two children to determine polymorphisms in the *CYP2D6* gene was performed together with a pharmacokinetic estimation in order to obtain information on the possibility of overdose as the cause of the intoxication.

Materials and methods

All drug standards (morphine, morphine-6-glucuronide (M6G), morphine-3-glucuronide (M3G), normorphine, codeine, codeine-glucuronide, and norcodeine as well as their deuterated analogs as far as available) were purchased from Promochem/Radian (Wesel, Germany). All solvents were of analytical grade. High-performance liquid chromatography (HPLC)-grade methanol, acetonitrile, and formic acid (analytical grade) were obtained from Merck (Darmstadt, Germany). Ammonium formate (analytical grade) was from Sigma (Deisenhofen, Germany). Deionized water was prepared with a cartridge deionizer from Memtech (Moorenweis, Germany). Blank serum samples were obtained from the University Hospital of Freiburg (Freiburg, Germany).

Instrumentation

The LC–MS/MS system consisted of an API 365 triple quadrupole mass spectrometer fitted with a turbo ion spray interface (Applied Biosystems, Darmstadt, Germany), a Shimadzu HPLC system (three LC10AD pumps and controller unit, Shimadzu, Duisburg, Germany), and a CTC/PAL liquid autosampler (CTC PAL, Chromtech, Idstein, Germany) controlled by Analyst 1.3 software (Applied Biosystems). Analyses were performed with electrospray ionization using a turbo ion spray source in the positive mode.

Sample preparation

For quantitation, calibration standards up to 2,000 ng/mL of all analytes in spiked serum samples were prepared. The pretreatment of the samples was as follows: to 0.2 mL serum or CSF, a volume of 5 μL of the internal standard mixture (morphine-D_3, morphine-6-glucuronide-D_3, codeine-D_3, and codeine-glucuronide-D_3 at a concentration of 10 μg/mL each) was added, and precipitation was performed by mixing the sample with 400 μL of cold acetonitrile. The solution was centrifuged at 13,000 rpm for 10 min and the supernatant was evaporated to dryness under nitrogen at 60ºC, reconstituted in 100 μL of a 0.1% formic acid solution and transferred to the autosampler vial, by filtering with an Acrodisc 13 mm, 0.45 μm GH Polypro membrane syringe filter (PALL, MI, USA). Due to the high concentration of the opiates in urine samples, these were diluted with deionized water 1:10 (*v*/*v*) prior to the addition of the internal standard. The subsequent sample pretreatment was the same as for serum samples.

Brain samples (approximately 1 g) were homogenized after addition of 40 μL of the internal standard mixture; 1.5 mL deionized water was added and, after vortexing, the sample was ultrasonicated for 45 min. The sample was centrifuged at 4,000 rpm twice for 5 min and the supernatant was collected. This supernatant was treated as described above for serum samples prior to analysis by LC–MS/MS. In the case of brain analysis, quantitation was accomplished by the standard addition method whereas, for body fluids, the internal standard method was used.

Chromatographic conditions

Following sample processing, analytes were separated on a pentafluorophenyl propyl silica column (Allure PFP Propyl 50x2.1 mm, 3 μm, Restek, Aschaffenburg, Germany) with a guard column (4×2 mm, same packing material) at 40°C. The mobile phase consisted of solvent A (0.1% formic acid with 1 mM ammonium formate) and solvent B (acetonitrile–0.1% formic acid 95:5, *v*/*v* with 1 mM ammonium formate). The following gradient elution was used at a flow rate of 0.3 mL/min: 0–4 min 3% B, 4–7 min 3–15% B linear, 7–11 min 15% B, 11–13 min 15–95% B linear, 13–15.5 min 95% B, 15.5–17 min 95–3% B linear, and 17–20 min 3% B for re-equilibration.

To enhance signal intensity, acetonitrile was added with a postcolumn "T" at a flow rate of 100 μL/min before the eluents entered the turbo ion spray interface. The turbo ion spray source was operated at 400°C with an ionization voltage of 5,250 V (positive mode) and nitrogen as curtain gas (10), nebulizer gas (12), turbo gas (3 L/min), and CID gas with an analyzer pressure of 2.5×10^{-5}Torr. Analysis was performed by multiple-reaction monitoring, using the precursor ions (protonated molecular ions) and the corresponding transitions which are shown in detail in Table 1 and unit and low resolution for Q1 and Q3, respectively. The dwell time was 50 ms for each transition.

Table 1 Summary of transitions used for mass spectrometric analysis (LC–MS/MS)

Compound	Transition	Internal standard	Retention time (min)
Morphine-6-glucuronide	**462→462** 462→286	Morphine-6-glucuronide-D_3 465→465	5.3
Morphine-3-glucuronide	**462→462** 462→286	Morphine-6-glucuronide-D_3 465→465	2.8
Morphine	286→286 286→153	Morphine-D_3 289→289	7.0
Norcodeine	**286→286** 286→225	Morphine-D_3 289→289	9.2
Normorphine	**272→272** 272→121	Morphine-D_3 289→289	4.7
Codeine	**300→300** 300→214	Codeine-D_3 303→303	10.2
Codeine-glucuronide	**476→476** 476→300	Codeine-glucuronide-D_3 479→479	8.2

Mass to charge (*m*/*z*) ratios used for quantitation are printed in bold

Genotype and pharmacokinetics

CYP2D6 *3, *4, *5, and *6 were genotyped from blood samples of the twins using a validated Drug Metabolism Genotyping Assay obtained from Applied Biosystems (Frankfurt, Germany). *CYP2D6* gene dose was determined according to the method of Schaeffeler et al. [4]. Polymerase chain reaction (PCR) coupled with fluorescent detection was used to assess the presence of CYP 2D6*3 (A 2637 Del) allele, 2D6*4 (G 1934 A) allele, and 2D6*6 (T1795 Del) allele.

For estimation of the dose administered, the Microsoft-Excel-based software AutoKinetic v3.2 was used [5]. The pharmacokinetic parameters (volume of distribution, elimination half-life, bioavailability, time to reach maximum concentration) that are necessary to establish a relationship between blood concentration and dose were obtained from the manufacturer of the cough medicine (Mack, Illertissen, Germany). Volume of distribution, elimination half-life, and bioavailability were varied (see Table 2) to simulate extreme conditions to explain the high concentrations of codeine and its metabolites.

Table 2 Pharmacokinetic parameters used for dose estimation

Formulation	Slow-release codeine		
	Mean	Vd 2.5	Vd 2.0
BW (kg)	14.0	14.0	14.0
BD	0.54	0.70	0.70
t max (h)	3.00	2.00	2.00
Vd/BW (L/kg)	3.70	2.50	2.00
$t_{1/2}$ (h)	6.50	10.00	10.00

BW body weight, *BD* relative bioavailability, *t max* time to reach the maximum serum concentration, *Vd* volume of distribution, $t_{1/2}$ elimination half-life

Results

Analysis of the serum samples (which were collected from the heart and femoral vein in the case of the dead child) of urine, CSF, and brain tissue revealed high concentrations of codeine, morphine, and the corresponding metabolites. Peripheral blood of the living child had been collected approximately 6 h after the last intake of the cough preparation, and the CSF sample had been obtained another 5.5 h later. Samples from the dead child were collected approximately 7 h postmortem. The results are summarized in Table 3 and a chromatogram derived from serum samples of the twins is shown in Fig. 1.

Therapeutic concentrations of codeine usually range between 30 and 250 ng/mL (Micromedex, Drugdex Drug Evaluations) and therapeutic concentrations of morphine are between 5 and 64 ng/mL [6]. According to the drug list of The International Association of Forensic Toxicologists, codeine serum levels are considered to be toxic between 300 and 1,000 ng/mL and fatal above 1,600 ng/mL. Toxic concentrations of morphine in serum range from 150 to 500 ng/mL and are regarded as being fatal between 50 and 4,000 ng/mL. These values strongly depend on the route of administration and whether tolerance to respiratory effects has been developed [7]. By example, a concentration of 22 μg/mL codeine in blood has been described in a case of fatal ingestion of this drug [8].

As shown in Table 3, the concentrations of morphine and codeine 6 h after the last intake were in the therapeutic range. However, since the time of codeine to reach the maximum blood concentration was approximately 3 h, it is likely that its concentrations which caused the intoxication were higher than the measured one. The levels of codeine and morphine found in the case of the dead child exceeded the highest reported therapeutic levels in living persons. From the analysis of the *CYP2D6* gene, it can be concluded that the twin brothers had characteristics of extensive

Table 3 Concentration of codeine and major metabolites in samples of the twin brothers

Surviving child				Deceased child			
Compound	Serum (ng/mL)	CSF (ng/mL)	Urine (μg/mL)	Serum[a] (ng/mL)	Serum[b] (ng/mL)	Urine (μg/mL)	Brain (ng/g)
Codeine	174.0	79.1	10.1	436.3	461.2	18.5	541.6
Norcodeine	7.6	5.1	1.1	20.5	20.6	3.1	ND
Codeine-glu	449.8	20.4	52.3	610.9	663.6	82.8	32.4
Morphine	25.6	9.7	2.7	138.7	153.9	6.2	70.8
Normorphine	30.0	ND	3.0	66.6	80.0	6.9	3.9
M6G	23.5	ND	3	39.5	58.4	3.4	ND
M3G	154.3	ND	15.3	134.8	167.6	18.7	ND

M6G morphine-6-glucuronide, *M3G* morphine-3-glucuronide, *Codeine-glu* codeine glucuronide, *ND* not detectable (LLOQ: 5 ng/mL for M3G, morphine, norcodeine, and codeine-glu; 10 ng/mL for M6G and normorphine; and 2 ng/mL for codeine)

[a] Serum derived from blood collected from the left chamber of the heart

[b] Serum derived from blood collected from the right chamber of the heart

metabolizers (EM). In the Caucasian population, the incidence of this genotype is the most abundant, whereas the incidence of poor metabolizers (PM) is about 7% and the ultrarapid metabolizer genotype is only present in 1% of Swedish, German, and Chinese populations [2].

After codeine application, reported codeine to morphine ratios range from 3 in serum to 7 in urine. A value higher than 1 indicates that intoxication is due to the intake of codeine. The ratio can also be indicative of different phenotypes of codeine metabolism including poor, intermediate, or ultrarapid metabolizers. A low ratio indicates that a significant amount of codeine has been metabolized to morphine. In the present cases, it is concordant with the EM phenotype [9].

Determination of the daily dose of codeine and quality control of the applied formulation

According to the mother, she applied ten drops of the codeine retard suspension daily instead of using the spoon supplied with the formulation to measure the target dose of 0.5 mL according to 10 mg of codeine. We therefore measured the weight of ten drops by repeated collection of ten drops (n=6)—by (1) holding the flask vertically and (2) slightly angled by 30°. The average weights of ten drops in these experiments were 847 and 672 mg of the suspension, respectively, corresponding to 1.06 and 0.84 mL and yielding doses of 21.2 and 16.8 mg codeine, respectively.

Furthermore, the quality of the formulation was confirmed by determination of the codeine concentration after acidic hydrolysis (to free codeine from poly(styrol, divinilbenzol) sulfonate which acts as vehicle) by HPLC.

Pharmacokinetic simulation

Using the AutoKinetic software and the mean values of the pharmacokinetic parameters supplied by the manufacturer (Heinrich Mack Nachf, Germany), for a daily dose of 10, 16.8, and 21.2 mg of codeine, the calculated maximum peak concentrations are 83, 140, and 174 ng/mL, respectively (see Fig. 2). This range covers the codeine serum concentration of 175 ng/mL in the sample obtained from the living child. However, the codeine concentrations in the samples from the dead child were higher than 400 ng/mL.

To explain this discrepancy, the calculation was repeated assuming modifications in the pharmacokinetic parameters and presuming administered doses of 16.8 mg due to counting drops instead of measuring 0.5 mL of the preparation. Figure 3 shows the prediction of codeine concentrations after six single doses of 16.8 mg/day using a single compartment model, with modifications of the expected volume of distribution (2.5–5 L/kg), elimination half-life (3–10 h), and bioavailability. These modifications were made because the children were ill for 6 days, which could have affected metabolic capabilities and were very thin which might reduce the volume of distribution. It has to be taken into account that the pharmacokinetic parameters supplied by the manufacturer were obtained in clinical studies with healthy adult volunteers.

Under these significant alterations in the pharmacokinetic parameters, a maximum theoretical codeine concentration of 430 ng/mL was estimated.

Discussion

Dosage errors when measuring liquid formulations can easily occur by using inadequate devices such as household teaspoons or tablespoons instead of a medicine cup [10]. Dosage by drops can also cause unintended high doses and has not yet been reported. Another common cause of intoxication in children is the accidental ingestion of medicines [11].

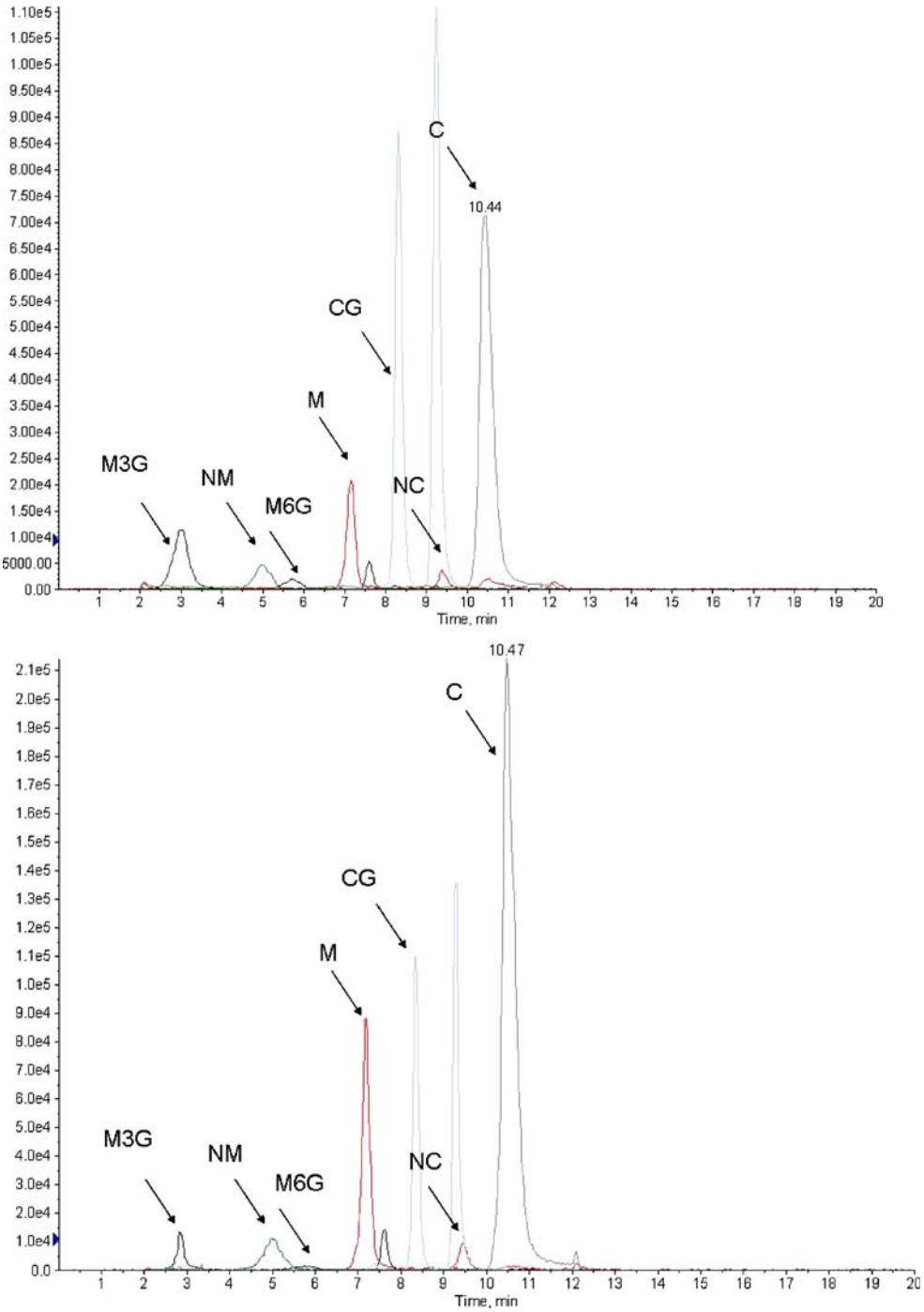

Fig. 1 LC–MS/MS chromatogram of a serum sample from the surviving child (*above*) and of a heart serum sample from the dead child (*below*). *C* codeine, *CG* codeine glucuronide, *M* morphine, *M3G* morphine-3-glucuronide, *M6G* morphine-6-glucuronide, *NC* norcodeine, *NM* normorphine

In the US, the most common types of substances involved in all fatalities were sedatives/hypnotics/antipsychotics followed by opioids [12]. In accordance with the American Association of Poison Control Centers, the most frequently involved drugs in human exposures reported in 2006 were analgesics (11.9%), and 89.5% of all cases occurred at the own residence. Of the reported exposures, 50.9% were in children younger than 6 years old but they only comprised 2.4% of the verified fatalities. In children under 5 years old, analgesics were involved in 8.4% of the intoxications and cold and cough preparations in 5.7%. The cause "inadvertently took/given medication twice" is responsible for 24.6% of the intoxications reported in children younger than 6 years old. Of the 21 drug-associated fatalities in this age group, six involved opioid-type drugs.

Codeine is generally administered to children in repeated doses of 1 mg kg^{-1} up to a maximum of 3 mg kg^{-1} per day [6]. When a slow-release formulation is administered, the intake of codeine is once a day and the dose ranges

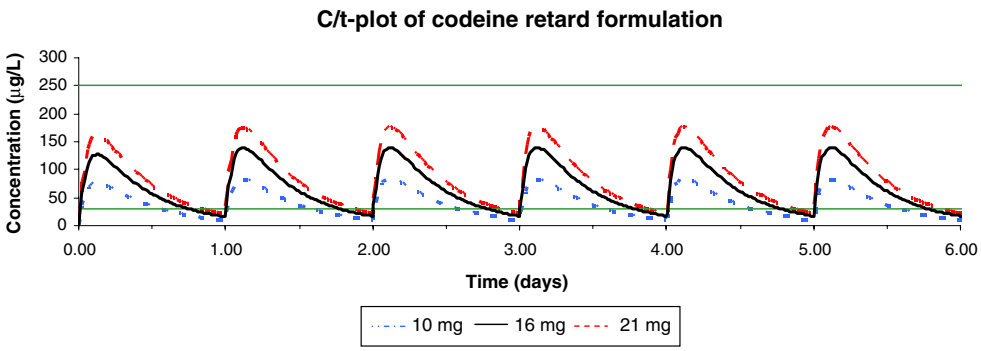

Fig. 2 Estimation of steady-state concentrations of codeine after administration of 10.0, 16.8, and 21.2 mg of the codeine slow-release formulation daily, using the mean values of the pharmacokinetic parameters provided by the manufacturer (see Table 2)

from 10 mg (children 2–4 years old) to 40 mg codeine (6–14 years old).

Codeine is metabolized mainly in the liver by O-demethylation to form morphine (5–15%), by N-demethylation to norcodeine (10–20%), and by partial conjugation to form glucuronides and sulfates of both the unchanged drug and its metabolites. Between 5% and 15% of codeine is excreted unchanged in the urine [2, 13].

O-demethylation of codeine to morphine depends on CYP2D6 [14]. There are a large number of genetic variants for CYP2D6, which leads to a wide spectrum of metabolic abilities within studied populations: individuals are normally classified as either PM or EM, depending on the activity of the enzyme [15]. CYP2D6 genotypes resulting in ultrarapid metabolism yield about 50% higher plasma concentrations of morphine and its glucuronides compared to the EM [9]. According to the present investigation, both twin brothers presented an EM genotype.

Morphine is further metabolized through glucuronidation by uridine diphosphate glucuronosyl transferases (UGT) in the liver. UGT2B7 and UGT1A3 are the major isoenzymes involved in the glucuronidation of morphine [16–18]. UGT2B7 primarily produces M6G and the UGT1A3, M3G [19]. M3G is produced to a greater extent than M6G and is mainly devoid of any opioid analgesic activity [20]. However, M6G is considered to be more potent as an analgesic than morphine itself [21], and inhibiting UGT2B7 could decrease the efficacy of morphine. On the other hand, the inhibition of UGT2B7 could increase the efficacy of morphine because of an increase of the parent drug concentration. UGT enzyme activities can be inhibited by several drugs such as amitriptyline, nortriptyline, and clomipramine [22] and there is also evidence that P450 enzymes can influence glucuronidation by direct protein–protein interactions with UGT [23].

The M6G to morphine and M3G to morphine ratios in serum are 0.9 and 6, respectively, for the surviving child and 0.3 and 1 (mean values of serum derived from heart blood) for the deceased one. This difference may be explained by postmortem distribution of morphine and its glucuronides. As Skopp [24] has suggested, there are differences among sample sites and matrices which can be explained by the hematocrit value and the water content of the analyzed samples. In the presented case, the hematocrit value was 30% for the surviving child and 49% for the deceased one. These values are within or slightly above

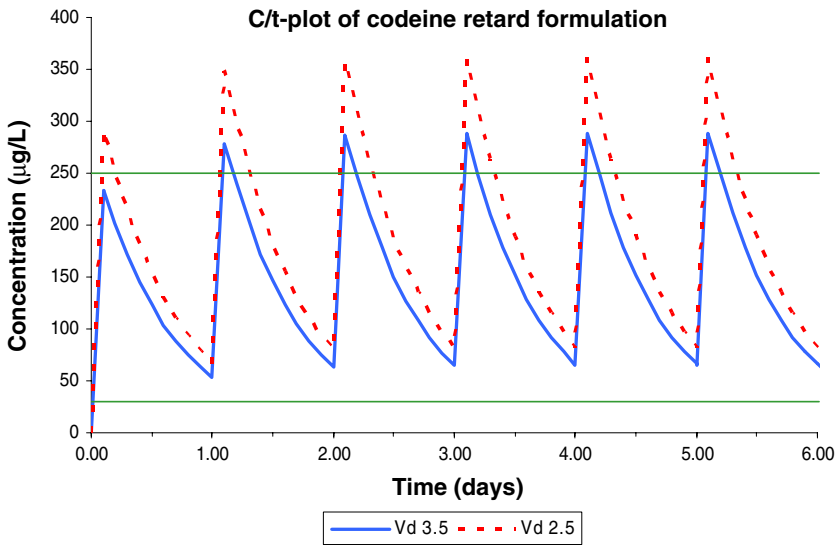

Fig. 3 Estimation of steady-state concentrations of codeine after administration of 16.8 mg of the codeine slow-release formulation daily, when bioavailability and elimination half-life are at the reported maximum; *t* max is lowered to 2 h, and different values for volume of distribution are used. The *horizontal lines* indicate the therapeutic range between 30 and 250 ng/mL

the normal range (30–45%) and do not fully explain the observed differences. Terminal events such as changes of the circulation or ischemia may also contribute to different glucuronide to drug ratios. The concentration of M6G was twice as high in the deceased child compared to the surviving child but these data could also have been influenced by antemortem or postmortem changes [25].

Cardiopulmonary resuscitation was attempted on the deceased child for 1.5 h. The exact time of the death is unknown but it is assumed that cardiac massage may promote absorption and redistribution of the drug in the organism. These processes could be favored by the slow-release formulation. The drug vehicle is a cation exchanger which exchanges codeine for: protons in the stomach and sodium or potassium ions in the intestine [26]. The formulation could have been releasing codeine (postmortem) which was then absorbed and distributed during the long period of cardiopulmonary resuscitation and also before autopsy. Morphine has a higher volume of distribution than its glucuronides and, as in the case of red blood cells, membranes of neuronal cells should also prevent the glucuronides from penetrating the intracellular space. Additionally, the blood brain barrier acts predominantly in one way and polar glucuronides are more easily eliminated than accumulated in brain tissue [27]. For these reasons, morphine glucuronide conjugates were not found in the brain tissue, but codeine and morphine presented high concentrations in brain tissue. However, codeine glucuronide was found in brain, which could indicate that codeine glucuronidation also happens in brain.

Although real-time PCR revealed the EM genotype for both children, which is responsible for high morphine concentrations, this does not explain the high concentrations of codeine in the case of the dead child. Quantitative analysis for codeine, morphine, and their metabolites revealed that intoxication was presumably caused by accumulation of codeine and its active metabolites during treatment for several days, either by changes in pharmacokinetic parameters, such as an elevated bioavailability and decrease of volume of distribution or of renal elimination. For reasons of product safety, an uncommon possible cause for accidental overdosage has to be discussed: while double dosage plays a role in many other intoxication cases of children, in this reported case, an elevated dosage due to counting drops instead of using the volumetric measuring spoon and due to irreproducible drop size depending on the remaining filling volume and positioning of the flask during collection of the highly viscous drops may have occurred. Furthermore, variation in the pharmacokinetic parameters in combination with a postmortem release of the drug from its formulation vehicle to the gastrointestinal tract, subsequent absorption, and distribution during resuscitation could explain the high levels of codeine and metabolites found in the dead child.

After reporting these intoxication cases to the German authorities and to the manufacturer, the originally used retarded formulation of codeine was withdrawn in Germany.

Acknowledgements The authors thank Dr. Andreas Pahl (Institute of Experimental and Clinical Pharmacology, Erlangen-Nuernberg, Germany) for performing the genotype study, and N. Ferreirós thanks the Basque Government for her postdoctoral grant.

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