Journal of Pharmacovigilance and Drug Safety

An Official Publication of Society of Pharmacovigilance, India.

Case Report

Who is pushing patients to death trap by improper use of codeine? Time now to reorient physicians or ban the use of codeine!

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ABSTRACT

A single case report of an elderly female patient was discussed in this present paper. The patient was admitted to a metropolitan tertiary care hospital as a case of analgesic nephropathy and ankylosing spondylitis. She was advised codeine and other groups of medicines, but her condition got worsened day by day and eventually expired. The case was found irrationally treated and led to alleged iatrogenic death and hence discussed here in terms of the patient's age, comorbidities, concomitant medicines, and dose calculation.

Keywords: *Codeine therapy, geriatric patient, physician's ignorance, physician's negligence, iatrogenic death, analgesic nephropathy*

DOI: 10.21276/jpds.2020.17.01.04

Received: 10.05.20
Accepted: 18.05.20

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INTRODUCTION

"Drug in very small dose proves ineffective to disorder like little water to flagrant fire. On the other hand, in excessive dose it becomes harmful like excessive water for the crop. Hence keeping in mind, the severity of disorder and potency of drug, the drug should be administered in neither too large nor too small dose". - C.A.2 Chikitsathanam 30. 313-314 (Charak Samhita).

Opioid agonist codeine is obtained naturally or by methylation of morphine. It has low affinity for opioid receptors and most of its analgesic effects results from its metabolism (about 10%) to morphine. Both free and conjugated morphine then can be found after therapeutic dose of codeine. Although, codeine has been used in the relief of pain, but depending on genetics, some people can metabolize or process, codeine quicker than others, leading to a

Access this article online	
Website: www.journalofsopi.com	Quick Response code
DOI: 10.21276/jpds.2020.17.01.04	

How to cite this article: Singhal KC, Garg KC, Rahman SZ. Who is pushing patients to death trap by improper use of codeine? Time now to reorient physicians or ban the use of codeine. J Pharmacovig Drug Safety. 2020;17(1):15-18.

Source of Support: Nil, **Conflict of Interest:** None

higher and faster concentration of morphine in the body that could be potentially toxic.[1]

Codeine is a pro-drug and its analgesic effect entirely dependent upon its metabolism to morphine, which shows large individual variation, thus the therapeutic effect as well as adverse reactions varies widely. Still, codeine is a widely used analgesic because of its availability as over the counter and ease of administration i.e. oral dosage.[2]

CASE REPORT

Mrs. KG 75 years old female with past history of ankylosing spondylitis for 40 years, hypertension for 5 years and lower backache for 1 and half years, came with a complaint of increased backache for past 8 months. The pain was not responding to either oral analgesic or intravenous paracetamol. She also developed pedal edema and periorbital edema for past two years.

As a known case of ankylosing spondylitis with analgesic nephropathy, she was admitted to hospital on 16th November 2013. Following drug therapy was started: Saaz (Sulfasalazine) I/M BD, Amlodipine 2.5 ml OD, Natrilix (indapamide) SR 2.5 mg OD, Moxifloxin (Moxifloxacin) 400mg OD, Inj. Tramadol 50 ml iv TDS, Lignocaine patches, Telmesartan 40 mg OD, Duloxetine (SSNRI) 20 mg BD and Vitamins, Calcium supplements.

On 18th November 2013, the treatment was modified and following drug were added: Tab. Paracetamol I gm. per 8 hours, Tab. Codeine sulphate (3 tabs of 15 mg per 6 hourly = 180 mg in 24 hrs.), Inj. Tramadol 50 mg BD (IV), Lignocaine patch and tab. Duloxetine 20 mg BD. USG abdomen showed hepatomegaly with simple hepatic Cyst.

On 19th November 2013, she developed tachycardia, bilateral occasional crepts in chest, abdominal pain, abdominal distension, hyperacidity, sluggish bowl sounds, increased abdominal girth and dilated stomach (USG). 1200 ml of fluid was also aspirated through Ryle's tube.

On 20th November 2013, she was advised to withhold codeine till further order. Abdominal girth charting was done every 2 hourly and was advised to take following medicines: Inj. Tramadol 50 mg SOS, Inj. Perfalgan (paracetamol) 1 gm. in three divided doses at 8.00 am, 4.00pm and 11.00 pm. Duloxetine was withhold.

On 21st November 2013, the patient developed fever, increased respiratory distress, irregular tachyarrhythmia – multifocal atrial tachycardia hypokalemia, Inj. Magnex 2 gm. BD, Inj. Metrogyl 500mg TDS, Inj. Moxifloxacin 400 mg OD, Inj. Tramadol 50 mg SOS, Inj. Augmentin 1.2gm TDS and others food supplements. The patient's husband, who is himself a physician and former professor of medicine noticed irregularity in pulse and informed the attending consultant of medicine in the evening. Her vitals were checked as pulse rate 136/mt and respiratory rate 32/mt. Immediately, the treatment for multifocal atrial tachycardia was started with Dilzem, Atorvastatin, Ecosprin, and Rancad. She was shifted to ICU under care of the Department of Anesthesia on and put on ventilator. At ICU, she remained on ventilator and was treated for induced bacterial infection, induced fungal infection. On 3rd January 2014, tracheostomy was done but the procedure was of little or no avail and patient collapsed and died.

DISCUSSION

In this case, codeine was started on 18th November 2013 in a dose of 15 mg 6 hourly and continued till the afternoon of 20th November 2013. She was treated symptomatically and developed opioid toxicity. On 21st November she was shifted to ICU and put on ventilatory support. Because of irreversible respiratory depression since 20th November, she could not be weaned out despite attempts. Her condition continued in this critical stage till 3rd January 2014 and ultimately died. This is a sheer example of iatrogenic death because of antidote naloxone was not given immediately after observing signs of opioid toxicity.

In addition, the patient was given tramadol, which is converted in the liver to O-desmethyltramadol, an opioid with stronger binding to the μ-opioid receptor. Tramadol is also a serotonin–norepinephrine reuptake inhibitor (SNRI). Tramadol may not provide adequate pain control for individuals with certain genetic variants of CYP2D6 enzymes as they metabolize tramadol to the active molecules. These genetic polymorphisms are not currently routinely tested for in clinical practice. Moreover, tramadol is contraindicated in elderly. The risk of opioid-related adverse effects such as respiratory depression, falls, cognitive impairment and sedation is increased.

Tramadol may interact with other medications and increase the risk for adverse events. The synergistic action of tramadol, codeine and duloxetine (SSNRI) might have played a role in this iatrogenic death.

The reported symptoms of codeine overdose are muscle spasticity, shallow breathing, slow breathing, depression of respiratory center and increased airway resistance acute respiratory failure.[3] Pinpoint pupil, acute pulmonary edema, itchy skins, bluish skin, nails and lips, cold and clammy skin, gastrointestinal spasms, weak pulse and reduced blood pressure, cardiac arrhythmia may also be induced. However, the characteristic triad of codeine poisoning is coma, pinpoint pupil and respiratory depression besides slow and shallow respiration, cyanosis and week pulse.

For adult codeine and its salts (sulphate and phosphate) are administered in doses of 15 to 60 mg at four and six times per day. The maximum daily dose of codeine, for the relief of pain is 360 mg.[4] Pediatric and geriatric patient may be more susceptible to the effect of codeine; especially to respiratory depression lower dose may be required for this type of patients.

Codeine is metabolized mainly in the liver where it undergoes O-demethylation to form morphine, N-Demethylation to form nor-codeine and partial conjugation to form glucuronides and sulphonamides of both the unchanged drug and its metabolites. These metabolites are also active and show pharmacological action. Codeine when converted to morphine in the liver then all its pharmacological effect is through μ- receptor including the adverse reactions like respiratory depression and constipation.[5] The respiratory depression if not reversed within few hours attains a state of irreversibility, where the one and only morphine antagonist, naloxone should be given.[6] When toxicity to codeine sulphate was noticed in the form of distension of abdomen, respiratory distress, cardiovascular, manifestation and altered sensorium. Naloxone, the antagonist to codeine (Morphine) was not administered, which only could have reversed the effects of codeine (morphine) and saved life. In this patient, the question now arises that why the antagonist to morphine was not administered within few hours when sign of toxicity (adverse drug reaction) were observed. This reflects upon the competency of treating physician, who are not conversant with even the basic principles of therapy, adverse outcome of drugs they use and to use antidote in the event of such happening.

The competitive antagonist of μ- receptor naloxone should have been administered intravenously (0.4-0.8 ml) which antagonizes all actions of morphine.[7] It not only normalizes respiration but even stimulate it probably due to sudden sensitization of respiratory center to the retained CO_2. Besides, naloxone normalizes level of consciousness, pupil size and bowl activity, it has no agonist activity.[8]

Ageing is characterized by a progressive loss of functional capacities of most of the organs, a reduction in response to receptor

stimulation and homeostatic mechanism and loss of water content and increase in fat content of the body.[9,10] Thus in this ageing patient, either codeine must have given in low dose or should have been avoided.

The dose in elderly must be appropriately adjusted. Most age-related physiological functions peak before the age of 30 years, with subsequent gradual linear decline reduction in physiological capacity and functions are cumulative, become more pronounced with age.[11] Kidney function is major consideration while deciding dose in the elderly because reduced function results in reduced elimination.[12]

Because reduced kidney function increases the possibility of toxic drug levels in the body and adverse drug effects, initial drug dosing in the elderly patient diagnosed as suffering from analgesic nephropathy (diagnosis provided on the case sheet of the hospital), the dose selected should have been much lower than usually prescribed for young healthy individual. This dose may be determined based on the patient's body weight, surface area, health and disease states, and pharmacokinetic factors.[13]

Concomitant therapy may affect drug/dose effectiveness. A drugs dose may produce adverse reactions and affect patients' adherence. As the body ages, muscle mass declines and preparation of body fat increases and there is reduction in total body water, which can affect the distribution of drugs that are water soluble. Codeine is highly soluble in water and with reduction in body water. The same dose will provide higher blood/tissue concentration. This will increase because older adults have less albumin, which binds the drug in the blood stream. Reduction in protein building increases the free concentration of drug. More drug becomes available to reach receptors, thus increasing the pharmacological effects and consequently the adverse reactions especially is an elderly.

Thus, the distribution volume and this protein binding are necessary to reduce the dose of a drug to produce desirable pharmacological action.[14] These factors result in this alteration of the half-life of the drug. Failure to take these changes into consideration results in drug toxicity. For drugs lacking such information on the dose should be reduced in dose and titrated for a specific response.

In a nutshell, the physician did not take into consideration the following factors in this case:

1. Age: Average doses adjustment for the aged can be derived from suitable equation and mean pharmacokinetic parameters from older and younger adults; however, these average dose adjustment factors negate the large variation in the decline in organ functions associated in the elderly. Using pharmacokinetic guidelines for dose adjustment, the same plasma drug content rations result in elderly as in younger adults.[15] However, the pharmacodynamics changes in elderly alter sensitivity to drug, irrespective of changes in drug disposition.[16] The CNS is especially vulnerable in the elderly; agents that affect brain functions (anaesthetics, opioids, anticonvulsant, and psychotropic drugs) must be used cautiously in this age group. Here in this case, the patient was 75 years old when she was admitted in AIIMS. The dose of any drug including codeine should have been reduced to 3/4th part of the usual adult dose provided that there is no other associated factors which need to be considered for dose notification.

Aging process can also affect metabolism. Several physiological changes can greatly influence metabolic capacity. In general, hepatic blood flow is reduced which can significantly affect metabolism, because drug is introduced to the liver at a much lower rate. Liver mass and intrinsic metabolic activity (includes CYP_{450} enzyme system) also is reduced during the aging process.[17] Because Age, Sex, genetics and other variables play such major role in metabolic capacity, any data formula for dose calculation based on hepatic functions alone would not be accurate however; the doses of hepatically cleared drugs in elderly patients should be reduced.

2. Liver Disease: The patient was subjected to ultrasonography; the report clearly show that she was suffering from hepatic ailment. The report "hepatomegaly with purple hepatic cyst" should have acted as warning to the physician to modify the dose of codeine to the lower level. Opioid group of drugs are contraindicated in hepatic damage (hepatomegaly and cyst in liver in the present case) as it is metabolized by liver.

3. Kidney Disease: The most important pharmacokinetic changes in old age is a decrease in excretory capacity of the kidney, in this regards, the elderly should be considered as renal insufficient patients. The decline in the rate of drug metabolism with advancing age is less marked, the volume of distribution and the oral bioavailability of drug may be changed in the elderly compared with younger individuals.[18, 19]

In the Case sheet of Mrs. KG from the day of admission and repeatedly thereafter it is written that she was suffering from ankylosing spondylitis with analgesic nephropathy. It is amazing that the treating physician did not take this fact into consideration while taking decision about the dose. Half-life of a drug is increased as renal function is reduced. As age increases, renal functions decline is the result of sometimes by a significant degree. This decline is the result of several physiological changes which includes reduction in blood flow to kidney, a decrease in renal mass and reduction in the size and numbers of functioning nephrons.

Continued re-evaluation of the patient receiving codeine sulphate is important with special reference to the maintenance of pain control and incidence of adverse reactions associated with the therapy. The fact that Mrs. KG was suffering from analgesic nephropathy, was not considered while deciding about the dose of codeine sulphate.

4. Doses Calculation according to age:

Gobin's Formula (this does not take into consideration of associated factors like associated renal or hepatic derangement)

Table: **Gobin's Formula to calculate dose in different age group**

Age	Dose
7-14	1/2 of adult dose
14-20	2/3 of adult dose
21-60	full adult dose
60-70	4/5 of adult dose
70-80	3/4 of adult dose
80-90	2/3 of adult dose
Over 90 years	1/2 of adult dose

The usual adult dosage of codeine sulphate is 15mg to 60 mg repeated up to every four hours as needed for pain. The maximum 24 hours dose is 360 mg. The initial dose should be titrated based upon this individual patient's response to their initial dose of codeine. This dose can then be adjusted to an acceptable level of analgesia taking with account the improvement in pain intensity and tolerability of this codeine by the patient.

Some individuals may be ultra-rapid metabolizers because of a specific CYP2D6 genotype L (gene duplication denoted as $^{x}1/^{x}1xN$ or $^{x}1/^{x}2xN$). The prevalence of this CYP 2D6 phenotype varies from 0.5-1% in Chinese to 16-28% in North Africans, Ethiopians and Arabs. Data are not available for Indian population. These

individuals metabolize codeine into its active metabolite morphine more rapidly and completely than other people.[20] The rapid conversion results in higher than expected serum morphine levels. Even at labeled dosage regimens individuals who are ultra-rapid metabolizers may have life threatening or fatal respiratory depression or experience signs of overdose?

In this case, she might be a rapid metabolizer of codeine and metabolism of codeine might have led to influence adverse drug reactions. The consequences of adverse reactions could have been move intense. Since no estimation of liver enzymes to assess the metabolizing ability of the individuals was done in this case, so in the absence of enzymatic study, no comments can be made.

When prescribing codeine, healthcare providers should choose the lowest effective dose for this shortest period of time and inform the patients and caregivers about these risk and signs of morphine overdose. Codeine may cause confusion and over-sedation in the elderly. In general dose selection for an elderly patient should be cautions generally starting at the low end of the dosing range.

5. Why Tramadol was co-administered in the event of ADRs due to Codeine (Morphine): Concurrent administration of any drug potentiating the effect by acting on same receptor site i.e. μ-receptor, use of tranquilizer with codeine sulphate may result is additive CNS depression, respiratory depression, hypotension, profound sedation or coma. Tramadol a μ-receptor agonist of morphine was administered in a dose of 50 mg IV as and when required. Acting on μ- receptor tramadol has actions similar to morphine on respiration system (depression) and on gastrointestinal tract (constipation, increase sphincter tone, decrease motility). Thus, delaying gastric emptying, tramadol, therefore; was additive to the adverse reactions to codeine (morphine) and should not have been prescribed in the event of respiratory depression and distension of abdomen.

CONCLUSION

Information was sought under RTI Act, 2005, vide application dated 13.5.2015, The head Department of Anesthesia where the pain clinic is conducted, stated that number of patients treated by the concerned physician with opiate analgesics cannot be provided since the records are not available and also no record is available to provide the number of patients who developed opiate toxicity following codeine therapy. There is no record available about the patients referred from other departments to the pain clinic. Further, there is no practice to record suspected adverse reactions. Monitoring of enzyme CYP2D2, which metabolizes codeine to morphine in the body, is not done. Information regarding suspected death due to drug is not submitted to ADR monitoring cell of the Institute or CDSCO. From the prescriptions of the patient, it is evident that there was gross negligence on the part of treating physicians on the following counts: she was administered codeine in a dose which was too high for a geriatric patient with nephropathy and damaged liver with hypertension, ankylosing spondylitis, altered serum protein profile along with tramadol. Such misconduct, ignorance, iatrogenic cases need to be reported and otherwise, this is the time to reorient physicians or ban the use of codeine.[21]

*The physician ignorant of place etc. and prescribing treatment only with formulations fails because there are so many variations in respect of age, strength, body, etc. - C.A.2 Chikitsasthanam.30.*320.[22]

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