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Unintentional mortality associated with paracetamol and codeine preparations, with and without doxylamine, in Australia

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ABSTRACT

Introduction: Misuse of paracetamol, codeine and doxylamine combination analgesics may lead to addiction and mortality. This study aimed to (1) identify unintentional deaths in Australia associated with use of combination analgesic products containing paracetamol, codeine and doxylamine; (2) describe cases characteristics, including demographics and additional medication use; and (3) identify common factors associated with misuse and mortality of these medicines in Australia.
Design: This retrospective case series analysed National Coronial Information System data to identify cases of unintentional death attributable to paracetamol, codeine and doxylamine products between 2002 and 2012.
Setting: Three Eastern Australian states: New South Wales, Queensland, Victoria, comprising a population of approximately 18.6 million people.
Results: 441 unintentional deaths attributed to paracetamol/codeine products were identified; doxylamine was detected in 102 cases (23%). Overall unintentional death rates rose from 0.9-per-million in 2002 to 3.6-per-million in 2009, declining to 1.9-per-million in 2012. Median age at time of death was 48, half of all cases occurred between 35-54 years of age, and 57% were female. Concomitant medication use was detected in 79% of cases, including benzodiazepines, other opioids, psychiatric medications, alcohol and illicit drugs. Behaviours consistent with drug misuse including doctor/pharmacy shopping, excessive dosages and extended use, were identified in 24% of cases.
Conclusions: This study identified 441 deaths associated with codeine-combination analgesic products across three Australian states; with an average of 40 deaths per year. Death commonly involved multiple substance use and abuse behaviours indicative of misuse and dependence.

1. Introduction

Paracetamol, a first-line therapy for mild-to-moderate pain due to its efficacy, tolerability and affordability, is often combined with codeine, a weak opioid and pro-drug of morphine [1]. Doxylamine, a first-generation antihistamine with anticholinergic effects, may be included in paracetamol/codeine products for additional relief [2]. In Australia, these medications are available without prescription ('over-the-counter', OTC) for temporary self-management of pain (codeine $\leq$ 15 mg, maximum 5-days' supply), or via prescription in increased strengths (codeine-30 mg) and quantities. Evidence suggests the proportion of people who receive effective analgesia from codeine is limited, with a number-needed-to-treat of 12 to achieve $\geq$50% pain relief with codeine-60 mg [3]. As OTC codeine-containing analgesics are restricted to codeine-15 mg/tablet, there is limited evidence that they offer effective pain relief compared to codeine-free preparations (e.g. paracetamol–ibuprofen). In addition, inactive CYP2D6 enzymes may cause some individuals to metabolise codeine poorly, receiving inadequate pain relief, while 'ultra-rapid' metabolisers, individuals with extra CYP2D6 enzymes, may experience adverse effects and overdose symptoms, even at recommended dosages [4]. Incorrect use of combination analgesics may result in serious harm. Supra-therapeutic paracetamol intake is associated with acute liver failure (ALF), hepatic necrosis, multiple-organ failure and death [1,5–7]. Codeine misuse may cause respiratory depression leading to bronchopneumonia or aspiration pneumonia, central nervous system (CNS) depression and coma [8]. Doxylamine toxicity is associated with sedation and renal injury [2]. Prolonged opioid use is associated with dependence and

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tolerance, and the mild euphoria and sedation caused by codeine or doxylamine may lead to misuse [8,9].

The potential for combination analgesic misuse, alongside their easy accessibility, has raised concern among medical and pharmacy experts [8,10]. Rates of OTC and prescription medication abuse have risen worldwide, and combination analgesic misuse is a growing public health problem [7,9,10]. In Australia, OTC codeine must be purchased with pharmacist supervision to allow screening for inappropriate or unsafe use; however surveys of people who have misused codeine reveal drug-seeking behaviours including doctor or pharmacy shopping: the practice of visiting several providers to avoid restrictions [10,11]. In December 2016, the Australian Therapeutic Goods Administration (TGA) announced the rescheduling of all codeine-containing analgesics to prescription-only from February 2018, drawing opposition from industry groups [12].

In Australia, ascertaining codeine misuse rates is difficult; OTC medications are excluded from Pharmaceutical Benefits Scheme data, and there is no compulsory monitoring for codeine sales [13]. Analysis of pharmacy purchasing data reported 27-million packs of codeine-containing products were purchased by Australian pharmacies in 2013; 55% were OTC products [14]. Previous research of codeine deaths in Australia determined that prescription products were used in 59.9% of cases, with OTC products used in the remainder [8]. Cross-sectional data suggest approximately 500,000 Australian adults engaged in non-medical use of codeine (prescription and OTC) in the preceding month; with higher reported use in respondents between 18–49 years of age [15]. US studies report combination analgesics are more likely to be abused by females and patients 40-years or over [7,16], while Australian studies of self-reported codeine misusers reveal higher proportions (70%) of females [10].

Recent research has described the incidence of intentional and unintentional deaths involving codeine products, and codeine–ibuprofen combinations [8,13,17]. However, there is little published data examining the use of codeine-paracetamol formulations, particularly when combined with doxylamine.

This study aimed to identify unintentional deaths reported to Australian coroners involving paracetamol, codeine and doxylamine products, and to describe case characteristics including demographics, trends, and factors associated with combination analgesic mortality.

2. Methods

2.1. Setting

A retrospective audit of the National Coronial Information System (NCIS) was conducted. A search of closed cases in three Australian states (New South Wales, Queensland and Victoria) from 2002 to 2012 for unintentional deaths related to paracetamol/codeine products, with or without doxylamine, was undertaken. The majority of recent Australian evidence has come from Eastern Australia and these three states represent almost 80% of the Australian population and thus were selected for this study [13,17]. Cases from 2013-onwards were omitted as many investigations were ongoing at time of analysis.

2.2. Case collection

Coronial reports including autopsy, toxicology, police reports and coronial findings were searched for relevant keywords (Table 1). An additional search was conducted for cause of death coded as 'paracetamol in combination with codeine/or other substances'.

The following exclusion criteria was applied:

1. Cases where the coroner determined death to be intentional
2. Deaths due to paracetamol alone
3. Deaths due to codeine alone or codeine products without paracetamol

2.3. Data analysis

Data collected from medico-legal reports included demographics, cause of death, and toxicology results. The coroner's report was reviewed, including the primary cause of death and findings. In cases where heroin use was identified, secondary evidence of codeine use was identified to exclude codeine appearing in toxicology as a heroin contaminant. Similarly, morphine was recorded when secondary evidence of morphine use was identified by either the police or coronial reports, to account for morphine appearing in toxicological reports as a codeine metabolite. Police and coronial reports were searched for reported behaviours associated with drug misuse such as excessive or extended use, and doctor/pharmacy shopping.

Population data from the Australian Bureau of Statistics was used to calculate rates of unintentional death-per-million of the population for each state [18]. To determine the significance of trends in mortality rates, post-hoc interrupted time-series analysis was conducted using linear regression modelling (Stata v14.2, StataCorp, College Station, Texas USA). Descriptive statistics were used for demographics and factors associated with mortality.

2.4. Ethics

This study was approved by the Victorian Institute of Forensic Medicine Research Advisory Committee (RAC6/14) and the Victorian Department of Justice Human Research Ethics Committee (CF/14/18348).

3. Results

3.1. Mortality

Keyword and coding searches returned 15,866 potential cases. Following application of exclusion criteria, 441 cases were identified where paracetamol–codeine combination products contributed to unintentional death from 2002 to 2012 (New

Table 1
Keyword searching methodology.

Report	Keywords/terms searched
Autopsy report Coroner's findings	Acute liver failure; liver damage; liver necrosis; drug induced liver damage; paracetamol toxicity; paracetamol overdose;
Toxicology report Coroner's findings	Drug names: paracetamol, codeine, doxylamine
Police reports Coroner's findings	Brand names: Panadeine; Mersyndol; Restavit; Dolased; Panalgesic; Fiorinal