ACW Lee 李志偉
R Chan 陳巧玲
KT So 蘇鈞堂

A case of probable codeine poisoning in a young infant after the use of a proprietary cough and cold medicine

一個幼兒服用止咳嗽傷風成藥後懷疑可待因中毒的病例

We report a case of probable poisoning with codeine phosphate in a 3-month-old infant, which was associated with excessive dosing and concomitant use of antihistamines. Investigation into the patient's drug history identified the recent use of a proprietary cough and cold medicine containing codeine phosphate and dexchlorpheniramine. The prescribing information, available from a popular prescribing handbook, listed only one dosage for children, without any adjustment for age or size, and did not bear any warning for its use in young children. A review of the handbook identified seven additional remedies that were similarly listed. Medical practitioners and pharmacists should be aware of this prescribing pitfall. Improvements are needed in the prescribing information pertaining to the use of cough and cold formulas containing opioid or opioid-like antitussives among young children, and clear warnings should be included in drug inserts and formularies.

本報告描述一個三個月大的嬰兒，由於用藥過量以及兼服抗組胺劑，懷疑磷酸可待因中毒。從患者的用藥紀錄，查知最近曾服食一種含磷酸可待因和右氯苯那敏的止咳嗽傷風成藥。我們發現一本流行的處方指南內，對於開處藥方的資料，標示的兒童服用劑量只有一個，並沒有按年齡、身材大小來調整用量，也沒有寫明給幼童服用藥物的警告。檢視該處方指南後，發現另外七種藥品亦有類似的問題。醫護人員和藥劑師應該當心這種處方的陷阱。此外，如何為幼童處方含有阿片或阿片類鎮咳劑的傷風咳嗽成藥的資料也需要改善，藥物說明書和藥典也應有明確的警告字句。

Key words:
Antitussive agents;
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關鍵詞：
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Tuen Mun Hospital, Tsing Chung Koon Road, Tuen Mun, Hong Kong:
Department of Paediatrics
ACW Lee, FHKAM (Paediatrics)
KT So, FHKAM (Paediatrics)
Department of Pharmacy
R Chan, MSc, RPh

Correspondence to: Dr ACW Lee
(e-mail: aclee@graduate.hku.hk)

Introduction

Respiratory illnesses are common ailments in children. While most of these conditions are usually self-limiting, the use of medications to control fever, cough, and nasal discharge is a common practice. Cough is a particularly troublesome symptom and the pharmaceutical market is replete with a wide variety of cough and cold medicines. The use of antitussives are generally well tolerated in children over 2 years of age.[1] Opioid-containing antitussives, however, should be avoided in infants because of uncertain pharmacokinetics and limited safety data. In this report, we describe a probable case of paediatric poisoning after the administration of a proprietary cough and cold medicine.

Case report

A 3-month-old boy was admitted to the paediatric ward of the Tuen Mun Hospital in December 2003 because of sudden-onset cyanosis that had lasted for approximately 1 minute on the previous day. He had been born at term to a non-consanguineous couple (birthweight, 3.39 kg) and had been healthy until 1 week before admission. He had been seen by a general practitioner 2 days before presentation because of a persistent cough without fever, for which he was given a prescription of ceftibuten 50 mg/d, L-chlorpheniramine 1 mg three times a day, and a proprietary product (DEC, Synco, Hong Kong) that contained codeine phosphate 2 mg/mL, ephedrine 1 mg/mL, dexchlorpheniramine 0.2 mg/mL, and ammonium 20 mg/mL (at a dosage of 2.5 mL three times daily). On the second day of treatment, the child's appetite had decreased, but there

had been no vomiting or diarrhoea. His parents had noticed that he had developed a dusky complexion, skin mottling, and poor response to external stimuli; there had been no muscle twitching or jerky limb movements. Despite a spontaneous recovery, his parents had decided to discontinue drug treatment and to take him to hospital the next day.

The patient's medical history, which was taken at hospital presentation, was unremarkable except for diphtheria-tetanus-pertussis vaccination 17 days before admission. There was no family history of convulsion. The child had fully recovered his usual activities and skin colour. Growth indicators were normal (weight, 7.6 kg). Neurological, cardiovascular, and respiratory examination results were also normal, as were findings from blood cell counts, electrolyte and blood glucose analyses, chest radiography, and electrocardiography. Furthermore, no respiratory symptoms were observed, and his blood pressure and pulse and respiratory rates during the next 48 hours were normal; thus, he was discharged home. The only medicine that he took during hospitalisation was oxymetazoline 0.1 mg/mL given topically in the nose whenever necessary.

Discussion

Codeine phosphate is a naturally occurring opioid that is commonly used clinically for its analgesic and antitussive effects. Its pharmacological effects and use in children have recently been reviewed.[2] The drug is readily absorbed orally and peak plasma levels occur within 1 to 2 hours. The duration of its analgesic or antitussive effect is 4 to 8 hours, and its elimination half-life is 3.0 to 3.5 hours. However, considerable variation in pharmacokinetics occur in young children: significantly longer elimination half-lives are observed in children with lower body weights. The profile of adverse effects of codeine is similar to that of

Table. Liquid preparations of cough and cold medicines containing opioid or opioid-like antitussives listed in a popular drug formulary[9]

Proprietary cough and cold medicine	Antitussive	Dose per 5 mL	Age-adjusted dosage for children included	Lower age limit (years) included	Warning for use in young children included
Actifed compound linctus	Codeine	10 mg	Yes	2	Yes, <2 years
Benylin CD	Codeine	5.7 mg	Yes	6	Yes, <6 years
Biocalyptol	Pholcodine	6.55 mg	Yes	2.5	No
Bromhexine	Codeine	4.5 mg	No*	Not specified	No
Cocillana compound Universal Pharm	Codeine	11.45 mg	Yes	5	No
Codipront	Codeine	11.1 mg	Yes	2	Yes, ≤ 1 year
Codipront N	Codeine	11.1 mg	Yes	2	Yes, ≤ 1 year
Codoplex (F2)	Codeine	10 mg	Yes	6	No
Coritussal	Dextromethorphan	6.67 mg	Yes	12	No
Cosyr (reformulated)	Dextromethorphan	10 mg	No†	Not specified	No
DEC	Codeine	10 mg	No‡	Not specified	No
Dextro GG	Dextromethorphan	20 mg	Yes	6	No
Dextro plus	Dextromethorphan	15 mg	Yes	6	No
DF night time cough & cold relief	Dextromethorphan	15 mg	Yes	2	No
Dhasedyl	Codeine	9 mg	Yes	2	Yes, <2 years
DM-cordyl	Dextromethorphan	10 mg	No§	Not specified	No
Duro-tuss decongestant	Pholcodine	5 mg	Yes	2	No
Duro-tuss regular	Pholcodine	5 mg	Yes	2	No
Ephedyl	Codeine	10 mg	No‖	Not specified	No
Fedac compound	Codeine	10 mg	Yes	2	No
Fendyl	Codeine	9 mg	Yes	5	No
Hexapneumine syr for children	Pholcodine	5 mg	Yes	2.5	No
Marsedyl	Codeine	9 mg	No¶	Not specified	No
P.E.C. syrup	Codeine	9 mg	Yes	2	No
Robitussin DM	Dextromethorphan	10 mg	Yes	2	No
Robitussin pediatric cough	Dextromethorphan	7.5 mg	Yes	2	No
Sigma relief	Dextromethorphan	10 mg	Yes	8	No
Sigma relief junior	Dextromethorphan	3.75 mg	Yes	2	No
Tripe 'P' cough syrup	Pholcodine	1.5 mg	Yes	2	No
Uni-fedra compound syrup	Codeine	10 mg	Yes	2	No
Uni-pholco	Pholcodine	5 mg	No**	Not specified	No
Uni-ramine C.E. syrup	Codeine	10 mg	Yes	1	No
Vida brown mixture	Opium tincture	0.15 mL	No††	Not specified	No

* Listed as "adult, 10 mL; child, 2.5-5 mL. To be taken qds."
† Listed as "adult, 5-10 mL; child, 2.5-5 mL; infant, 1.25-2.5 mL. To be taken tds-qds."
‡ Listed as "adult, 5-10 mL; child, 2.5 mL. To be taken tds-qds."
§ Listed as "5-10 mL tds."
‖ Listed as "adult, 5-10 mL; child, 2.5-5 mL. To be taken tds."
¶ Listed as "5-10 mL qds."
** Listed as "adult, 5-10 mg; child, up to 5 mg according to age. To be taken tds-qds."
†† Listed as "5 mL tds."

other opioids. Indeed, 10% to 15% of the drug absorbed is converted to morphine in vivo.

Respiratory depression or apnoea has been reported in children who have been given codeine at high doses, either alone or in combination with paracetamol. In Saudi Arabia, a 7-year-old boy with sickle cell disease developed apnoea and seizure after receiving an intravenous injection of codeine phosphate at a dose of 2 mg/kg for veno-occlusive crises, and he required mechanical ventilation in the intensive care unit.[3] In the United States, a 5-year-old boy with renal impairment had undergone tonsillectomy-adenoidectomy and was discharged home with a paracetamol-codeine elixir (containing codeine at 0.71 mg/kg), which was taken every 4 hours. He was found to be apnoeic, cyanotic, and convulsive the next morning, and was admitted to the intensive care unit for ventilatory care.[4] Charlton and Fielding[5] reported their experience of administering codeine 1 mg/kg intramuscularly to 121 newborn infants for postoperative pain relief. Seven babies subsequently developed respiratory failure and required intubation, although the authors still concluded that the analgesic was safe and effective. In a report of a fatal case, a 1-month-old infant had been treated with two doses of codeine 0.63 mg/kg 6 hours apart; postmortem biochemical analysis showed opiate intoxication.[6] Tong and Ng[7] also reported a case of life-threatening administration of a propriety cough mixture containing codeine 6.6 $mg \cdot kg^{-1} \cdot d^{-1}$ to a baby.

Although the exact cause of the cyanosis and possible apnoeic spell in the patient described in our case, which might have had an infective, convulsive, or metabolic origin, could not be determined because of the delay in medical evaluation, the temporal sequence of events and symptoms suggested that the cough and cold remedy was the probable cause. The amount of codeine phosphate taken (2 $mg \cdot kg^{-1} \cdot d^{-1}$) was double the recommended dose of 1 $mg \cdot kg^{-1} \cdot d^{-1}$.[8] The concomitant use of antihistamines might have added to the sedative effects of the opioid.

The published recommended dosages of codeine and other antitussives have not been vigorously tested in children.[8] Despite the lack of efficacy studies in children and of proven effectiveness of proprietary cough mixtures in the paediatric age-group, and despite the possibility of adverse effects, the use of such medicines is a common practice. A popular handbook that is used for routine prescribing of pharmaceutical products available in Hong Kong contains 33 liquid preparations of "cough and cold remedies" containing opioid or opioid-like antitussives (Table).[9] Among them, 16 contain codeine phosphate, 10 contain dextromethorphan hydrobromide, six contain pholcodine, and one contains opium tincture.

According to the prescribing information listed in the handbook,[9] the proprietary agents can be broadly classified into three groups with respect to paediatric use: (1) paediatric use with age-adjusted dosing, together with special precaution when used in younger children; (2) paediatric use listed with age-adjusted dosing only, implying a lower age limit for use; and (3) paediatric use listed without age- or weight-adjusted dosing. Five proprietary products belong to the first category, and warnings are specified for use in younger children below a certain age. Twenty preparations are listed for use in children with age-adjusted dosing only; the implied lower age limit is between 1 year and 12 years of age, the majority being 2 years.

Of concern are the eight proprietary products that are listed for use in children without specification of age- or weight-adjusted dosing. None of them carries a precautionary note in the formulary for use among young children. It is difficult to imagine how a single 5-mg dose of codeine suits the needs of both a 3-month-old infant and a 10-year-old child. In particular, prescribing information in the formulary for the medicine relevant to this case report listed only one dosage for children, without any adjustment for age or size, and did not bear any warning for its use in young children. When the local distribution company for the proprietary remedy mentioned in this case report was contacted, it did not provide us with a separate drug insert or paediatric prescribing information.

In summary, cough and cold preparations containing opioid or opioid-like antitussives should be used with great caution in young children. If the dose of the opiate compound is not checked to ensure that it is appropriate for the age and body weight of the patient, use of these medicines may lead to adverse effects and even death. We recommend that prescribing and precautionary information of proprietary products be improved, such that age-adjusted dosage and risks associated with their use can be clearly communicated to doctors and parents.

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