

RESEARCH ARTICLE

Could Codeine Containing OTC Analgesics Sold in Romania be Used as Recreational Drugs?

Croitoru Mircea Dumitru, Fogarasi Erzsébet*, Varga Erzsébet, Chelaru Adelina, Căliman Monica-Simina, Fülöp Ibolya

University of Medicine and Pharmacy Tirgu Mures, Romania

Objective: Analgesic medicines containing combinations of nonsteroidal anti-inflammatory drugs and codeine are available without prescription. Codeine, in these combinations can not be used recreationally due to the high toxicity profile of the nonsteroidal anti-inflammatory drugs. However, methods for extracting codeine from these types of medication are available on the internet. The purpose of this work is to evaluate if codeine can be extracted from codeine containing analgesics sold without prescription.

Methods: High Performance Liquid Chromatography (HPLC) with UV detection was used to measure the amounts of codeine and nonsteroidal anti-inflammatory drugs recovered after applying an extraction method described on the internet.

Results: The results show that codeine can be very easily separated from NSAID as aspirin, acetaminophen, ibuprofen using the cold water extraction method. However, very large differences (20 to 90%) were recorded for the recovery of codeine depending on the OTC product that was used. That large difference increases the risk of potentially lethal overdoses when the user switches between "similar" products.

Conclusions: Our work shows that analgesic medication with codeine content can be recreationally used after the extraction of codeine. In order to prevent this, the sell of this type of products should be regulated or products that do not allow the extraction of codeine should be developed.

Keywords: codeine, recreational drugs, cold water extraction, HPLC

Received: 28 July 2016 / Accepted: 13 September 2016

Introduction

Pain is a serious disabling condition often associated with worsening of the health condition. People in pain may experience greater functional impairment, depression, decreased appetite, impaired sleep, social isolation than the persons that do not experience pain [1]. Pain management is considered an ethical issue due to the significant discomfort that is produced to the individual experiencing it and every available measure should be taken in order to alleviate pain, regardless that is chronic or acute in nature [2,3].

Most of the time, pain is the sign of an illness and fades when efficient treatment is used. There are however cases, when the health condition of the individual cannot be improved or when the cause of the pain is not known as in the case of many migraines. In such conditions, the only treatment available are the substances able to reduce the ability of an organism to feel pain: analgesics. There are analgesics as non steroidal anti-inflammatory drugs (NSAID) and opioids designed to reduce sensation of pain, but nowadays, even substances that were not designed as analgesics (carbamazepine, antidepressant medication, etc) are sometimes tried [4,5].

One of the most efficient pain medications, used for moderate to high intensity pain, are the opioids. Unfortunately, even if efficient pain control can be attained, these substances are prone to induce fearsome psychological and physical addiction, effect that excludes their use as OTC

medication [6]. Another option to reduce pain intensity are the NSAIDs, but these substances are also known to have negative health effects (risk of myocardial infarction, stroke, gastric bleeding, kidney failure, etc.) especially when used in high doses for a long time. Due to the lack of addictive properties, the NSAIDs with low toxicity profile as acetylsalicylic acid, acetaminophen, ibuprofen, etc are available as OTC pain medication. Combinations of opioids and NSAIDs are, however, sold in most countries worldwide as OTC pain medication. This combination has the advantage of dosage reduction of both components and high efficiency in reducing low intensity pain. The dosage reduction greatly increases the safety of the combinations since the toxicity of opioids and NSAIDs is not overlapping. The presence of the NSAIDs, with high acute toxicity in large doses, prevents the user to increase the dosage until the recreational dose of the opioid is attained (it is well known that the recreational dose of an opioid is significantly larger than its analgesic dose) [7-9].

The opioid of choice for OTC analgesic combinations is codeine phosphate, while the NSAID of choice is acetaminophen. The NSAID to codeine ratio is too high for a recreational use in these products. However, drug users take advantage of the low cold water solubility of the NSAID compared with that of codeine phosphate in order to separate the codeine from the NSAID. This way, extracted codeine can be recreationally used without the limitations brought by the significant NSAID's toxicity in high doses. The extraction method described in detail on several internet forums (named CWE from cold water extraction) is

* Correspondence to: Erzsébet Fogarasi
E-mail: fogarasi.erzsebet@umftgm.ro

extremely easy to apply by anyone without any chemistry background and requires only a regular freezer and a coffee filter [10-15].

The purpose of this work is to check if the CWE method described on the internet forums is usable to extract codeine from the OTC products sold in Romania and to evaluate the risks involved by such practice.

Materials and methods

Materials: all common chemicals and reagents (acetonitrile, methanol, anhydrous Na_2HPO_4 , H_2SO_4 96%, H_3PO_4 85%) were purchased from local providers and were used without any further purification. Codeine, caffeine, acetaminophen, salicylic acid and ibuprofen were of pharmaceutical quality. Ultra-pure water was obtained using a Mili-Q purification system (Milipore Corporation, USA). The following pharmaceutical products were purchased from pharmacies: Fasconal (Gedeon Richter Romania SA, Romania), Aspaco (SC Bioeel SRL, Romania), Codamin P (Terapia SA, Romania), Solpadeine (GlaxoSmithKline, Ireland), Nurofen Plus (Reckitt Benckiser Healthcare International Limited, Great Britain), Tusocalm (Arena Group SA, Romania), Ultracod (Zentiva KS, Czech Republic). Coffee filter no 2 and no 4 were purchased from a local supermarket.

Apparatus: High Performance Liquid Chromatography (HPLC) analysis was carried out on a Merck HPLC system consisted of: quaternary pump Merck Hitachi L-7100, auto sampler Merck Hitachi L-7200, column thermostat Merck Hitachi L-7360, DAD detector Merck Hitachi L-7455, interface Merck Hitachi L-7000, solvent degasser Merck Hitachi L-7612, software D-7000 HSM-Manager, LichroCART 250-4, Rp-Select B (5 μm) column, Merck KgaA, Germany.

Methods:

- HPLC method: mobile phase consisted in: 20 mM phosphate buffer brought to pH=2.5 with phosphoric acid (A) and acetonitrile (B); the gradient elution program is shown in table I: injection volume 100 μl using the loop method; DAD domain 190-400nm with the extraction of the best chromatogram at 205nm.
- CWE method: 10 tablets were grinded in a mortar, the powder was brought in a graduated cylinder and purified water was added up to 100 ml, followed by mixing and ultrasonication. The suspensions were then placed in a freezer and when the first crystals of ice were formed, were filtered through the coffee filters no 2 and 4. Solutions were diluted 1:1000, filtered through an HPLC nylon filter (0.45 μm) and injected into the HPLC system.

Table I. Gradient elution program

Time (min)	A (%)	B (%)	Flow (ml/min)
0.0	85	15	1.000
4.0	85	15	1.000
9.0	30	70	1.000
12.0	30	70	1.000
12.1	85	15	1.000
14.0	85	15	1.000

Results

Performance of the analytical method

Specificity

Standard blanks (also called placebo by the pharmaceutical industry) could not be obtained. Large variation in the type of the NSAID that was used in these combinations together with the high similarity in the auxiliary substances present in the products allowed us to use one product as blank for the other products. For example Nurofen Plus that contains ibuprofen as NSAID could be used as blank for all other NSAIDs used in the tested products. No interferences of the blanks were observed in this study. Chromatograms for the standard solutions and for Fasconal are shown in figures 1 and 2, respectively.

Linearity

Calibration curves were prepared for all tested substances in the range of 0.1-10 $\mu\text{g}/\text{ml}$ (N=3, average value was used for

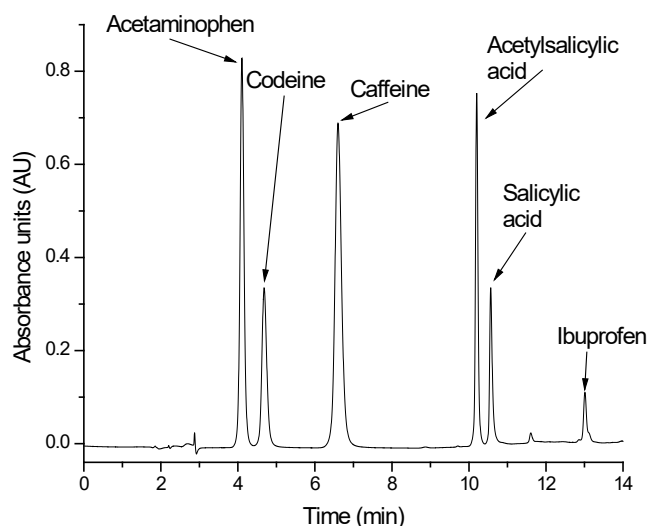


Fig. 1. Chromatogram of the standard solution (10 $\mu\text{g}/\text{ml}$)

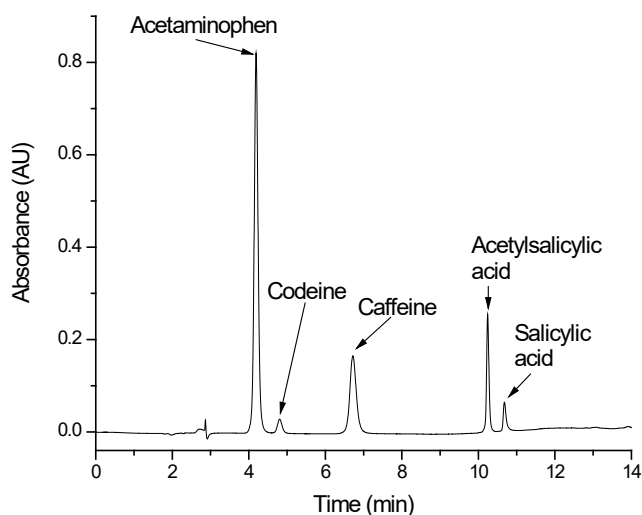


Fig. 2. Chromatogram of cold water extracted and diluted 1:1000 Fasconal

calculations). Good linearity was obtained in the concentration range tested as shown by the coefficient of correlation higher than 0.999 in all cases, the residuals with values lower than 10% and the lack of correlation between the residuals and the theoretical concentration. Slope values for slope were: 151863, 302161, 414018, 259383, 30374 and the intercept values were: -9197, 18157, 13246, -8673, 2335, for codeine, acetaminophen, caffeine, acetylsalicylic acid and ibuprofen, respectively.

Limits of detection (LOD) and quantification (LOQ)

Concentrations in the cold-water extracted samples were so high that a 1:1000 dilution was needed in order to make possible the measurements, therefore, the LOD and LOQ values were not determined. No analyte in any sample yielded a peak with an area lower than the lowest concentration etalon in the calibration curve.

Cold water extraction efficiency for codeine

The recovered percent of codeine in the tested products is shown in table II. Name of the products is not mentioned here in order to prevent illegitimate use of the presented information.

Cold water extraction efficiency for the NSAIDs and caffeine

The recovered percents measured for NSAIDs and caffeine are shown in table III; different order of the products is used compared with the one used in table II.

Discussions

The developed HPLC-UV method is suitable to quantify codeine, caffeine and all the commonly used NSAIDs for analgesic combinations. Performance of the analytical method was verified using solutions obtained after cold water extraction of codeine from OTC analgesic combinations; therefore it can be used to help medical care personnel to identify the substances that were employed if an

intoxication following the CWE procedure occurs. This is very important in an emergency department because, in the case of intoxication with a CWE liquid, not always the opioid identified by rapid tests is the source of the intoxication but also the NSAID (if the CWE was not done properly), or even both of them. Having a relatively quick method is an advantage to obtain information about the identity and amounts of substances that were ingested.

Our results show that unfortunately the CWE method described and developed by the drug users really work, has high reproducibility (RSD less than 10%, N=3) and it is very easy to employ using cheap household items and OTC drugs freely bought from pharmacies or even internet. The highly large differences in the extraction efficiencies of codeine observed in the case of different analgesic combinations is a high risk of overdose and even death when product replacement is made (when for example the preferred product is not available for a certain interval of time). This difference is probably brought by the composition in some auxiliary substances, which were used by different manufacturers.

In the worst case scenario, when product C is replaced with product A four time the dose is obtained. The increased risk of overdose when product replacement is made is the belief of the opioid users that highly important for the intensity of the euphoric effect is the speed of the blood concentration increase, therefore the "best effects" are obtained by ingesting the whole dose at once rather than taking small doses at certain interval of time.

The extracted codeine can be also used to be transformed into desomorphine, resulting a mixture of several highly toxic compounds that can lead to horrifying skin and other organ lesions that can be very difficult to treat and can lead to disabling or death [16].

Conclusions

This work proves that products that are recreationally usable are freely available as OTC medication. If the number of users that perform CWE will increase, there is a risk to ban very useful and safe analgesic medication. In order to prevent this, strategies to obtain OTC analgesic medication with content of codeine that could not be extracted with cold water should be employed by pharmaceutical companies. Another way to overcome purchase of large amounts of codeine containing OTC analgesics for sustaining an addiction is to sell these products with an identity card, and every sell should be introduced in a national data base as successfully employed in the USA.

Table II. Recovery of codeine from the tested tablets

Pharmaceutical product	% of recovered codeine
Product A	89.0
Product B	65.1
Product C	21.2
Product D	40.4
Product E	47.4
Product F	43.4
Product G	79.3

Table III. Recovery of NSAIDs and caffeine from the tested tablets

Pharmaceutical product	% of recovered acetaminophen	% of recovered caffeine	% of recovered acetylsalicylic acid	% of recovered ibuprofen
Nurofen Plus				4.2
Solpadeine 2	18.7	49.0		
Codamin P 2	15.7	33.4		
Aspaco 2	36.3		10.8	
Fasconal 2	45.1	90.1	13.5	
Ultracod 2	17.8			

Acknowledgement

The research was supported by the University of Medicine and Pharmacy of Tirgu Mures and Gedeon Richter Romania SA, internal research grant number 15221/02.11.2015.

Conflicts of interest

The authors report no conflicts of interest.

References

1. Malec M, Shega JW. Pain Management in the Elderly. *Med Clin North Am.* 2015;99(2):337-350. doi: 10.1016/j.mcna.2014.11.007.
2. Pappagallo M, Heinberg LJ. Ethical issues in the management of chronic nonmalignant pain. *Semin Neurol.* 1997;17:203-211.
3. Lome B. Acute pain and the critically ill trauma patient. *Crit Care Nurs Q.* 2005;28:200-207.
4. Richer L, Billingham L, Linsdell MA, et al. Drugs for the acute treatment of migraine in children and adolescents. *Cochrane Database Syst Rev.* 2016; doi: 10.1002/14651858.CD005220.pub2.
5. Buescher JJ. Carbamazepine for Acute and Chronic Pain. *Am Fam Physician.* 2006;73:1549-1550. doi: 10.1002/14651858.CD005451.
6. Huber E, Robinson RC, Noe CE, Van Ness O. Who Benefits from Chronic Opioid Therapy? Rethinking the Question of Opioid Misuse Risk. *Healthcare (Basel).* 2016;4(2). doi: 10.3390/healthcare4020029.
7. Sweetman SC (ed): *Martindale, The Complete Drug Reference.* London. Pharmaceutical Press. 2009.
8. Moore RA, Derry S, Aldington D, Wiffen PJ. Single dose oral analgesics for acute postoperative pain in adults - an overview of Cochrane reviews. *Cochrane Database Syst Rev.* 2015;(9):CD008659.
9. Pfaffenrath V, Diener HC, Pageler L, Peil H, Aicher B. OTC analgesics in headache treatment: open-label phase vs randomized double-blind phase of a large clinical trial. *Headache.* 2009;49:638-645.
10. Nielsen S, Van Hout MC. Over-the-Counter Codeine-from Therapeutic Use to Dependence, and the Grey Areas in Between. *Curr Top Behav Neurosci.* 2016. doi: 10.1007/7854_2015_422.
11. Hamer AM, Spark MJ, Wood PJ, Roberts E. The upscheduling of combination analgesics containing codeine: the impact on the practice of pharmacists. *Res Social Adm Pharm.* 2014;10:669-678. doi: 10.1016/j.sapharm.2013.08.004.
12. Van Hout MC, Norman I. Misuse of non-prescription codeine containing products: Recommendations for detection and reduction of risk in community pharmacies. *Int J Drug Policy.* 2016;27:17-22. doi: 10.1016/j.drugpo.2015.09.007.
13. Barkin RL. Acetaminophen, aspirin, or Ibuprofen in combination analgesic products. *Am J Ther.* 2001;8:433-442.
14. *** Cold Water Extraction of Opioids available at: https://drugs-forum.com/forum/showwiki.php?title=Cold_Water_Extraction_of_Opioids, accessed on 15.06.2016.
15. Van Hout MC. Nod and wave: an Internet study of the codeine intoxication phenomenon. *Int J Drug Policy.* 2015;26:67-77. doi: <http://dx.doi.org/10.1016/j.drugpo.2014.06.016>.
16. Alves EA, Soares JX, Afonso CM, et al. The harmful chemistry behind "krokodil": Street-like synthesis and product analysis. *Forensic Sci Int.* 2015;257:76-82. doi: 10.1016/j.forsciint.2015.07.042.