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Case Report

A Combined Bolus-Infusion Approach over Pure Bolus Regime in Stabilizing Hypotension and Maintaining Consciousness in A Case of Methadone Poisoning

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Abstract

Naloxone is an opioid antagonist that competitively binds to opioid receptors and reverses their effects. It is indicated for use in respiratory depression caused by opioid overdose. We provide a case study approach to discuss the advantages of employing a combined Naloxone bolus- infusion administration to stabilize blood pressure and maintain responsiveness during the critical care phase of treatment.

Keywords: Methadone, Overdose, Naloxone, Bolus, Infusion

Background

From the 1980s to the early 21st century, Malaysia's drug policy was based solely on a prohibitionist approach. Non-medical institutional rehabilitation approach was the main modality for rehabilitating people who use drugs (PWUD). The introduction of harm reduction programs in the country opened the door for public health approaches to be introduced. Hence, Methadone was approved in 2003 and there are currently 814 health facilities providing methadone in government (449) and private (365) clinics. At the time of preparing this manuscript, a total of 67,438 patients were currently undergoing methadone maintenance treatment in Malaysia, with 35,663 in government and 31,805 in private settings respectively [1]. The rapid expansion of methadone use may have somewhat translated to its easier availability and this has resulted in some cases of poisoning[2], which we believe is likely an underestimate of the real problem.

Introduction

Non-medical use of methadone and the increasing number of deaths due to methadone poisoning is a serious problem in the modern age. Besides the mortality rate and worsening of medical outcomes, the increase in health care cost with a majority of the cases requiring endotracheal intubation and a 50% admission rate to the Intensive Care Unit (ICU) poses a burden that is no longer negligible [3].

The half life of methadone is approximately 10 times that of morphine and hence, a prolonged course of intoxication has been noted [4]. Toxic effects may persist up to 24 hours [5]. In general, the clinical efficacy for opioid antagonism lasts for 45-70 minutes [6]. The rapid onset of action of Naloxone and its relatively short duration of activity are due to its high lipid solubility and its rapid entry to the brain. However, its short duration is related to its egress from the brain and not its metabolism. Hence, to maintain adequate brain levels of Naloxone, either multiple doses or a constant infusion is required [4]. Use of a continuous infusion should be considered when repeat bolus doses are required.

The recommendation for the use of Naloxone infusion in cases of Methadone overdose has been described from as

early as four decades ago. Considering that toxic effects from Methadone overdose may persist for 24 hours, Waldron, Klimt & Seibel (1973) described a case wherein slow and constant infusion of Naloxone seemed the preferred treatment [5]. Thereafter, Bradberry & Raebel (1981), taking into account the safety profile of Naloxone, determined that it may be possible to keep a patient from relapsing into narcosis (re-narcosis) after narcotic overdose by administering it as an infusion, more especially in the treatment of longer-acting agents such as Methadone [7].

Case Report

A 39 year old opioid-naïve Chinese lady weighing 50kg was found by her family unconscious and barely breathing with froth around her mouth around 4 a.m. She was already in cardio-respiratory arrest upon arrival at the Emergency Room with arterial blood gases showing uncompensated respiratory acidosis. She was successfully resuscitated, an endotracheal tube inserted and was sent to the ICU. A history of accidental ingestion of 50mls of her partner's Methadone syrup (estimated total dose of 250mg) was obtained and thereby, a diagnosis of Methadone poisoning confirmed. She alledgedly had a toothache and was self-medicating and therefore, may have taken painkillers concomitantly. Although she had also consumed some alcohol prior to the alledged accidental overdose, no estimated amount (nor her recent drinking pattern) was ascertained. Given radiological findings of possible chemical pneumonitis from aspiration and dropping oxygen saturation (lowest recorded SpO2 78%), her prognosis was considered poor. She was ventilated and the decision to commence Naloxone therapy was made.

The initial intravenous bolus given at 0.4mg stat awakened her momentarily but she rapidly became unconscious soon after, thus a regimen of 0.4mg every half to one hour was commenced with a plan not to exceed a total of 4mg Naloxone per day - we followed the recommended regime rather than basing it on her body weight. Whilst being vigilant for life-threatening adverse events caused by Naloxone such as arrythmias, QT prolongation and pulmonary oedema [6], we were instead alerted to another form of cardiovascular problem in the form of a dropping diastolic blood pressure (DBP) trend (lowest recorded BP 72/38mmHg). Hence, the frequency of Naloxone delivery had to be reduced to two-hourly doses, with the maximum dose at each administration limited to 0.2mg. Although this dose adjustment settled her low DBP issue, re-narcosis on the other hand predictably occurred soon after each bolus administration given the ultra-short acting property of Naloxone. She still could not stay awake beyond a few minutes even after being given a total of 1.6mg Naloxone the first day, nor after being successfully weaned off the ventilator and converted to a continuous positive airway pressure (CPAP) apparatus towards the end of Day 2 post-overdose. She received a total of 2.4mg of Naloxone on the second day.

Although she was extubated by the end of Day 3, she was still found to have problems maintaining consciousness and was therefore, unable to be fed orally as she could not swallow properly whenever she dipped into a semi-responsive state. Nasogastric feeding was carried out but the aspirate showed undigested feeds. The total daily dose of Naloxone given on the third day was fairly low at 0.8mg as her BP had not picked up and hence, a decision was made to instead employ Naloxone infusion, with allowances for as and when necessary (PRN) bolus dosing whenever she dipped again into semi-consciousness. The infusion was administered at a rate of 0.2mg per hour from Day 4, after which her low DBP began to improve. It finally stabilized around the time when the dosage regime was further decreased to 0.1mg per hour after her periods of consciousness became more frequent. The Naloxone infusion had to be continued for a further two days and although she only required a total of 2.8mg Naloxone on that fourth day, the need was considerably higher with doses of 7.2mg and 4.6mg respectively on Days 5 and 6 post-poisoning to maintain a steady level of consciousness. Only a further 0.5mg of Naloxone infusion with no further need for PRN bolus doses was required in the early hours of the seventh day, after which the infusion was discontinued and she was then hemodynamically stable enough to be transferred to the ward.

She was noted to be confused for a couple of days thereafter but there were no observable Methadone withdrawal signs. She was later able to verbalize relevantly and it was found that she may have had problems with her worker(s) running her stall selling oysters at a popular tourist spot and was under extreme mental stress prior to the alleged overdose. Further collateral history revealed unstable behavior and relationships for years, impulsivity and chronic unhappiness suggestive of underlying borderline traits. Psychological intervention was not possible as she was not cognitively clear enough to process at the time. Despite her clouded mental state, she was allowed home when family support was enlisted and the risk of suicide considered low.

She was seen as an outpatient four days after discharge and although her confusion appeared outwardly to be less prominent, a Mini Mental State Examination (MMSE) performed still confirmed some degree of cognitive impairment with a score of 23/30. Her motor movements and gait were still slow but she seemed psychologically stable. There was no indication of mood problems or suicidal behavior.

She was seen again 18 days later and although she still could not remember many details surrounding the period of the alleged overdose, she nevertheless maintained that she had not attempted suicide or acted impulsively, nor was she overly stressed at the time – she claimed she was merely desperate to relieve the toothache she suffered and assumed she could consume what she mistook for cough syrup so as to numb the pain and get to sleep. She denied suicidal behavior in the past but admitted to inflicting cuts on herself when feeling very sad. She then admitted to having had unstable mood spells over the years but said it was mainly as a result of bankruptcy and not due to interrelationship problems. Her mood was normal and her movements were more brisk than they were when seen during the earlier appointment and she had gone back to work soon after discharge. However, she could not appreciate the critical state she was in just a month earlier and a repeat MMSE found a deterioration in

her scores to 20/30.

Discussion

Naloxone has been proven effective in increasing the level of consciousness, minute ventilation, and blood pressure in their patients with narcotic overdose [6], Due to its short half-life, repeated dosing is often required to prevent the recurrence of respiratory depression [8].Given that Naloxone can sometimes cause hypertension, our patient experienced hypotension instead. Although it may have been possible that the drop in her BP was due to the latent effects of the initial Methadone overdose, we were also open to the idea of considering that the analgesic effect of Naloxone that could have numbed her senses, in addition to the expected precipitated acute withdrawal from Methadone. We started a continuous infusion when her BP failed to pick up and she could not stay conscious for long after each bolus administration of Naloxone. Lewis et al (1984) recommended continuous infusion to prevent relapse if patients showed recurrent respiratory or central nervous system depression after initial improvement with bolus therapy, as well as in patients who ingested long-acting poorly antagonised narcotics such as Methadone [9]. Goldfrank et al (1986), in a two-phase study on the pharmacokinetics of Naloxone, reported that continuous infusion of two-thirds of the bolus dose resulted in reversal each hour will maintain the plasma Naloxone levels equal to or greater than the Naloxone levels that would have existed 30 minutes following the bolus dose.[8] Thus, continuous infusion is more convenient than administering repeated boluses and provides sustained tissue levels of Naloxone, successfully preventing relapse of narcotic effects [6].

Clarke & Dargan (2002) described a large variation in factors determining plasma Naloxone concentrations between people; those eliminating it rapidly are not likely to experience a reduction in opioid levels, thereby increasing the risk of re-narcotization. This would then invariably lead to an over-estimation of the infusion rate for those eliminating Naloxone more slowly, with the subsequent theoretical risk of precipitating acute withdrawal symptoms. Although they also found no evidence from their search to suggest that subcutaneous or intramuscular routes were inferior to intravenous administration of Naloxone, they conceded still that significant theoretical concerns had not been addressed. Hence, they calculated a practical regimen for titrating Naloxone by infusion in opioid overdose as follows:

i. Titrate the initial bolus of Naloxone against clinical effect,

ii. Start an infusion of Naloxone, giving two-thirds of the initial bolus per hour, then,

iii. Consider second bolus (at half the initial dose) after 15minutes, if there are signs of reduced respiratory rate or conscious levels.[10]

A total of 19.9mg of Naloxone was given throughout the seven days in the ICU to fully stabilize our patient. She required substantially higher doses (7.2mg and 4.6 mg on days 5 and 6 respectively) to maintain her level of consciousness, therefore exceeding the recommended regime of a maximum dose of 4mg per day. However, that appeared to be the amount needed to maintain her level of consciousness before she was medically stable enough for the dose to be tapered off before leaving the ICU. Tenenbein (1984) stressed that there should not be hesitancy in trying a higher dose of Naloxone in a patient who does not respond to a recommended standard dose. Parenteral doses of six to 50mg have been given with impunity in adults. Basing a reversal dose purely on the weight of the patient is not rational; the dose of Naloxone should also take into account the amount of narcotic agent ingested, its brain penetration, as well as Naloxone's affinity to opiate receptors in relation to the narcotic drug. Due to the fact that most of these factors are unknown, the optimal required dosage of Naloxone is usually empirical.[4] Last but not least, being opioid-naïve had definitely put our patient at a disadvantage where toxic effects of and reversal from Methadone were concerned. This then raised concerns as to whether instituting Naloxone infusion at the outset may have somewhat reduced the respiratory depression caused by the initial Methadone overdose, thereby minimizing cerebral hypoxia that likely resulted in her cognitive disturbance.

Finally, we were curious about the effects of cytochrome P (CYP) 450 inhibition on Methadone metabolism. It is well-known that alcohol is a liver enzyme inhibitor and determining our patient's alcohol consumption at the outset could have guided us better in her management. Nonetheless, even if there was an interim elevation in alanine aminotransferase (ALT) level, it would not have necessarily signalled a serious liver problem. Also, knowledge and confirmation of the type of painkillers she used would have also been helpful as that would have given us an idea of the duress her liver may have been under.

Conclusion

Employing Naloxone infusion after initial bolus administration in Methadone overdose was found to stabilize BP and possibly decrease the likelihood of emergent hypotension in the opioid-naive. It also helped to maintain consciousness, albeit requiring higher doses, but helped to reduce critical care needs.

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