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(CASE REPORT)

Opioid toxicity following a therapeutic dose of dihydrocodeine: A case report

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Abstract

Dihydrocodeine (DHC) is a synthetic analogue of codeine used in the treatment of moderate to severe pains. However, it has safety concerns to draw attention to the possible occurrence of DHC toxicity even in therapeutic doses. An 84-year-old known diabetic, hypertensive, and hormone-refractory, advanced carcinoma of the prostate male patient were admitted to our ICU for pain management and close monitoring. Shortly before admission, he had received DHC 60 mg in the surgical ward, which was to be followed with 30 mg 8 hourly. Within 10 hours of admission, he developed a classic triad of features of opioid toxicity (respiratory depression, coma, and pinpoint pupils). He was managed with naloxone at 0.4 mg and another 0.4 mg, 10 minutes later. The patient recovered initially and then relapsed into a coma after a short while before the next dose of naloxone was given and could not be resuscitated. Opioid toxicity even with therapeutic doses of DHC can occur during treatment.

Keywords: Opioid toxicity; Dihydrocodeine; Naloxone

1. Introduction

Dihydrocodeine (DHC) is a semisynthetic analogue of Codeine, which was formed by the hydrogenation of the double tie in the main chain of the codeine molecule [1]. DHC compared to codeine possesses a single bond instead of a double bond between carbon 7 and 8 [2]. It is used as an analgesic, antitussive, and the treatment of opioid addiction [1].

DHC administered by the oral route possesses similar analgesic potency to codeine, and approximately twice as potent as tramadol [3]. It is especially useful for patients suffering from chronic pain of moderate to strong intensity especially with concomitant cough and dyspnoea. This may be a very common situation in patients with advanced lung cancer [4].

However, in common with all opiates, it has the potential to cause significant respiration depression, and it has been identified as one of the common culprits in opiate-related deaths [5].

Previous studies have documented various complications associated with DHC, including respiratory depression, [6] renal failure [7], and even death [8] following different regimens of DHC.

In our environment, DHC commonly marketed as DF-118 is frequently prescribed in the management of moderate and severe pains, however, reports on the complications of DHC in therapeutic doses is scarcely reported. We report a classic case of opioid toxicity following a therapeutic dose of DHC.

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2. Case Presentation

An 84years old known Diabetic and Hypertensive man, who was being managed for hormone-refractory carcinoma of the prostate with bone metastasis, was admitted to our Intensive Care Unit (ICU) for close monitoring and pain management. Six days prior to the index admission, the patient had been managed in the ICU for urosepsis when he presented with altered consciousness and hypokalemia (2.7mmol/l).

He was treated with intravenous infusions, blood transfusion, Rocephin, levofloxacin, and potassium chloride. His routine medications included abiraterone, amlodipine, telmisartan, glibenclamide, metformin, in addition to paracetamol and diclofenac for bone pains. He regained full consciousness; the serum potassium was 3.4mmol/L and was discharged to the ward.

Shortly before his readmission in the ICU, he was given DHC 60 mg stat, to be followed with 30mg 8 hourly, in addition to diclofenac suppository 100mg 12 hourly, and other routine medications. Within 10 hours of admission and commencement of treatment, the patient developed a rapid and steady decline in consciousness and other parameters. His Glasgow Coma Scale (GCS) decreased to 8, then 3 within 30 minutes and the pupillary size became pin-point bilaterally. Also, his respiratory rate declined from 35 cycles per minute to 12 cycles per minute, and the peripheral capillary oxygen saturation (SPO2) from 94 % to 82 % on supplemental oxygen via Hudson's mask. A diagnosis of opioid toxicity secondary to DHC was made.

The oxygen therapy was continued through the anesthesia machine using an anesthetic face mask at 6L/min. Intravenous naloxone was given at 0.4 mg stat, followed by two additional doses of 0.4 mg at 10 minutes interval. Other supportive care in ICU was continued, while DHC was discontinued.

Following the initial resuscitative effort, a remarkable improvement in the patient's clinical state was observed. The GCS increased to 9, the pupils were about 2mm in size and reactive to light, the respiratory rate increased to 24cycles per minute, while the SPO2 rose to 96 – 98%.

Naloxone was prescribed for continuous infusion at 0.08 mg/hr, however, the patient's condition started deteriorating again after a short while, he relapsed into a coma before the next dose of naloxone was given and could not be resuscitated despite the intense effort at resuscitation.

3. Discussion

Our patient had the classic triad of symptoms of narcotic toxicity [respiratory depression, coma, and pinpoint pupils] [9] and recovered almost immediately following the initial naloxone treatment. In a previous study, Whipple *et al*., [9] evaluated the difficulties in diagnosing narcotic overdose in 43 hospitalized patients who received naloxone for clinically suspected narcotic overdose.

They found that 15 (35%) patients were misdiagnosed due to the failure of improvement in symptoms following naloxone treatment. Also, only two of these patients had the classic triad of symptoms, while the majority had only one or two of the classic signs. It is, therefore, a difficult diagnosis to make. Thus, a high index of suspicion is required to detect this condition.

DHC toxicity is commonly reported when it is taken in high doses beyond the recommended dose, either accidentally or deliberately [1,6,10] The recommended dose regimen for DHC in adults and children greater than 12 years is 30mg every four to six hours or at the discretion of the practitioner. The maximum dose in 24 hours is 180mg [6 Tablets] [11]. Our patient took 60mg of DHC, to be followed by 30mg 8 hourly, and developed toxic features within 10hours of commencement of treatment. Similarly, Park and colleagues [7] reported severe narcosis and acute renal failure following therapeutic doses of DHC in two patients.

The possible risk factors for opioid toxicity in our patients were age, severe pains, and a history of diabetes mellitus and hypertension which might have affected the kidney function (although the kidney function tests were fairly normal). Perhaps continuing with DHC at 30mg 8 hourly regimens, in addition to paracetamol and diclofenac would have prevented that complication.

Naloxone is the mainstay of treatment for acute opioid poisoning, in addition to general supportive measures including a clear airway and monitoring of vital signs until stable [11,12]. The British National Formulary recommends a dosing

regimen of 0.8 – 2 mg boluses, repeated as necessary up to 10mg for adults (10 mcg/kg followed by 100mcg/kg boluses for children) [12]. However, there is no consensus in the literature on the best dosing regimen. Different regimens have been used successfully by different researchers [6, 10] in an earlier study, Parker and Thomas [10] used naloxone 0.4 mg bolus, followed by a repeat bolus of 0.8 mg and a continuous infusion at 0.67 mg/hour for eight hours to resuscitate a 51 year old woman who developed acute poisoning after taking 60 tablets of DHC. Also recently, a 61 year old woman has treated successfully for DHC overdose with naloxone 0.4 mg bolus, then 0.4mg repeated after 20 minutes, followed by 50mcg/hour infusion for 27 hours [6]. Our patient received 0.4mg bolus, which was repeated two times at 10 minutes interval, to be followed afterward with an infusion at 0.08 mg/hr. Unfortunately, the patient who initially had recovered from the toxic symptoms later relapsed into a coma before the next dose of naloxone was given and could not be resuscitated. This might have been due to narcotization following the rapid redistribution of naloxone away from the brain [12].

4. Conclusion

Opioid toxicity even with therapeutic doses of DHC can occur during treatment.

Compliance with ethical standards

Acknowledgments

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Disclosure of conflict of interest

The authors declare that they do not have any conflict of interest.

Statement of informed consent

Informed consent was obtained from all individual participants included in the study.

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