

Amitriptyline and tianeptine poisoning treated by naloxone

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Abstract

Introduction: Severe amitriptyline toxicity may cause cardiac dysrhythmias, severe hypotension, convulsions and CNS depression, including coma. Management with gastric lavage, activated charcoal, alkalization and supportive care with mechanical ventilation, antiarrhythmics and anticonvulsants, if required, is the general approach. **Case report:** A 33-year-old woman who has taken overdose antidepressants (amitriptyline and tianeptine) was admitted to the emergency service. She was intubated because she had pure respiratory arrest. Besides hypotension (80/60 mmHg), she was unresponsive to verbal and painful stimuli and her Glasgow coma score was 6. Hemogram and serum biochemical parameters and electrocardiography were within normal limits. The patient was examined for substance dependence and no trace of the injector was found in the body. Patient underwent a coma cocktail (naloxone 2 mg/kg, 5% dextrose 25 g/body and tiamin 100 g/body). Activated charcoal and intravenous alkalization by NaHCO₃ were initiated. Spontaneous respiration started again 20 min after being given the coma cocktail. She became responsive to verbal stimuli first hour after the coma cocktail, and her Glasgow coma score improved to 13. She had spent 2 days in the service and was discharged by the second day of admission, without any complications. **Discussion:** Herein, we report successful treatment in a case of severe amitriptyline and tianeptine poisoning by naloxone in addition to the above supportive care. Naloxone treatment may have a beneficial role in lethal doses of amitriptyline ingestion because amitriptyline may affect opioid receptors.

Keywords

amitriptyline, tianeptine, naloxone, acute poisoning

Introduction

Antidepressants increase the risk of suicidal thinking and behavior in children, adolescents and young adults compared to placebo. It has been shown in short-term studies of major depressive and other psychiatric disorders. Deaths may occur from overdosage with this class of drugs. Multiple drug ingestion is common in deliberate tricyclic antidepressants (TCAs) overdose. Critical manifestations of overdose include cardiac dysrhythmias, severe hypotension, convulsions and central nervous system (CNS) depression, including coma. We report the beneficial use of naloxone in a case of severe amitriptyline poisoning with coma unresponsive to pH manipulation. To our knowledge, the use of naloxone in the setting of TCA toxicity has not been reported yet. In the highlight of this case, we have discussed the mechanism of naloxone's reversal properties and the effect of amitriptyline on opiate receptors.

Case report

A 33-year-old woman (71 kg) who has taken overdose antidepressants (20 × 25 mg amitriptyline (Laroxyl[®]) and 35 × 12.5 mg tianeptine (Stablon[®])] was admitted to the emergency service, having been referred from a local hospital after gastric lavage was performed 3 hours post-ingestion. She was intubated because she had pure respiratory arrest. Besides hypotension

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(80/60 mmHg), she was unresponsive to verbal and painful stimuli and her Glasgow coma score was 6. Pupil reflexes were weakly positive bilaterally and pupils were pinpoint. Hemogram and serum biochemical parameters were within normal limits. Blood gas analysis revealed pH 7.37, HCO_3^- 22.4 mEq/L, pO_2 110.7 mmHg and pCO_2 38.8 mmHg. Electrocardiography (ECG) was within normal limits. The patient was examined for substance dependence and no trace of the injector was found in the body. Also, there was no history of substance dependence on opiates. There was no hypersalivation or hypersecretion. We have given atropine (1 mg/kg) to exclude possible organophosphate poisoning. In this case, the pulse rate rose to 136/min from a level of 98/min. Computerized tomography (CT) of the brain stem was taken to evaluate hemorrhage and infarction because patient's condition had not improved in this stage. There was no pathologic change in the CT of brain stem. Patient underwent a coma cocktail (naloxone 2 mg/kg, 5% dextrose 25 g/body and tiamin 100 g/body). Activated charcoal and intravenous alkalization by NaHCO_3 were initiated. Spontaneous respiration started again 20 min after the coma cocktail was given. She became responsive to verbal stimuli, first hour after the coma cocktail and her Glasgow coma score improved to 13. Patient's Glasgow coma score was 14 after 8 hours and pupils were midriatic, tension 110/70 mmHg and pulse 88/min. The patient's baseline pulse rate was 72/min and blood pressure was 100/65 mmHg on the second day. She had spent 2 days in the service and was discharged by the second day of admission, without any complications.

Discussion

There was no QRS prolongation in this case. It has been reported that life-threatening complications are more likely when the QRS interval is longer than 100 milliseconds in TCA poisoning. However, complications can occur in the absence of significant ECG abnormalities.¹ Patient had received 7.4 mg/kg dose of amitriptyline and 6.3 mg/kg dose of tianeptine. However, life-threatening symptoms of TCA toxicity have been shown mostly to occur in adults who have ingested greater than 10 mg/kg TCA.¹ Tianeptine causes less cardiac toxicity than classical TCAs.² It has been reported that TCA-related fatalities commonly are associated with ingestions of greater than 1 g.³ These data may explain why cardiac arrest has not occurred in this patient. Respiratory

arrest and coma may be caused by the co-ingestion of amitriptyline with tianeptine. It has been shown in some previous studies that amitriptyline can induce miosis, although amitriptyline produces mydriasis in usual.^{4,5} On the other hand, there is no evidence of tianeptine-induced myosis.

In recent years, the relationship between antidepressants and opiate systems are being investigated intensively. Selective norepinephrine reuptake inhibitors can significantly increase the intensity and duration of morphine antinociceptive activity via both $\alpha(2)$ -adrenergic and opioid receptors.⁶ The antihyperalgesic effect of repeatedly administered clomipramine is mediated by the opioidergic system in mononeuropathic rats.⁷ Some studies showed that opioid antagonists can block the acute antidepressant-induced analgesia.^{8,9} Antidepressants-induced antinociception in animals or humans was antagonized by the opioid antagonists, naloxone or naltrindole.¹⁰⁻¹² Probably, antidepressants are operating via a direct and indirect mechanism on opioid receptors and the indirect pathway involves the release of endogenous opioid peptides.⁸ Several studies indicate that amitriptyline can affect opioid receptors. Amitriptyline and other TCAs, such as nortriptyline, desipramine and imipramine, exert direct agonist activity at distinct opioid receptor subtypes. These agents show higher selectivity for the kappa-opioid receptor.¹³ Researchers demonstrated that the delta-opioid receptors are critical for the antiallodynic property of chronic nortriptyline treatment.¹⁴ Benbouzid et al. also showed that TCAs exert their therapeutic effect by recruiting the endogenous opioid system, as their effect can be acutely blocked by a single injection of a delta or kappa-opioid receptor antagonist.¹² It is obvious that amitriptyline can affect opioid system, although the predominant effect of amitriptyline on distinct opioid receptors is controversial.

Amitriptyline may affect opioid receptors and naloxone may block the effects of these agents on the opioid receptors. On the other hand, repeated administrations of tianeptine induce alterations in the levels of met-enkefalin (a member of opioid peptide family) in the anterior lobe of pituitary, adrenal glands and plasma.¹⁵ It is possible that tianeptine potentiates the effects of amitriptyline on opioid receptors.

Limitations

The plasma opioid levels were not examined. It is difficult to distinguish the effects of drugs (amitriptyline

or tianeptine) because patient co-ingested the two drugs at the same time.

Conclusion

In conclusion, high dose amitriptyline and tianeptine may affect opioid receptors and naloxone can block the effects of these agents on the opioid receptors. We suggest that, firstly, clinicians should also consider TCA poisoning in patients who have pinpoint pupils and, secondly, naloxone and other opioid antagonists may be used to treat TCA poisoning.

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