Misuse of over-the-counter codeine-containing analgesics: dependence and other adverse effects

Geoffrey M Robinson, Sophie Robinson, Patrick McCarthy, Christina Cameron

Abstract

Aim To review cases of codeine dependency from over-the-counter (OTC) combination analgesics admitted to a hospital detoxification unit.

Method Case records of all admissions following an index case were reviewed over a 2-year period.

Results There were 7 cases reporting chronic excess of Nurofen Plus, of which 6 had prior or current histories of alcohol dependency. Complications which were likely contributed by excessive ibuprofen consumption included: gastric ulcer (4 patients), gastrointestinal bleeding (3), hepatotoxicity (1), and inflammatory bowel conditions (2).

Conclusions This pattern of admissions is new to the detoxification unit, and may relate to higher codeine content in the combination product, and marketing strategies. These cases likely represent the severer end of the spectrum of codeine dependency acquired from OTC pharmacy sources. The paucity of evidence to support additional benefit from the inclusion of codeine in analgesic combination products is concerning. There is a need for increased pharmacovigilance around these and other OTC medications.

For many decades codeine phosphate has been available OTC in combination with aspirin or paracetamol for analgesia. There was some scrutiny of this situation in the 1980s during the period of “homebaking” when large quantities of Panadeine (paracetamol 500mg and codeine 8mg per tablet) were purchased for/by homebakers who converted codeine to morphine for illicit use. However, no restrictions on sale were imposed.

Homebaking was a particular issue arising from the dearth of imported heroin into New Zealand, which continues to this day. Currently the over-riding concern is the increasing practice of prescribed Class B drugs, such as morphine, being diverted to the street market.

Over recent years codeine (Class C) has become available OTC also in combination with non-steroidal anti-inflammatory (NSAID) drugs, particularly ibuprofen. A variety of codeine-containing analgesics products are currently available as shown in Table 1.
Table 1. Over the counter codeine-containing analgesics 2009

<table>
<thead>
<tr>
<th>Product</th>
<th>Codeine dose (mg)</th>
<th>Other analgesics dose (tablets/box)</th>
<th>Box size (tablets/box)</th>
<th>Maximum number of tablets/24 hour (as per product information)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Ibuprofen (mg)</td>
<td>Paracetamol (mg)</td>
<td></td>
</tr>
<tr>
<td>Nurofen Plus</td>
<td>12.80</td>
<td>200</td>
<td></td>
<td>12,24,48,72</td>
</tr>
<tr>
<td>Panadeine</td>
<td>8.00</td>
<td>500</td>
<td></td>
<td>12,24,48,50,100</td>
</tr>
<tr>
<td>Panadeine Plus</td>
<td>15.00</td>
<td>500</td>
<td></td>
<td>12</td>
</tr>
<tr>
<td>Mersyndol*</td>
<td>9.75</td>
<td>450</td>
<td></td>
<td>20</td>
</tr>
<tr>
<td>Paracotene</td>
<td>8.00</td>
<td>500</td>
<td></td>
<td>12,20</td>
</tr>
<tr>
<td>Panafen Plus</td>
<td>12.80</td>
<td>200</td>
<td></td>
<td>24,48</td>
</tr>
<tr>
<td>Codalgin</td>
<td>8.00</td>
<td>500</td>
<td></td>
<td>100</td>
</tr>
</tbody>
</table>

* Also contains 5mg doxylamine.

Despite labelling on combination products including maximum dosage, as in Table 1, and cautions regarding potential adverse effects from codeine (drowsiness, driving, and interaction with alcohol), and the NSAID (gastrointestinal, renal adverse effects, exacerbation of asthma, and in pregnancy), there remains a potential for misuse because of the dependency potential of codeine. Despite a call for more research into OTC drug dependence,2 little is known about this issue. Addiction warnings are being considered on labelling in the UK.

We have been prompted to report a change in pattern over the last 2 years of patients being admitted to the Kenepuru Hospital Detoxification Unit with codeine dependency from OTC preparations and various likely complications of excessive ibuprofen.

Patients

All 7 patients with a substantive history of OTC codeine abuse are reported since the first one in August 2007. During this period there has been only one admission for codeine dependence which related solely to prescribed codeine.

These cases are summarised in Table 2.

Clearly there was difficulty discerning the confounding contribution to complications in those patients with current active alcoholism (4 cases) and the effects of the NSAID. However, it is likely the high-dose NSAID significantly contributed, as these patients had ulcers as opposed to gastritis which is much commoner with alcohol excess alone. The patient with hepatotoxicity had an atypical pattern of liver tests for alcohol per se, and other causes of acute hepatotoxicity were excluded.
Table 2. Detoxification Unit admissions 2007–2009 with OTC codeine dependence

<table>
<thead>
<tr>
<th>Date of admission</th>
<th>Gender/age</th>
<th>Product/report dosage tabs per 24hrs/duration</th>
<th>Comorbidities</th>
<th>Likely complications of NSAID</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aug 07</td>
<td>M 52</td>
<td>Nurofen Plus 60-80/2 years</td>
<td>Alcoholism*</td>
<td>Hepatotoxicity</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Gastric ulcer and GI bleeding</td>
</tr>
<tr>
<td>Oct 07</td>
<td>F 31</td>
<td>Nurofen Plus 48/2 years</td>
<td>Depression</td>
<td>Pptic ulcers and anaemia 76 g/l on admission</td>
</tr>
<tr>
<td>Aug 08</td>
<td>F 63</td>
<td>Nurofen Plus (and prescribed codeine) 20/3 years</td>
<td>Alcoholism* Bronchiectasis* Depression*</td>
<td>Gastric ulcer (diagnosed during detox)</td>
</tr>
<tr>
<td>May 09</td>
<td>F 47</td>
<td>Nurofen Plus Up to 72/1 year</td>
<td>Alcoholism* Depression/anxiety* Psychosis* Gastric bypass 2000 Headache* Partial colectomy</td>
<td>“Inflammatory bowel disease”</td>
</tr>
<tr>
<td>June 09</td>
<td>M 52</td>
<td>Nurofen Plus 80/1 year</td>
<td>Alcoholism and opiate dependency</td>
<td>Ileal resection</td>
</tr>
<tr>
<td>July 09</td>
<td>F 31</td>
<td>Nurofen Plus Up to 120/2 years</td>
<td>Chronic pelvic pain* Alcohol abuse* Depression* Cannabis*</td>
<td>Gastric ulcer and bleeding Gastrectomy 03/07</td>
</tr>
<tr>
<td>July 09</td>
<td>M 35</td>
<td>Nurofen Plus 48/2 years</td>
<td>Previous alcohol abuse Benzodiazepine dependency</td>
<td></td>
</tr>
</tbody>
</table>

* current
These patients described patterns of visiting multiple pharmacies, sometimes travelling considerable distances, to obtain the Nurofen Plus. Many of the patients suffered significant opioid withdrawal symptoms despite treatment with ancillary medications.

Discussion

The seven patients demonstrate a new pattern of admissions with OTC codeine dependence, and this has occurred since the introduction of combination products containing codeine and ibuprofen. This may reflect issues of marketing and availability, as well as increased doses of codeine per tablet.

We consider that ibuprofen likely contributed to proton pump inhibitor-resistant gastric ulceration in four, hepatotoxicity in one and bowel inflammation in two. None had renal impairment, or hypokalaemia as has been reported with ibuprofen excess. It is perhaps remarkable that these patients tolerated the reported dosages of ibuprofen without sustaining greater morbidity.

A recent report from Australia described 77 cases who had escalated to average dose of 50 tablets a day of OTC analgesics containing codeine over a mean of two and a half years because of codeine dependence. Amongst the 77 there were 39 cases of gastrointestinal haemorrhage or perforation, seven cases of renal failure and five cases of serious hypokalaemia.

Our cases probably represent one end of a spectrum, being those referred for admission for medical detoxification as part of their addiction treatment. It is important to note that six had pre-existing or current other substance or alcohol dependency diagnoses. The extent of OTC codeine misuse with lower degrees of severity is unknown. Ford refers to two UK websites http://over-count.org.uk/ and http://codeinefree.me.uk) with 4000 people self-reporting having codeine dependency problems.

Enquiry to the NZ Pharmacovigilance Centre (NZPhVC) revealed 5 notifications attributed to Nurofen Plus (2 gastrointestinal, 1 jaundice, 2 allergic reactions). The National Poisons Centre reported 136 ibuprofen intentional overdoses (Slaughter R- personal communication) from a variety of OTC products. There was only one report relating to chronic abuse.

Whatever may be the true prevalence of adverse effects from OTC analgesics containing codeine, it remains remarkable that the combinations have not been given more scrutiny regarding their efficacy versus risks of adverse effects. In particular we understand that for codeine to have significant effect additional to paracetamol, that doses of 30mg or more are recommended. In addition, regular use of combination products produces more adverse effects. Indeed the British National Formulary itself is lukewarm stating “compound analgesics preparations containing paracetamol or aspirin with a low dose of opioid analgesic (e.g. 8mg of codeine phosphate per compound tablet) are commonly used but the advantages have not been substantiated.

The low dose of opioid may be enough to cause opioid side effects (in particular constipation)…yet may not provide significant additional relief of pain. A full dose of opioid component, e.g. 60mg of codeine phosphate in compound analgesic
preparations effectively augments the analgesic activity but is associated with the full range of opioid side effects...”

The lack of supportive pharmacological evidence for combinations of lower dose codeine in compound analgesics, and the risk of adverse effects prompts the need for a review on the rationale for the continuing provision of these commonly used OTC products.

The Medicines Classification Committee (Ministry of Health NZ) has considered the classification of codeine in combination products as a restricted medicine with limitations on codeine dosage and pack size, and a requirement for a labelling warning on addiction potential to come into effect 4 October 2010.

It would seem that the public uptake and marketing of OTC analgesics (combination or not) is increasing. Thus in this culture of convenience, and increased consumer involvement, there are distinct risks around the overuse of these drugs, and the level of advice around safe use that can be provided.

There are clearly reasons for pharmacovigilance systems on non-prescribed drugs to be equivalent to those of prescribed. We have reported seven cases of codeine dependency arising from an OTC combination product, with various other medical complications, but suggest these are one end of a broad spectrum involving many more cases. Practitioners need to report their experiences on patients, who are likely to present to addiction/psychiatric services as well as acute services (including gastroenterology, surgical, renal and internal medicine), to build a wider database on the adverse effects and morbidity from OTC medicines.

Competing interest: Nil

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Acknowledgements: This is a joint paper from CCDHB and the Medical Research Institute of New Zealand under the framework of the Health Education Research Collaborative Centre (HERCC).

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