Case Report

Reversal of the effects of clonidine using naloxone

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Summary

An 18-year-old man underwent surgery for correction of idiopathic scoliosis. Due to the requirement for intra-operative spinal cord monitoring, propofol and remifentanil total intravenous anaesthesia was chosen as the anaesthetic technique. Clonidine was given intra-operatively as part of his analgesic regimen. No long-acting opioids were administered. There was delayed emergence after switching off total intravenous anaesthesia and he remained sedated with a bispectral index of approximately 60 for 90 min. The common causes of delayed emergence were excluded. Shortly after administering naloxone, there was an increase in bispectral index and emergence from anaesthesia. We describe the successful use of naloxone to reverse the sedation effects of clonidine.

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Introduction

Clonidine is a centrally acting alpha-2 adrenergic agonist that is used increasingly in anaesthetic practice for analgesia, sedation, as an antihypertensive and as an adjunct to neuraxial procedures. It reduces sympathetic outflow from the central nervous system via G protein-coupled potassium and calcium channels on the cell membrane, preventing neuronal firing and action potential propagation [1]. We describe a case where an 18-year-old man undergoing spinal surgery exhibited delayed emergence from anaesthesia after clonidine administration but who promptly responded to treatment with naloxone. This is rare but there have been isolated reports describing an improvement in conscious level during clonidine toxicity in paediatric cases after administration of naloxone [2].

Report

An 18-year-old man presented for elective idiopathic scoliosis correction surgery. His only significant previous medical history was mild attention deficit hyperactivity disorder. He was not taking any regular medication and was otherwise fit and well. Due to the requirement for intra-operative spinal cord monitoring, the conduct of anaesthesia was total intravenous anaesthesia (TIVA) with propofol and remifentanil. The surgery was uneventful and he was haemodynamically stable throughout. No muscle relaxants were administered. A multi-modal analgesic approach consisting paracetamol 1 g, ketamine 30 mg and 1% lidocaine infusion (total dose 430 mg) were administered intra-operatively. The adjuncts administered were magnesium sulphate 8 mmol and clonidine 150 μg. Bispectral index (BIS) monitoring was used, and a value of 40–45 was maintained throughout surgery.

Towards the end of the procedure the TIVA level was gradually reduced in order to facilitate a stable emergence. BIS remained approximately 50. On completion of surgery, the TIVA was switched off and the patient was returned to the supine position. BIS remained at approximately 60. Approximately 90 min after stopping all anaesthetic agents, the effect-site concentration (C_{et}) of propofol was 0.5 $\mu g.ml^{-1}$ and the C_{et} of remifentanil was 0.2 $ng.ml^{-1}$. At these C_{et} levels, one would expect the patient to show signs of emergence from anaesthesia [3]. The patient was breathing spontaneously

but was otherwise unresponsive. All potential causes of delayed recovery were considered and excluded. The doses of paracetamol, magnesium and lidocaine were not considered excessive enough to cause a reduced conscious level. The bolus dose of ketamine given was only moderate. Clonidine can cause sedatory effects but the dose administered was within the recommended therapeutic range. At this point, intracranial causes of delayed recovery were being considered and an urgent computed tomography (CT) scan of the brain was being organised as well as a critical care bed. A member of the team suggested the use of naloxone to reverse the sedation effects of clonidine, as it had been reported to be successful in the paediatric population. This patient had not received any long-acting opioids intra-operatively and the effects of remifentanil would be expected to have long ceased to exist. Naloxone was administered in 400 μg boluses. The total dose given over 10 min was 2 mg. At this point, the BIS increased to 85, the patient started making purposeful movements and opened his eyes. Tracheal extubation was performed when his Glasgow Coma Scale score was 15. Despite the large dose of naloxone, the patient was comfortable. FA fentanyl patient controlled analgesia was commenced for postoperative pain management and the CT brain request was cancelled.

Discussion

The incidence of clonidine toxicity seems to be on the increase probably due to its increasing use in psychiatric disorders and its current popularity in anaesthesia, critical care and pain practice [1]. Delayed emergence from general anaesthesia can be classified into neurological causes, drug effects and metabolic issues. These were each addressed in turn when considering the differential diagnoses; A CT head was being arranged, there was no suggestion of disturbance in acid/base balance or electrolyte concentrations and the patient's temperature was normal.

There were few administered drugs that could satisfactorily explain the conscious level – in particular there were no long-acting opioids. We excluded common causes of delayed emergence even though the BIS remained at 60 for approximately 1.5 h, but after naloxone administration promptly increased to 85 within 10 min and the patient regained a normal conscious level.

Although supportive management is the mainstay of treatment in clonidine overdose, naloxone has been successfully administered to patients who have suffered its ill effects, primarily in the paediatric population. Patients may present with coma, respiratory depression, meiosis, hypotension and bradycardia, and this is usually due to accidental ingestion of a family member's tablets. It has been postulated that administration of clonidine may trigger the release of endogenous opioids, or directly stimulate opioid receptors. As a competitive opioid receptor antagonist, administration of naloxone would therefore reverse any side-effect brought about via those mechanisms.

The dose of naloxone for the treatment of clonidine toxicity is unknown; in our case, 2 mg was administered in divided doses, but some have suggested the use of up to 10 mg ('high dose'). Given that it tends to be administered in divided doses in the order of micrograms, a wide dose range exists in the literature.

A recently published retrospective cohort study looked at cases of clonidine overdose in children. It aimed to determine if naloxone was effective, and whether its use caused any harm. Forty out of 51 patients suffering a reduced conscious level responded to treatment. The authors found it was less effective at improving hypotension and bradycardia. In the 21 patients who received a high dose of 10 mg, no adverse outcomes were reported [2]. Another retrospective review of 133 adult cases of clonidine toxicity found a reduced conscious level in 68%, and that 23 patients who were given naloxone (in a mean dose of 2 mg) there was documented improvement in conscious level in only one patient, concluding that it is not associated with improved outcomes [4]. We accept that there is no firm evidence to prove the mechanism, however, it has been suggested that given the favourable side-effect profile of naloxone and the potential to avoid tracheal intubation that in a risk/benefit sense it is prudent to administer the drug.

In our case of delayed emergence from anaesthesia, we observed a prompt response to administration of naloxone at a time when the level of anaesthetic agents had reached negligible levels. Despite mixed reports in the literature regarding the efficacy of naloxone to treat clonidine toxicity, we believe that in our case the treatment avoided a CT scan and potentially prolonged critical care ventilation for the patient.

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