Serious morbidity associated with misuse of over-the-counter codeine–ibuprofen analgesics: a series of 27 cases

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ABSTRACT

Objective: To investigate morbidity related to misuse of over-the-counter (OTC) codeine–ibuprofen analgesics.

Design and setting: Prospective case series collected from Victorian hospital-based addiction medicine specialists between May 2005 and December 2008.

Main outcome measures: Morbidity associated with codeine–ibuprofen misuse.

Results: Twenty-seven patients with serious morbidity were included, mainly with gastrointestinal haemorrhage and opioid dependence. The patients were taking mean daily doses of 435–602 mg of codeine phosphate and 6800–9400 mg ibuprofen. Most patients had no previous history of substance use disorder. The main treatment was opioid substitution treatment with buprenorphine–naloxone or methadone.

Conclusions: Although codeine can be considered a relatively weak opioid analgesic, it is nevertheless addictive, and the significant morbidity and specific patient characteristics associated with overuse of codeine–ibuprofen analgesics support further awareness, investigation and monitoring of OTC codeine–ibuprofen analgesic use.

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While extensive overseas evidence is accumulating about the non-medical use of prescription opioids[1-5] and the serious consequences of such use,[1-4,6,7] literature on non-prescribed or over-the-counter (OTC) opioids is mainly confined to case descriptions.[8-11] This is despite indications, such as in the 2007 Australian National Drug Strategy Household Survey, that over half a million Australians used pain killers for non-medical purposes,[12] the third most common category of substance use in Australia after cannabis and ecstasy.

Although codeine is often described as a weak opioid analgesic, codeine dependence is a well recognised complication of long-term use.[13-15] Codeine-containing medications are available in Australia either through a doctor's prescription or in combination OTC formulations with simple analgesics. Substance-dependent individuals who escalate their dose of medication above recommended amounts are at risk of harm from the accompanying simple analgesic,[16] including toxicity from non-steroidal anti-inflammatory drugs (NSAIDs)[17-19] such as ibuprofen.

We collected data on a series of 27 patients as a response to clinical interest in anecdotal reports of misuse of an OTC pharmaceutical product containing codeine phosphate 12.8 mg and ibuprofen 200 mg.

METHODS

Clinicians in a network of specialist addiction treatment services (the Victorian Addiction Inter-hospital Liaison Association) in several Victorian health regions collected and submitted the cases for this study. These services cover nine hospitals across Melbourne metropolitan regions and rural Victoria. They range from small, specialist consultation–liaison teams to large, multidisciplinary suites, including alcohol and other drug outpatient treatment services. The 27 patients either presented for treatment of opioid dependence, or were inpatients referred to hospital addiction medicine services between May 2005 and December 2008.

A case report form was used to collect standardised information about OTC codeine–ibuprofen cases. The form included the following details: the harm experienced by the patient; the minimum and maximum doses of OTC codeine–ibuprofen consumed; the patient's drug use history; the main brand of OTC codeine–ibuprofen used; the drug source; a description of the patient's presentation; and patient outcomes.

Details of the study and the case report form were disseminated to participating addiction medicine clinicians. Addiction medicine specialists completed all but two of the case report forms, and two forms were received from specialist addiction medicine clinical nurse consultants. Four separate addiction services, from southern, eastern, western and central metropolitan Melbourne contributed cases.

Descriptive analysis was conducted with SPSS, version 14.0 (SPSS Inc, Chicago, Ill, USA). The study was approved by the Victorian Department of Human Services Human Research Ethics Committee.

RESULTS

Of the 27 patients in the cases collected, about half were male (sex was not reported in one case).

Most of the sample (17) did not report a history of injection drug misuse. Just over half the patients (14) reported only using pharmaceutical drugs (Box 1). Three patients had a history of alcohol use disorder.

Opioid dependence and gastrointestinal complications (attributed to ibuprofen) were the most common morbidities, with 10 cases of each. Three patients had hypokalaemia and one patient required dialysis. These complications (hypokalaemia and renal failure) are associated with

1 Characteristics of the 27 patients treated for misuse of OTC codeine–ibuprofen analgesics

Case characteristics	*n*
Male	14
Age (years)	
20–29	8
30–39	7
⩾ 40	9
History of intravenous drug use	10
Reported only using pharmaceutical opioids	14
Reported no other substance use with OTC codeine	15
Reported prolonged codeine use	26
Anaemia	12
Codeine use	**Mean**
OTC codeine use (range)	3.6 years (2 days – 11 years)
Minimum daily dose (range)	34 tablets (10–72)

OTC = over the counter. ◆

2 Summary of presentations and outcomes for the 27 patients treated for misuse of OTC codeine–ibuprofen

Patient presentation	Daily intake (tablets)	Outcome/management
Mainly GI medical complications		
GI haemorrhage, perforated duodenal ulcer	48	Treated with buprenorphine–naloxone
Persistent vomiting, GI haemorrhage requiring gastrectomy	20	Discharged on slow-release oxycodone
Admitted with duodenal haemorrhage, anaemia and hypokalaemia	24	Opioid withdrawal treated; LTFU
Referred while an inpatient with haematemesis, anaemia (Hb 55 g/L); initiated use for chronic back pain	20–40	Treated with pantoprazole; referred to community AOD clinic
Multiple ED presentations with complications of ibuprofen-related anaemia and haematemesis	48–72	Stabilised on buprenorphine
GI haemorrhage, perforated peptic ulcer	50	Stabilised on methadone solution
Second GI haemorrhage in 2 years; initiated use for back pain and escalated dose	24–48	Treated with buprenorphine
Mainly other medical complications		
Acute renal failure, GI haemorrhages; required transfusion and ICU admission	24–48	Treated with methadone
Hypokalaemia; initiated use for arm pain	24–48	Admitted to ICU and stabilised
Mainly medical complications and dependence or overdose		
Opioid-dependent; initiated use for back pain. Presented for detoxification, hypokalaemic at admission	48–100	Treated with buprenorphine
Admitted for opioid withdrawal; mild anaemia (Hb 99 g/L)	72	Stabilised on buprenorphine–naloxone
Unintentional drug overdose; gastric erosion; initiated use for headaches	12–24	Treated with buprenorphine
Admitted following overdose; hypokalaemia (potassium 2.2 mmol/L); initiated use for back pain	48	7-day inpatient admission
Detoxification; nausea, vomiting and insomnia	72	Treated with buprenorphine–naloxone
Referred by mental health team for withdrawal from codeine–ibuprofen; peripheral oedema; initiated use for dental pain	24–48	Treated with buprenorphine–naloxone
Withdrawal from Nurofen Plus; mild anaemia, gastric erosions; initiated use for headaches and escalated dose	50–70	Withdrawal managed with buprenorphine
Referred for opioid pharmacotherapy; reported injecting oxycodone and taking zolpidem; previous GI haemorrhage; initiated use for chronic back pain and escalated dose	20–50	Referred for treatment of opioid dependence
Detoxification; previous peptic ulcer; initiated use for headache and escalated dose	72–75	Stabilised on buprenorphine–naloxone
Mainly opioid-dependence or overdose		
Detoxification; opioid-dependent; initiated use for dental pain	10–20	Withdrawal managed with buprenorphine
Opioid withdrawal	40–50	Treated with buprenorphine
Codeine dependence; assessment for withdrawal treatment	12	LTFU
Pharmacotherapy for opioid dependence; initiated use for headaches	12–24	Treated with methadone
Opioid withdrawal	50	LTFU
Management of codeine dependence; initiated use for stress fracture pain	48–72	Treated with buprenorphine–naloxone
Codeine dependence; referred by mental health services; initiated use for back pain	12–24	Transferred to codeine phosphate tablets
Treatment for opioid dependence; initiated use for back pain and escalated dose	24–48	Treated with buprenorphine–naloxone
Detoxification; initiated use for headache and escalated dose	20–24	Stabilised on buprenorphine–naloxone

OTC = over-the-counter. GI = gastrointestinal. LTFU = lost to follow-up. Hb = haemoglobin. AOD = alcohol and other drugs. ED = emergency department. ICU = intensive care unit. ◆

use of high doses of NSAIDs such as ibuprofen. Four patients were admitted to a hospital intensive care unit, and 12 had documented anaemia.

However, 26 of the 27 patients reported prolonged use (longer than 6 months) of supratherapeutic doses of OTC codeine–ibuprofen, with a mean duration of use of 3.6 years (Box 1). In the 15 cases where the OTC codeine–ibuprofen source was documented, the patient reported using multiple pharmacies to acquire these medications.

A mean dose range of 34–47 tablets per day was reported in this case series. This number of tablets would provide a mean daily dose of 435–602 mg of codeine phosphate and 6800–9400 mg of ibuprofen. Most patients did not document a brand of OTC codeine–ibuprofen. Nurofen Plus was the brand specified by all nine patients who reported the brand.

A significant proportion of patients ($n = 15$) reported initiating use of OTC codeine–ibuprofen products for painful conditions,

including back pain and headaches, and subsequently escalating the dose (Box 2).

Most patients ($n = 16$) were treated with some form of opioid pharmacotherapy, with three patients undertaking buprenorphine-assisted detoxification, and 13 were started on opioid substitution treatment (OST). Of those who received OST, most ($n = 10$) received sublingual buprenorphine–naloxone, and three received methadone solution.

DISCUSSION

To our knowledge, this is the largest collection of cases examining the complications of prolonged use of supratherapeutic doses of OTC codeine–ibuprofen. As with the published case studies on OTC analgesic misuse, we found serious morbidities consistent with NSAID toxicity[20] including gastrointestinal disease, renal failure, anaemia and severe hypokalaemia.[8,9] Many of our study's patients differ from previously described opioid-using treatment populations,[21] with most reporting no drug and alcohol treatment history, and around half having no history of other current or past illicit substance use. Despite this, more than half the patients described in this series received OST for opioid dependence.

As a case series relying on clinical data opportunistically collected by specialist hospital addiction medicine services, this study has limitations. Our study is not able to estimate the prevalence of codeine–ibuprofen misuse or associated morbidity. While our case series suggests an association between chronic use of supratherapeutic doses of OTC codeine–ibuprofen and medical complications, we have not looked at toxicity associated with therapeutic doses. It is unclear whether these cases represent a small proportion or a sentinel group of OTC codeine–ibuprofen misusers in the Australian community. Despite these limitations, this study is consistent with, and broader than, previously published reports.[8,9,20]

Information about morbidity resulting from misuse of OTC medications is scant, as comprehensive surveillance of adverse events associated with OTC medications relies on patient reporting and health professional documentation and submission of the event. Amounts of OTC medications purchased by individuals (eg, through "pharmacy shopping") are also difficult to monitor in the absence of a routine recording system, such as that used to limit sale of pseudoephedrine, a methamphetamine precursor drug.[22] At time of writing, pharmacists were only required to supervise dispensing of large pack sizes of OTC codeine–ibuprofen (more than 24 tablets). Due to concerns about harm from misuse of these preparations, rescheduling on 1 May 2010 requires that all OTC codeine–ibuprofen products be supplied directly by a pharmacist.

In many of these cases, serious morbidity resulted from use initiated for therapeutic reasons, such as persisting pain. Given that these drugs are likely to remain available without prescription in Australia, physicians should ask specifically about non-prescribed analgesics when taking a medication history, and pharmacy personnel should consider the risk of misuse when supplying these combination analgesic products. We believe the response of health professionals to opioid dependence from OTC codeine–ibuprofen misuse is an important area for future research.

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COMPETING INTERESTS

Matthew Frei has received financial support from Reckitt Benckiser (manufacturers of Suboxone and Nurofen Plus) to attend a conference. Suzanne Nielsen has worked on a project (unrelated to this study) funded by Reckitt Benckiser and administered through Turning Point Alcohol and Drug Centre, and Reckitt Benckiser has funded her attendance at a meeting unrelated to this work. Claire Tobin participated in the Victorian Public Health Training Scheme, funded by the Victorian Department of Health, while this study took place.

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