

Codeine dependence – case report

Uzależnienie od kodeiny – opis przypadku

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Streszczenie

Wstęp. Kodeina to substancja o działaniu przeciwkaszlowym, przeciwbiegunkowym i przeciwbólowym. Wykazuje oddziaływanie na receptory opioidowe i jest sklasyfikowana jako substancja odurzająca. Dostępna również bez recepty, kodeina jest często nadużywana ze względu na właściwości poprawiające nastrój. Do uzależnienia dochodzi często na skutek niewłaściwej terapii kodeiną np. w przypadkach przeziębienia i kaszlu, kiedy pacjent zażywa większą niż zalecana dawkę lub/i przez dłuższy niż zalecany okres czasu. Powikłaniami nieprawidłowego stosowania kodeiny oraz oznakami uzależnienia może być szereg objawów, takich jak zaparcia, nudności, wymioty, zaburzenia nastroju, senność, zawroty głowy, spowolnienie psychoruchowe, drażliwość i napady złości. Mimo nałożonych regulacji i ograniczeń sprzedaży preparatów zawierających kodeinę, problem uzależnienia od tej substancji nadal stanowi duży problem, szczególnie wśród osób młodych ale także ich bliskich. **Material i metody.** Przedstawiamy przypadek 15-letniego pacjenta, u którego wystąpiły problemy ze snem, niechęć do jedzenia, zmiany nastroju i drażliwość po przedłużonym stosowaniu kodeiny, która pierwotnie zażywana była w preparacie złożonym (kodeina+sulfogwajakol) w celu leczenia objawów przeziębienia. Po odstawieniu leku nastąpił nawrót objawów grypopodobnych, pojawił się brak chęci do działania, problemy ze snem, bóle głowy, co skłoniło pacjenta do ponownego zażywania kodeiny. **Wyniki.** Po konsultacji z lekarzem pierwszego kontaktu pacjent został skierowany na wizytę psychiatryczną. **Wnioski.** Opisany przypadek potwierdza ryzyko wystąpienia działań niepożądanych i ryzyko uzależnienia na skutek nieprawidłowego stosowania preparatów zawierających kodeinę. (*Farm Współ 2021; 14: 68-73*) doi: 10.53139/FW.20211410

Słowa kluczowe: kodeina, działania niepożądane leku, uzależnienie od kodeiny

Summary

Background. Codeine is a substance characterized by antitussive, antidiarrheal and analgesic properties. It acts by affecting opioid receptors and is classified as a narcotic substance. Available also over the counter, codeine is often abused for its mood-enhancing properties. An addiction often occurs due to improper treatment of codeine, e.g. in cases of colds and coughs, when the patient takes more than the recommended dose and/or for longer than the recommended period of time. Complications of improper use of codeine and signs of addiction may include several symptoms, such as constipation, nausea, vomiting, mood disorders, somnolence, dizziness, psychomotor slowness, irritability and tantrums. Despite the imposed regulations and restrictions on the sale of codeine-containing preparations, addiction to this substance is still an important issue, especially among young people and their relatives. **Material and methods.** We describe a case of a 15-year-old patient who developed sleep problems, reluctance to eat, mood changes and irritability after prolonged use of codeine, which was initially taken in a combined preparation (codeine+ guaiacolsulfonate) to treat cold symptoms. After discontinuation of the drug, flu-like symptoms returned, lack of willingness to act, sleep problems, and headaches appeared, which prompted the patient to take codeine again. **Results.** After consulting the family doctor, the patient was referred for a psychiatric consultation. **Conclusions.** The described case confirms the risk of adverse reactions and the risk of addiction due to improper use of codeine-containing preparations. (*Farm Współ 2021; 14: 68-73*) doi: 10.53139/FW.20211410

Keywords: codeine, adverse drug reaction, codeine dependence

Introduction

Addiction to psychoactive or psychotropic substances and intoxicants is a set of mental or somatic phenomena resulting from the action of narcotic drugs or psychotropic substances on the human body [1]. In 1969, the World Health Organization (WHO) published a definition of addiction which reads as follows: "Drug dependence. A state, psychic and sometimes also physical, resulting from the interaction between a living organism and a drug, characterized by behavioural and other responses that always include a compulsion to take the drug on a continuous or periodic basis in order to experience its psychic effects, and sometimes to avoid the discomfort of its absence. Tolerance may or may not be present. A person may be dependent on more than one drug." [2]. According to The Tenth Revision of the International Classification of Diseases and Health Problems (ICD-10) the dependence syndrome is "a cluster of physiological, behavioural, and cognitive phenomena in which the use of a substance or a class of substances takes on a much higher priority for a given individual than other behaviours that once had greater value." [3]. This state is characterized by behavioral changes or other psychophysical reactions. Addicted people also experience the need to use these substances either constantly or periodically, in order to experience their influence on the psyche or to avoid the consequences caused by their lack [1]. The return to substance use after a period of abstinence may even lead to a more rapid reappearance of other features of the syndrome in comparison with nondependent individuals [3]. A substance, that can be psychologically and physically addictive, is codeine- the most commonly used opioid analgesic in the world (International Narcotics Control Board 2012). Codeine is a naturally occurring substance (alkaloid) present in opium (the milk juice of unripe poppy seeds), which was used as an analgesic in antiquity. Currently, apart from relieving mild-to-moderate pain, this substance is also used in the treatment of dry cough and diarrhoea. Codeine has a low affinity for opioid receptors; thus, its analgesic effects are due to metabolic conversion to morphine. In addition, this substance acts on the cough center in the medulla, inhibiting the cough reflex and slowing down intestinal peristalsis and gastric emptying, which results in its constipating effect [4].

The preparations available on the market include codeine combined with paracetamol- effective in the treatment of acute nociceptive pain (caused by damage

to the body, such as joint pain, osteoarthritis, sports injuries or post-operative pain), acetylsalicylic acid, ibuprofen, guaiacolsulfonate or caffeine. In Poland, preparations with codeine are available both as OTC (over the counter) drugs and by prescription in the oral form (tablets, capsules, syrups, effervescent tablets). From January 1, 2017, patients can only buy one small package of the drug with codeine (up to 150 mg of the substance in the package) at a time at a pharmacy without a prescription. Due to the risk of codeine addiction, preparations containing this drug should not be used for more than a few days, nor should the recommended doses be exceeded [5].

Case report

A 15-year-old patient reported to the family doctor (an online consultation) with sleep problems and, noticed by his parents, aversion to food, mood changes and irritability. A month before this consultation, the patient started taking paracetamol at a dose of 2 g/day (for three days) and an antitussive preparation- 60 mg codeine phosphate hemihydrate, 1,200 mg guaiacolsulfonate, due to a cold with not very high fever (not exceeding 38 °C), bone and muscle pain, headache and a dry cough. A two-week treatment of dry, persistent cough with codeine made the patient experience a "sense of inner peace and well-being". These effects made the patient continue taking codeine for another month at a dose of 60-90 mg/day, despite emerging sleep problems. Patients' parents noticed the changes in their son's behaviour (apathy, mood changes and irritability) and ordered him to stop taking codeine. Unfortunately, the symptoms that appeared after discontinuation of the drug- lack of willingness to act, flu-like symptoms, sleep problems, headaches- led the patient to start taking codeine again at a dose of 90-120 mg/day to eliminate them. The teenager's parents noticed disturbing symptoms in their son- reluctance to eat, changes in mood and irritability- and forced him to contact the family doctor, who, after an interview, referred the patient for a psychiatric consultation.

Discussion

Codeine (3-methylmorphine) is a drug classified as a narcotic drug (group II-N and III-N in Poland), known to act by affecting opioid receptors (a selective agonist of the μ opioid receptor). It exhibits a central antitussive effect and a mild sedative and analgesic effect (through μ -opioid receptors). Codeine may act

on three primary opioid receptors (there are also subtypes)- mu, delta, and kappa; all of them are G-protein coupled. The binding of the opioids to these receptors leads to a series of intracellular events, resulting in a decreased intracellular cAMP, decreased neurotransmitter release and hyperpolarization of the cell and neuronal cells. Activation of mu receptors in the midbrain is the primary mechanism providing analgesic effects of opioids. In the case of antitussive effect, codeine acts to mediate cough reflex primarily through the opioid receptors present in the medulla [6]. Codeine content in combined preparations ranges 8-30 mg in the form of tablets and 15 mg in 10 ml of solution (in syrups). The maximum tolerated dose is 360 mg per day considering immediate-release preparation and 600 mg per day in case of controlled-release preparation. This drug is characterized by a half-life of 3 hours. It is metabolized by a hepatic enzyme CYP2D6, which converts (O-demethylation) codeine into its active metabolite, morphine. However, only about 5-10% of codeine is metabolized in this pathway. The remaining ~80% of the drug's administered dose is converted to inactive metabolites and excreted. Some variants of the CYP2D6 gene may increase, whereas others decrease the metabolism of codeine, which may influence the analgesic potency and abuse liability[7-8]. In general, codeine is a safe drug when taken for a short period of and preferably after consulting a healthcare professional first. The drug is contraindicated in case of: respiratory failure (e.g. sleep apnea), regardless of its severity, due to codeine's depressant effect on the respiratory centers; in children and adolescents (0 to 18 years of age) undergoing tonsillectomy and/or pharyngeal surgery (adenoidectomy) as part of the treatment of obstructive sleep apnea syndrome due to an increased risk of severe and life-threatening side effects (a black box warning); bronchial asthma or respiratory failure; patients who are known to have a very rapid metabolism involving the enzyme CYP2D6 and while breastfeeding as the drug passes into the breast milk. Moreover, animal studies have shown codeine to be teratogenic. High doses of codeine, even used for short periods in the perinatal period, may inhibit the newborn's respiratory centre. Also, outcomes such as premature birth, low birth weight, hypoxic-ischemic brain injury, heart defects, and neonatal death may occur. Long-term use of codeine during the third trimester of pregnancy may cause neonatal withdrawal syndrome, irrespective of the dose taken by the mother.

Codeine is contraindicated in the first trimester of pregnancy. Single doses of the product may be used in the second and third trimesters of pregnancy only when necessary[5-6].

Codeine applied in therapeutic doses may cause adverse effects similar to those seen with other opioids, but they occur less frequently and are less severe. These effects include:

- constipation- one of the most common adverse effects, following the initiation of therapy or increases in dose
- nausea, vomiting- commonly seen adverse effect, expected to diminish the following days to weeks of continued codeine exposure.
- sedation, clouded mentation, euphoria, mood disorders,
- drowsiness, dizziness
- miosis (constriction of the pupils), blurred vision,
- urinary retention,
- hypersensitivity reactions (itching, hives and rash), pruritis,
- bronchospasm, respiratory depression,
- sharp abdominal pain with characteristics of biliary or pancreatic disease, indicating the sphincter of Oddi dysfunction; this mainly affects patients who have had the gallbladder removed,
- hypogonadism and lower levels of dehydroepiandrosterone sulfate (in case of chronic use of controlled release codeine)- resulting in, e.g. decreased libido, fatigue, or sexual dysfunction.

The use of codeine in doses higher than the therapeutic dose carries a risk of addiction and withdrawal symptoms following the drug's abrupt discontinuation. Withdrawal symptoms can occur in the treated person or a newborn born to a codeine dependent mother [5-6,9].

Codeine is abused because of its mood-enhancing properties. After taking a higher than recommended dose of this drug, one may experience pleasant symptoms, such as a sense of inner peace, euphoria, unjustified well-being. According to an online cross-sectional survey by Kimergård et al., out of 316 respondents, 14.1% were faking and exaggerating symptoms to get a prescription for codeine, from three or more prescribers in 6 months [10]. However, codeine exerts also less desirable effects, such as psychomotor sluggishness and drowsiness, constipation and reduction of hunger, pain and sexual needs may appear. Sudden discontinuation of codeine-containing drugs can cause very unpleasant

symptoms, such as sleep disturbances and mood changes, irritability and tantrums, changes in vision, muscle pains, abdominal pain, diarrhoea, nausea, vomiting, watery eyes, runny nose, yawning, sneezing. Long-term codeine abuse may lead to an increase in lung infections, bowel damage, sleep disorders, irregular heart rate, and even brain damage [1,11]. According to the study of Sproule et al., the aim of which was to describe the characteristics of dependent and nondependent users of codeine, the significant reasons for using codeine were most often related to pain- headaches (41%), back pain (22%), and other types pain- muscle/joint pain or other body parts (25%). In comparison with a nondependent group, people from the dependent group were more likely to have initially intake this drug for other reasons, respectively: pleasure (2% vs 22%), to prevent withdrawal from another drug (0% vs 12%), and to relax/reduce stress (7% vs 19%). Most of the participants obtained the drug (combination preparation) from a physician (66%) or by purchasing it over the counter (54%). People from the dependent group also obtained the drug from friends (32%) or family (11%), off the street (19%), and through prescriptions from more than one doctor (11%). Of the 339 participants, only 15 (4%) were identified as codeine abusers, 10 of which were female. The mean age of these individuals was 42 years, and they were using a mean dose of 90 mg (range, 16-192 mg) of codeine per day. 47% of these individuals have been taking codeine three to four days a week. About 60% of the abusers indicated developing tolerance to codeine, while the withdrawal symptoms were experienced only by 27% [12]. A qualitative interview study by Kinnaird et al. performed on a group of 16 individuals (mean age 32.7 years) who had used codeine in the last 12 months other than as directed or as indicated, for a diverse period of time (mean period of use was 9.1 years). All of them started to use this drug to treat physical pain. Various environmental factors present in a risk environment have contributed to the development of codeine dependence in these patients. These were: unsupervised and long-term codeine prescribing, poor access to non-pharmacological pain treatments, barriers to the provision of risk education of codeine related harm and breakdown in structures to reduce the use of over the counter codeine other than as indicated [13]. Frei et al. performed a prospective case series on severe morbidity associated with misuse of OTC codeine-ibuprofen preparations. They collected data on a series of 27 patients, which were taking mean

daily doses of 435-602 mg of codeine phosphate and 6800-9400 mg ibuprofen. All but one patient reported prolonged use (longer than six months) of supratherapeutic doses of OTC codeine-ibuprofen, with a mean duration of use of 3.6 years. The most common morbidities were opioid dependence and gastrointestinal complications (attributed to ibuprofen), with 10 cases of each. Twelve patients had documented anaemia. Three patients had hypokalemia, and one patient required dialysis – these complications are associated with high doses of NSAIDs. Moreover, four patients were admitted to a hospital intensive care unit. The majority of patients were treated with some form of opioid pharmacotherapy; three patients had buprenorphine-assisted detoxification, and thirteen were started on opioid substitution treatment (buprenorphine-naloxone or methadone solution)[14].

An interesting case of codeine dependency was described by Anil et al. A 33-year-old man (married for the past two years) was presented with a history of consuming 200–300 ml/day of cough syrup containing codeine (10 mg/100 ml) for the past 28 months. The patient reported a problem with premature ejaculation that appeared shortly after the marriage. The patient suffered from acute bronchitis (three months after marriage), which he treated with a prescribed cough syrup containing codeine. After noticing an ejaculatory response correlated with the use of this codeine preparation, he started consuming 100 ml of the OTC cough syrup each day (purchased from different medical shops). Over the past 25 months, the patient increased the amount of cough syrup up to 200–300 ml/day to improve his time to ejaculation. After cessation of the syrup, he experienced a craving for it, episodes of headaches, nausea, and sweating, which subsided upon the syrup's consumption. Any other symptoms such as increased sedation, mood changes or problems at work or family were not reported. The patient's attempts to quit the syrup consumption were unsuccessful during the past three months, and thus, he decided to seek treatment for his problem. Although opioids have been considered an aphrodisiac aforesaid, these substances have not been indicated in the treatment of premature ejaculation. [15]

Incidents of codeine misuse in children have also been reported. O Reilly et al. described a case of an acute confusional state in a previously healthy 14-year-old girl ultimately attributed to inappropriate codeine use. The patient was presented to the Emergency

Department with a 5-day history of fluctuating confusion and anterograde amnesia. She had a decreased attention span, suffered from intermittent headaches, and slept up to 20 h a day. Before visiting the hospital, the patient had flu-like symptoms for 15 days (absence from school). Apart from that, the girl was asymptomatic; there were no abnormalities on general examination, the neurological examination was normal, there was no history of head injury. She denied illicit drug use. A urine toxicology screen occurred positive for codeine. The patient admitted to the use of an OTC codeine cough suppressant in the amount of 2–3 spoonfuls daily for the 15 days duration of her flu-like illness. Although she had not exceeded the recommended daily dosage of 3–6 spoonfuls, the maximum recommended duration of usage of 3 days was surpassed. As one spoonful equates to 15 mg of codeine, she consumed a total of 450–675 mg over 15 days, while the recommended maximum dosage is 270 mg during any given course of treatment.[16]. Fatal cases have also been reported among children taking codeine. Between 1969 and May 2012, FDA's Adverse Event Reporting System identified ten deaths and three overdoses in children (age ranged from 21 months to 9 years) treated with appropriate doses of codeine, mainly in the setting of adenotonsillectomy or respiratory tract infection. For the seven children, (CYP2D6) metabolizer status was mentioned. Three of them were characterized as ultra-rapid metabolizers, three as extensive metabolizers, and one as a likely ultra-rapid metabolizer [17]. Kelly et al. described two deaths and one severe apnea case among young children administered standard doses of codeine [17]. Furthermore, a report by Friedrichsdorf et al. describes the incidents of death of three obese children (4-10 years) due to codeine intoxication.[18]. In these cases, the main culprit is a genetic variation in CYP2D6. Extensive (CYP2D6 EM) and ultra-rapid (CYP2D6 UM) metabolizers are at risk of poor anal-

gesic effect and risk of opioid toxicity and oversedation of codeine. [17].

Conclusion

Codeine is an antitussive, antidiarrheal and analgesic substance available in OTC preparations. Over-the-counter opioid abuse, including codeine, has been a growing problem worldwide. The majority of the abusers use it for recreational purposes; however, many become dependent on codeine after having used it to treat pain or cough. The misuse and abuse of codeine can lead to addiction and result in renal and liver damage caused by ibuprofen and paracetamol, ingredients that are often present in the preparations containing codeine. Moreover, codeine intake may also lead to dependence on opioids or other narcotic substances. The solution might be more strict regulations and closer monitoring of OTC sales. Accessibility to drug addiction treatment is essential to cope with the consequences of codeine addiction. Family and friends also play an essential role in the process of discontinuing codeine-containing drugs. Educating patients and their families to take all medications in accordance with medical recommendations is vital.

Conflict of interest

None

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