

Cold water extraction of codeine containing combination analgesics available prescription free in Australia

Thompas Rippers and Cornelia Locher

Pharmacy Program & Centre for Optimisation of Medicines
University of Western Australia
Crawley WA 6009, Australia
connie.locher@uwa.edu.au

Abstract—The abuse of codeine containing combination analgesics leads to significant non-opioid toxicities. Cold water extraction (CWE) reduces these side effects but can also provide access to highly restricted codeine phosphate. This study aims to assess the effectiveness of CWE for a range of drug combinations available on the Australian market as 'pharmacist-only' medicines. Six products containing codeine phosphate in combination with paracetamol, ibuprofen or aspirin as well as an excipient free mixture of codeine phosphate and ibuprofen lysinate were treated by CWE and the resulting drug content in the filtrate analysed by HPLC. The effect of an additional acidification step was also assessed for combinations containing aspirin and ibuprofen lysinate. It was found that CWE is able to remove almost all ibuprofen (up to 97%), but significant amounts of paracetamol (between 70% and 80% depending on the formulation) and aspirin (nearly 60%) remain in the filtrate. An additional acidification step can reduce the residual amount of dissolved aspirin to about 42%. The substitution of ibuprofen with ibuprofen lysinate allows the removal of the NSAID from the filtrate (via CWE followed by acidification) but lysinate as a water soluble impurity remains.

Keywords-Cold water extraction (CWE), HPLC, codeine phosphate, codeine containing combination analgesics, ibuprofen lysinate

I. INTRODUCTION

Globally and also on the Australian market, codeine phosphate containing analgesics are popular, potent therapeutics. They are promoted to relieve mild to moderate pain and are also used in cold and flu formulations to alleviate body aches. In these analgesic formulations codeine phosphate is usually combined with a non-opioid agent like ibuprofen, paracetamol or aspirin. Since codeine is partially metabolized to morphine and hence causes neurological effects, abuse of these products by heroin and morphine addicts is common. According to the 2013 Australian National Drug Strategy Household Survey [1], for example, the percentage of Australians aged 14 years or older who use pain killers for non-medical purposes has nearly doubled from 1.7 to 3.3% over the past 20 years. In 2009 the number of deaths specifically related to codeine use also more than doubled over the previous decade to 8.7 per million. In more than half of the investigated cases paracetamol, ibuprofen or doxylamine were also detected, indicative of the dangers associated with the accidental or intentional abuse of codeine containing combination analgesics [2]. These Australian trends are also replicated in many other countries.

The maximum daily dose of codeine considered safe is 240 mg. Overdosing can lead to physical and psychological dependence and respiratory depression [3]. However, the focus of this paper is not primarily the potential harm associated with codeine abuse itself. In light of a concerning body of evidence documenting the addiction potential and abuse of codeine containing combination analgesics (CCAs), this study directs attention to the toxicity of non-opioid pain killers associated with an intake of large doses of CCAs. Well documented non-opioid toxicities include, for example, the hepatotoxic effect of the paracetamol metabolite N-acetyl-p-benzoquinone imine that causes severe liver damage in case of paracetamol overdose [4], whereas ibuprofen and aspirin can lead to NSAID toxicity including gastrointestinal ulceration and bleeding, renal failure, anaemia and also hypokalaemia [5-7]. Acknowledging these problems, in 2010 the Australian Government's National Drugs and Poisons Schedule Committee changed the scheduling of combination analgesics containing up to 5 days treatment and up to 12 mg codeine (equivalent to 15.4 mg codeine phosphate) per divided dosage unit (e.g. tablet, capsule) from 'pharmacy medicines' (S2) to 'pharmacist-only medicines' (S3). Undivided preparations such as mixtures have been reclassified in a similar manner and combinations with a codeine content exceeding these limits have since been classified as 'prescription only medicines' (S4) [8]. At present, Australia's Therapeutic Goods Administration considers to move even a step further with its Advisory Committee on Medicines Scheduling seeking comments on a proposed reclassification of all codeine formulations from S3 to S4 to take effect in July 2017 [9].

Most chronic users are aware of the dangers of analgesic abuse. To avoid non-opioid toxicities a simple chemical manipulation of CCAs is currently promoted on many websites and forums popular amongst opioid addicts. Known as cold water extraction (CWE) warm water is added to crushed tablets, the resulting suspension is cooled and filtered to remove the unwanted non-narcotic analgesics (the filtrate contains the water soluble codeine phosphate). While only sparse scientific data exists on the effectiveness of this method, chemically the approach is very plausible, as the solubility of codeine phosphate in water is about 250 mg per ml [10], whereas the solubility of paracetamol is only approximately 14 mg per ml, that of aspirin 4.6 mg per ml and of ibuprofen only 0.02 mg per ml [11].

However, while CWE might be a strategy to avoid excessive non-opioid toxicities associated with the abuse of CCAs, if successful, it also opens up a convenient avenue to obtain large quantities of codeine phosphate, a highly controlled and restricted Schedule 8 drug in Australia. Codeine obtained in this way could for example be used as starting material for the manufacture of home bake heroin [12-13].

TABLE I. INVESTIGATED COMBINATION ANALGESICS

Sample label	Dosage Form	Type of NSAID	NSAID per dose (in mg)	Codeine phosphate per dose (in mg)
A	Tablet	Paracetamol	500	6.0
B*	Tablet	Paracetamol	450	9.75
C	Tablet	Paracetamol	500	15.0
D	Tablet	Paracetamol	500	8.0
E	Tablet	Ibuprofen	200	12.8
F	Effervescent tablet	Aspirin	300	8.0
G	-	Ibuprofen Lysinate	200	12.8

*Also contains doxylamine succinate 5 mg

CWE can thus be seen as a double edged sword – to avoid associated NSAID toxicities on the one hand its success is desirable for those intending to abuse CCCAs in large quantities; intake of 40 tablets a day is common, with some abusers taking up to 100 tablets daily [6]. On the other hand, however, it opens up simple and convenient access to a highly restricted Schedule 8 drug.

In this light the aim of this study was to investigate the effectiveness of CWE for six popular CCCAs available as pharmacist-only medication (S3) in Australia (Tab. 1). Taking into account the solubility and chemical characteristics of the non-opioid analgesic, for the combination containing aspirin the effectiveness of an additional acidification step was also assessed. In all cases the success of CWE was judged via HPLC analysis by the purity and yield of the obtained codeine phosphate solution. Beside the commercially available analgesic products a mixture of codeine phosphate with ibuprofen lysinate was also investigated to see if a change in formulation might impede on the accessibility of pure codeine phosphate via CWE (including acidification of the obtained filtrate) without compromising its effectiveness in minimising non-opioid toxicities in those abusing these combination analgesics in large quantities.

II. MATERIALS AND METHODS

A. Materials

Samples analysed in this study are listed in Table 1. Products A-F are commercially available, Product G is an excipient free mixture of codeine phosphate and ibuprofen lysinate, which was synthesised following a method reported by Kumudhavalli et al. [14]. Pure codeine phosphate, aspirin and ibuprofen were sourced from PCCA Australia Pty Ltd. (Matraville, NSW, Australia) and paracetamol from Sigma-Aldrich Australia (Castle Hill, NSW, Australia). DL-Lysine 98% monohydrate was purchased from Alfa Aesar Heysham, UK, hydrochloric acid (32%) was obtained from ACE Chemicals (Camden Park, SA, Australia), monobasic potassium dihydrogen phosphate (KH_2PO_4), acetonitrile (ACN, HPLC grade) and formic acid were sourced from Ajax FineChem (Tarren Point, NSW, Australia) and ninhydrin (analytical grade) from Chem Supply (Gillman, SA, Australia). Deionised water was obtained by reverse osmosis using a Boss 031-4P filtration system (PSI Water Filters, Tasmania, Australia).

B. HPLC and UV-Vis Assays of Codeine Phosphate, Paracetamol, Aspirin, Ibuprofen and Ibuprofen Lysinate

A Hewlett Packard Series 1100 Pump and Autosampler with a diode

array detector ($\lambda=254$ nm) (Agilent Technology, Australia) fitted with a Gemini NX-C18 column (150 X 4.6 mm, 5 μm particle size) obtained from Phenomenex (Lane Cove, NSW, Australia) was used for HPLC analyses at a flow rate of 1.0 mL/min.

In the assay of codeine phosphate, paracetamol and aspirin solvent A was ACN and solvent B was a phosphate buffer (0.015M KH_2PO_4 , pH 2.5 \pm 0.2). A gradient was run with 70% B for the first 9 minutes, then linearly converted to 0% B over 6 minutes, and changed back to 70% B over 2 minutes, with a complete run time of 22 min [15-16]. For the HPLC analysis of ibuprofen and ibuprofen lysinate a mixture of 60% ACN, 39.9% deionised water and 0.1% formic acid was used as mobile phase. The runtime of this assay was 10 min [17]. All standards and samples were analysed in triplicates.

The UV-Vis analysis of lysine was carried out on a Varian Cary 50 Bio UV-Vis Spectrophotometer at 570 nm after colorimetric reaction of the samples with ninhydrin reagent (8% in acetone) in accordance with a method developed by Meyer [18].

C. Cold Water Extraction

For Products A-E 24 tablets and for Product F 20 tablets respectively were crushed to a powder using a porcelain mortar and pestle. Samples of approximately 4g powder were accurately weighed into 250ml volumetric flasks and made up to volume with deionised water heated to 40 °C. The suspension was cooled for 4 hours at 4 °C and then filtered through a Whatman 15cm filter paper. The filtrates were diluted 1:10 with deionised water and analysed via HPLC. Further, samples were prepared by mixing accurately weighed amounts of approximately 1.6 g ibuprofen lysinate and 102 mg codeine phosphate, a mixture that is equivalent in drug content to 8 tablets of Product E. The powder mixture was subjected to CWE as described above, also diluted 1:10 with deionised water and analysed via HPLC. All recovered drug amounts in the filtrates are expressed as mean percentage content (n=3) \pm standard deviation.

D. Additional Acidification Step

An additional acidification step was carried out with the filtrates obtained from Products F and G after CWE. 10 ml of each filtrate were acidified either with 1 ml of HCl or 5 ml of commercially available lemon juice (to mimic the home environment of abusers). The resulting precipitate was removed via gravity filtration, the collected acidified filtrates were diluted 1 in 10 with deionised water and analysed by HPLC. Recovered drug amounts in the acidified filtrates are expressed as mean percentage content (n=3) \pm standard deviation.

III. RESULTS

Table 2 summarises the results obtained from the CWE of the six commercially available formulations as well as the mixture of codeine phosphate and ibuprofen lysinate. Table 3 summarises the effect of the additional acidification step on filtrates obtained from CWE of samples containing aspirin or ibuprofen lysinate as a non-opioid analgesic component.

IV. DISCUSSION

As can be seen from the data presented in Table 2 CWE provides a simple avenue to partly remove non-opioids from CCCAs. However, the degree of success, expressed as the yield of codeine phosphate in the obtained filtrate as well as of the residual non-opioid analgesic, varies significantly depending on the type of NSAID in the analgesic combination. In line with their respective aqueous solubilities CWE is able to remove almost all ibuprofen (up to 97%), but significant residual amounts of paracetamol (between approximately 70% and 80% depending on the formulation) and aspirin (nearly 60%) remain

in the filtrate after CWE is carried out as described in a number of internet drug fora.

TABLE II. DRUG RECOVERY RATE IN FILTRATE AFTER CWE

Sample label	Type of NSAID	Codeine phosphate % recovery (mean ± SD, n=3)	NSAID % recovery (mean ± SD, n=3)
A	Paracetamol	75.61 ± 8.67	75.53 ± 5.92
B	Paracetamol	93.15 ± 0.93	68.91 ± 1.63
C	Paracetamol	103.53 ± 9.72	83.51 ± 4.00
D	Paracetamol	100.28 ± 4.75	61.18 ± 1.32
E	Ibuprofen	79.94 ± 9.61	2.87±0.22
F	Aspirin	62.43 ± 2.60	56.96 ± 6.24
G	Ibuprofen lysinate	100.04 ± 12.43	93.05 ± 13.98

TABLE III. DRUG RECOVERY RATE AFTER CWE AND ACIDIFICATION

Type of NSAID	Codeine phosphate % recovery		NSAID % recovery	
	HCl (mean ± SD, n=3)	Lemon juice (n=1)	HCl (mean ± SD, n=3)	Lemon juice (n=1)
Aspirin	89.70 ± 5.49	-	41.75 ± 4.62	-
Ibuprofen lysinate	102.07 ± 2.72	100.01	2.33 ± 0.20	2.57

It can be speculated that CWE might originally have been devised for ibuprofen containing combinations and then, without further chemical considerations, been extended to other combinations containing different NSAID components. This is of concern as abusers might have a false sense of security carrying out CWE with combinations other than those containing ibuprofen and be unaware of the potential residual non-opioid toxicity of these filtrates. For example, based on the findings of this study, taking 10 tablets of Product F after CWE still leaves a residual aspirin amount of about 1.7 g. Similarly, in the case of Products A-D such a dose would result in between 3.1 and 4.2 g of paracetamol, which is well above the recommended dose of 300–900 mg every 4–6 hours [3].

As a relatively strong acid with a pKa of 3.49 [19], aspirin can be expected to be mainly ionised in the slightly acidic drug powder suspension (approximately pH 5) leading to a large amount of the drug dissolved and carried over into the CWE filtrate. For this reason an acidification step with HCl, but also with household lemon juice (to better reflect the home environment where CWE would normally be carried out) was trialled and its impact on the yield and purity of the obtained codeine phosphate solution assessed. As can be seen from the obtained data (Tab. 3), this simple additional acidification step, independent of the nature of the acid used, was successful in reducing residual amounts of dissolved aspirin from the original CWE filtrate, lowering the percentage residual amount of aspirin from about 57% to 42% of the original dose. While, to our knowledge, currently not promoted in relevant internet fora, such an acidification step should make the abuse of aspirin-codeine phosphate combination analgesics safer, although there will still be the danger of significant residual NSAID toxicity.

In terms of potential access to relatively pure codeine phosphate the combination with ibuprofen is most concerning. While the opioid yield after CWE is with about 80% not as high as with some of the other investigated formulations, the filtrate is by far the purest

showing only very small amounts (approximately 3%) of residual NSAID. This concern has prompted the investigation of a potential change in drug composition for this particular combination analgesic, replacing ibuprofen with ibuprofen lysinate, a highly water soluble salt that is currently found in a number of formulations as a fast acting analgesic. The rationale for this substitution is two-fold: Due to its salt properties ordinary CWE will lead to a highly contaminated codeine phosphate solution. For those who intend to abuse this combination and thus aim to remove ibuprofen to avoid associated NSAID toxicities, a simple acidification step following CWE will be sufficient (Tab. 3) since, based on pH and solubility, ibuprofen free acid will almost quantitatively precipitate out of solution (approximately 2% residual ibuprofen in acidified filtrate) and can thus easily be removed by gravity filtration. However, in contrast to other ibuprofen-codeine phosphate combinations currently on the market, the use of ibuprofen lysinate leaves lysinate as a water soluble impurity in the acidified filtrate as was demonstrated by UV Vis analysis after colorimetric reaction of the samples with ninhydrin. As a naturally occurring basic amino acid lysine is not anticipated to cause any health concerns but as a contaminant in the filtrate will impact negatively on access to a highly restricted Schedule 8 substance. While explored only at a conceptual level without consideration of formulation issues, using ibuprofen lysinate in CCCAs might thus be an interesting approach warranting further investigation. As is illustrated in Figure 1, it should still be possible for abusers trying to avoid non-opioid toxicities to effectively remove the NSAID component via CWE followed by acidification, but due to significant contamination of the acidified filtrate with lysinate access to large quantities of relatively pure codeine phosphate is impeded.

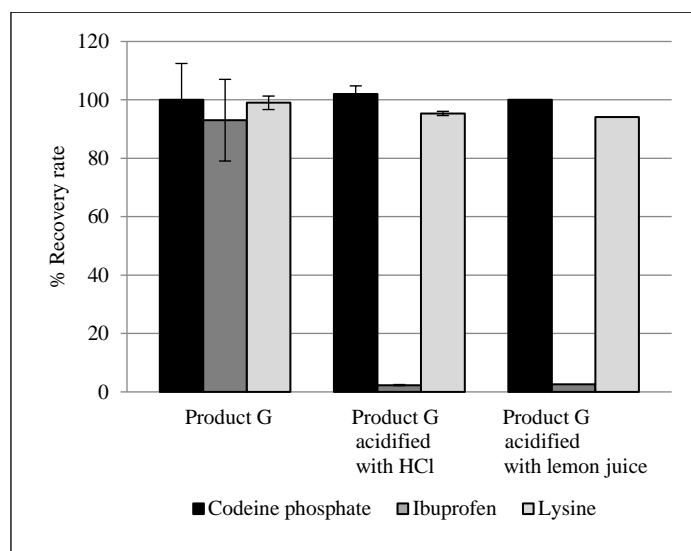


Figure 1. Drug recovery from Product G

V. CONCLUSION

This study contributes to the still sparse scientific data on the effectiveness of CWE of CCCAs. It has been shown that depending on the NSAID used codeine phosphate of varying purity and yield can be obtained from these analgesics that are currently in Australia sold as Schedule 3 (pharmacist-only) products. The data set thus weighs into the current debate on a possible rescheduling of these formulations to a prescription only (S4) status. With codeine phosphate and ibuprofen lysinate a new analgesic combination has been explored at a conceptual level that might in the future be considered as an alternative to the ibuprofen containing combination

formulations currently on the market. This combination might still allow abusers of these products to avoid NSAID toxicity via CWE followed by acidification while at the same time prohibiting easy access to relatively large quantities of pure codeine phosphate, which in Australia is a highly regulated and restricted drug (S8). The findings of this study might therefore also be of interest to manufacturers and regulatory authorities.

REFERENCES

- [1] Australian Institute of Health and Welfare (AIHW), National Drug Strategy Household Survey Detailed Report 2013. Drug Statistics Series No. 28. Cat. No. PHE 183. Canberra: AIHW, 2014.
- [2] A. Roxburgh, W.D. Hall, L. Burns, J. Pilgrim, E. Saar, S. Nielsen and L. Degenhardt, "Trends and characteristics of accidental and intentional codeine overdose deaths in Australia," *Med. J. Australia*, vol. 203(7), pp. 299.e7, 2015.
- [3] N. Buckley (ed), Australian Medicines Handbook, Adelaide: Australian Medicines Handbook, 2015.
- [4] J.A. Hinson, D.W. Roberts and L.P. James, "Mechanisms of acetaminophen-induced liver necrosis," *Handbook of Experimental Pharmacology*, vol. 196, pp. 369-405, 2010.
- [5] M.Y. Frei, S. Nielsen, M.D.H. Dobbin and C.L. Tobin, "Serious morbidity associated with misuse of over-the-counter codeine-ibuprofen analgesics: A series of 27 cases," *Medical Journal of Australia*, vol. 193(5), pp. 294-296, 2010.
- [6] J.L. Pilgrim, M. Dobbin and O.H. Drummer, "Fatal misuse of codeine-ibuprofen analgesics in Victoria, Australia," *Medical Journal of Australia*, vol. 199(5), pp. 329-331, 2013.
- [7] B.T. Dyer, J.L. Martin, J.L. Mitchell, N.C. Sauven and B. Gazzard, "Hypokalaemia in ibuprofen and codeine phosphate abuse," *International Journal of Clinical Practice*, vol. 58(11), pp. 1061-1062, 2004.
- [8] Pharmacy Guild of Australia, "Scheduling changes for combination analgesics containing codeine," retrieved from <https://www.guild.org.au/issues-resources/archive/codeine-schedule-changes>.
- [9] Therapeutic Goods Administration (TGA), "Consultation: Proposed amendments to the Poisons Standard (Codeine)", retrieved from <https://www.tga.gov.au/consultation-invitation/consultation-proposed-amendments-poisons-standard-codeine>.
- [10] G.F. Fleming, J.C. McElnay and C.M. Hughes, "The separation of codeine from non-prescription combination analgesic products," *Subst. Use and Misuse*, vol. 38(9), pp. 1217-1226, 2003.
- [11] S.H. Yalkowsky, Y. He and P. Jain, *Handbook of Aqueous Solubility Data* (2nd ed.). Boca Raton FL: CRC Press, 2010.
- [12] G.M. Robinson, S. Robinson, P. Mccarthy and C. Cameron, "Misuse of over-the-counter codeine-containing analgesics: Dependence and other adverse effects," *New Zealand Medical Journal*, vol. 123(1317), pp. 59-64, 2010.
- [13] K.R. Bedford, S.L. Nolan, R. Onrustand and J.D. Siegers, "The illicit preparation of morphine and heroine from pharmaceutical products containing codeine: 'Homebake' laboratories in New Zealand," *Forensic Science International*, vol. 34(3), pp. 197-204, 1987.
- [14] M.V. Kumudhavalli, M. Chandira, D. Sripriya and B. Jayakar, "Studies on synthesis, method development, characterization and antimicrobial activities of ibuprofen lysinate," *Int. J. Pharma Bio Sci.*, vol. 1(2), pp. 1-25, 2010.
- [15] W.R. Sisco, C.T. Rittenhouse and L.A. Everhart, "Simultaneous high-performance liquid chromatographic stability-indicating analysis of acetaminophen and codeine phosphate in tablets and capsules," *Journal of Chromatography A*, vol. 348(1), pp. 253-263, 1985.
- [16] W.R. Sisco, C.T. Rittenhouse and W.M. Maggio, "The rapid quantitative analysis of codeine phosphate drug substance by reverse-phase high-performance liquid chromatography," *Chromatographia*, vol. 20(5), pp. 289-292, 1985.
- [17] J.C. Tsao and T.S.S. Savage, "High-Performance Liquid Chromatographic determination of ibuprofen in bulk drug and tablets," *Drug Develop. Ind. Pharm.*, vol. 11(5), pp. 1123-1131, 1985.
- [18] H. Meyer, "The ninhydrin reaction and its analytical applications," *Biochem. J.*, vol. 67(2), pp. 333-340, 1957.
- [19] M.J. O'Neil, A. Smith and P.E. Heckelman (eds), *The Merck Index* (13th ed.), Whitehouse Station NJ: Merck, 2001.