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TOXICOLOGY OBSERVATION

Intrathecal Clonidine Pump Failure Causing Acute Withdrawal Syndrome With 'Stress-Induced' Cardiomyopathy

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Abstract Clonidine is a central alpha(2)-agonist antihypertensive used widely for opioid/alcohol withdrawal, attention deficit hyperactivity disorder and chronic pain management. We describe a case of clonidine withdrawal causing life-threatening hypertensive crisis and stress-induced cardiomyopathy. A 47-year-old man with chronic back pain, treated with clonidine for many years via intrathecal pump (550 mcg/24 h), presented following a collapse and complaining of sudden worsening of back pain, severe headache, diaphoresis, nausea and vomiting. A few hours prior to presentation, his subcutaneous pump malfunctioned. On presentation, vital signs included pulse 100 bpm, BP 176/103 mmHg, temperature 37.8 °C and O_2 saturation 100 % (room air). Acute clonidine withdrawal with hypertensive crisis was suspected. Intravenous clonidine loading dose and a 50 mcg/h infusion were commenced. Five hours later, severe chest pain, dyspnoea, tachycardia, hypoxia, with BP 180/120 mmHg and pulmonary edema ensued. ECG showed sinus tachycardia with no ST elevation. Repeated intravenous clonidine doses were given (25 mcg every 5–10 min), with ongoing clonidine infusion to control blood pressure. Glyceryl trinitrate infusion, positive pressure ventilation and intravenous benzodiazepines were added. Bedside echocardiogram showed stress-induced cardiomyopathy pattern. Serum troponin-I was markedly elevated. His coronary angiography showed minor irregularities in the major vessels. Over the next 3 days in the ICU, drug infusions were weaned. Discharge was 12 days later on oral clonidine, metoprolol, perindopril, aspirin and oxycodone-SR. Two months later, his echocardiogram was normal. The intrathecal pump was removed. We report a case of stress-induced cardiomyopathy resulting from the sudden cessation of long-term intrathecal clonidine. This was managed by re-institution of clonidine and targeted organ-specific therapies.

Keywords Intrathecal · Clonidine · Withdrawal · Sympathomimetic · Cardiomyopathy

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Introduction

Sudden cessation of clonidine therapy after long-term use may result in a significant withdrawal syndrome manifested by hypertension and other sympathetic nervous symptoms and signs. Most cases of clonidine withdrawal occur after cessation of chronic oral or intravenous administration. We report a case of severe withdrawal resulting from failure of an intrathecal clonidine pump used for management of chronic pain. Pump failure led to a rapid onset of life-threatening sympathomimetic crisis with associated takotsubo-type cardiomyopathy.

Case Report

A 47-year-old man presented to the Emergency Department (ED) after an episode of collapse at home with complaints of back pain, stomach cramps, nausea and vomiting. His only relevant past medical history included back pain from a work injury 15 years prior. He had undergone lumbar spinal surgery with limited success resulting in chronic lower back pain. This was managed by a rehabilitation and pain specialist with a continuous intrathecal infusion of clonidine at 550 mcg/24 h via an implanted infusion pump in his subcutaneous anterior abdominal wall (Medtronic Implantable programmable Synchromed-EL pump). The pump had a battery life of 3–7 years.

The patient revealed that during the day, the pump had emitted a warning beep to indicate malfunction but as he had a planned review with his pain specialist the following morning, he decided to wait until then to mention the alarm. However, during the evening, he developed worsening symptoms of severe back pain, headache, nausea, vomiting and general malaise. Whilst collecting mail in his front yard, he felt unwell and collapsed. He was found a few minutes later and an ambulance was called. On arrival at the scene, the paramedic found him to be hypertensive and diaphoretic. He was treated with sublingual glyceryl trinitrate (GTN).

On arrival to the ED, he was alert and oriented but complaining of severe generalized pain. His vital signs were: temperature 37.8 °C, pulse 90 bpm, BP 176/103 mmHg, oxygen saturation 100 % on room air. His blood sugar level was 11.8 mmol/L(3.0–7.7). A 12-lead ECG showed a sinus rhythm with normal QRS and QT.

From the history of potential pump failure, it was recognized that the patient might be suffering from acute clonidine withdrawal. He was promptly given an intravenous bolus of 150 mcg of clonidine and started on an infusion at 50 mcg/h. Laboratory examination revealed haemoglobin 166 g/L (130–180 g/L), white blood cell count 18.9×10^9/L (4.0–11.0), platelets 222×10^9/L (150–450), with normal urea, electrolytes, creatinine and liver function tests.

The patient was admitted to the ED short stay unit (SSU) on an intravenous clonidine infusion with a plan for him to be reviewed by his pain specialist in the morning. Five hours post-presentation, he became acutely unwell, reporting severe crushing retrosternal chest pain and severe dyspnoea. His pulse was 150 bpm, BP 180/120 mmHg and oxygen saturation 82 % on room air. Examination of his chest revealed widespread inspiratory crackles. An ECG done at this time showed a sinus tachycardia with non-specific ECG changes (Fig. 1). Chest x-ray showed a normal heart size with acute pulmonary oedema. He was commenced on non-invasive bi-level ventilation. At this stage, the on-call clinical toxicologist was consulted who advised administration of titrated doses of intravenous clonidine (25 mcg) for blood pressure and symptom control and an increase in the clonidine infusion rate. Intravenous GTN was also commenced along with intravenous diazepam for associated anxiety.

The patient was transferred to ICU for ongoing management and cardiac and invasive blood pressure monitoring. As there was no documented dose equivalence between intrathecal and intravenous clonidine, his IV doses were titrated to blood pressure and symptoms. Intermittent intravenous doses of clonidine totaled 575 mcg in the first 24 h post-presentation with the associated ongoing infusion titrated from 0.5 to a maximum of 4 mcg/kg/h. A summary of haemodynamics and clonidine dosing is shown in Fig. 2.

His ECG showed dynamic ischaemic changes and with a troponin-I of 8.44 mcg/L (0–0.08) which peaked at 14.34. A bedside transthoracic echocardiogram performed the following morning showed reduced overall systolic function with severe hypokinesis of all segments except for vigorous contractions of the apex and mid to apical septum, consistent with a reverse-takotsubo cardiomyopathy. A subsequent angiogram 10 days post-presentation showed only minor non-critical coronary stenosis, again confirming the likely diagnosis of a stress-induced cardiomyopathy. Catecholamine concentrations and myocardial biopsy were not performed as there was an obvious precipitant for his cardiomyopathy. The patient was treated with non-invasive ventilation for a total of 14 h. Whilst in ICU, the GTN infusion was weaned in the first 24 h and the intravenous clonidine infusion was switched to oral clonidine after 2 days. He was also treated with oral metoprolol, clopidogrel, ramipril and aspirin. His clinical state stabilized on oral clonidine replacement (150 mcg five times a day) and after 4 days in ICU, he was transferred to a general medical ward for ongoing care. He was discharged home 12 days after presentation on oral clonidine 150 mcg orally five times a day and oral opiates for back pain. An outpatient transthoracic echo performed six weeks post-discharge showed normal left ventricular systolic function with complete resolution of the cardiomyopathy. The patient was maintained on oral clonidine and opiates for his back pain. The intrathecal pump was eventually surgically removed.

Discussion

Clonidine is primarily a centrally acting alpha-2 adrenoreceptor agonist used in a variety clinical conditions. This includes the treatment of hypertension, as an analgesic adjunct, in the management of opioid and alcohol withdrawal and the treatment of attention deficit hyperactivity disorder [1–5].

In hypertension, clonidine exerts an agonist effect on central nervous alpha-2 adrenoreceptors and imidazoline receptors in the nucleus tractus solitarius and the locus ceruleus.

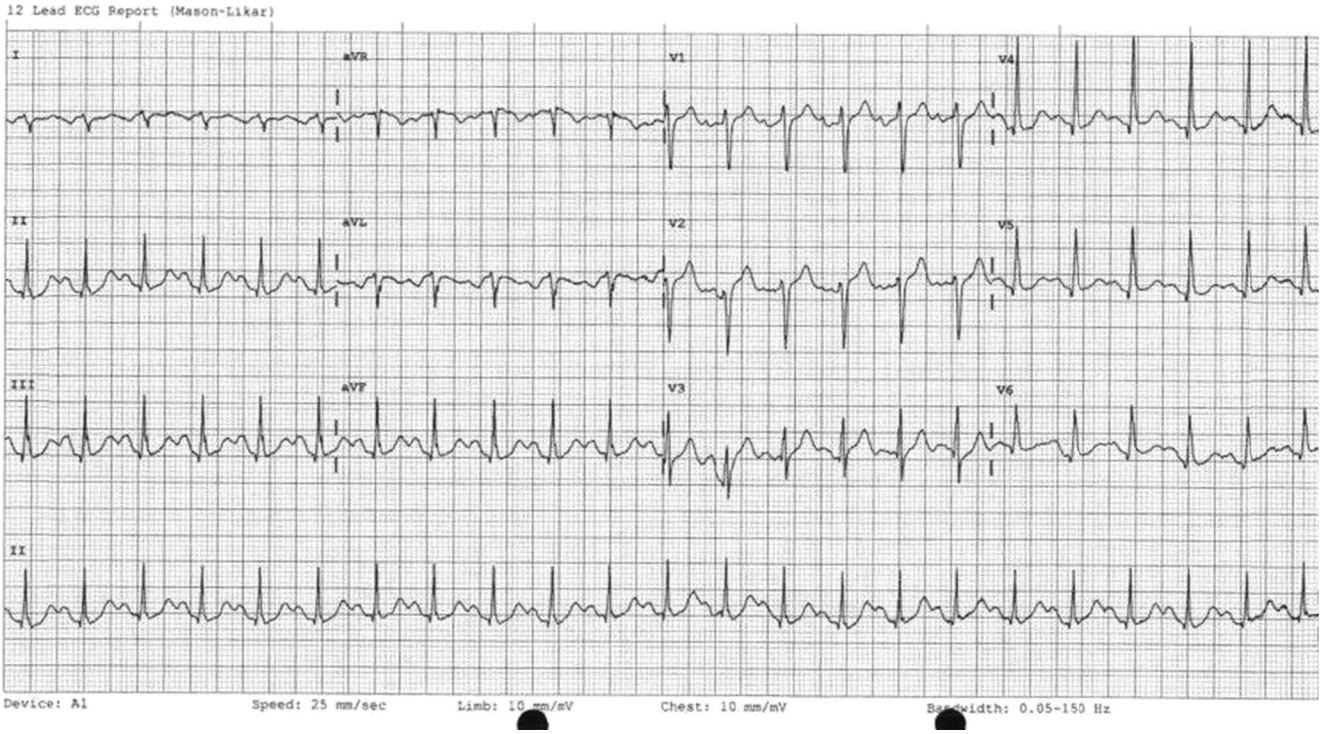

Fig. 1 ECG done 5.5 h after presentation when the patient acutely deteriorated

Central sympathetic drive is reduced thus decreasing peripheral noradrenaline release. In the peripheral nervous system, it also acts on presynaptic alpha 2 adrenoceptors at the sympathetic terminal to decrease the release of noradrenaline. It also activates imidazoline receptors in the lateral reticular nucleus which contributes to its hypotensive activity. The usual maintenance dose used in the treatment of hypertension is 200–600 mcg/day [1–3].

In opioid and alcohol withdrawal states, symptoms such as anxiety, irritability, sweating, hypertension and insomnia are mediated by excess noradrenaline release in the locus ceruleus. The agonist effect of clonidine on alpha-2 adrenoreceptors in this area inhibits central noradrenaline release and alleviates these symptoms [4].

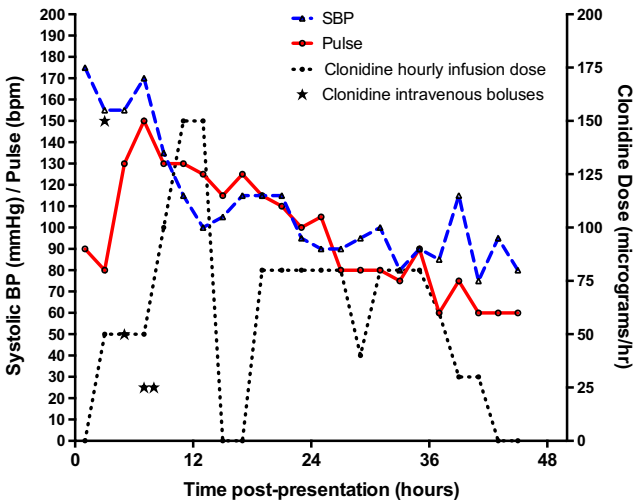

Fig. 2 Graph of hemodynamics and clonidine dosing over time

The analgesic effect of clonidine is due to its agonist effects on alpha 2 adrenoreceptors in the spinal cord [3]. Intrathecal administration of clonidine may be useful in the management chronic pain, particularly if neuropathic pain plays a part in the pain syndrome [6]. Eisenbach et al (1996) reported 10 cases of intrathecal clonidine administration for chronic pain, of which nine were in-patients with cancer. Intrathecal doses in these cases included individual doses of 30–150 mcg with continuous infusions of 8–400 mcg/day, usually in combination with morphine. The duration of treatment was from 1 day to 3 months [3].

Reports of Clonidine Withdrawal

Withdrawal developing after cessation of oral dosing of clonidine is well documented. Symptom onset is usually between 12 and 24 h and up to 72 h after the last dose. Restlessness, insomnia, irritability, abdominal pain, nausea, headache, tachycardia and hypertension are commonly observed [2, 7–9]. More severe and life-threatening symptoms have also been reported, including ventricular tachycardia [7, 10, 11], acute myocardial infarction [9, 12] and vertebral artery dissection [13]. The clonidine withdrawal syndrome is due to an increase in central nervous catecholamine release, resulting in hypertension, tachycardia, anxiety, agitation and sweating which may mimic the hypertensive crisis seen with phaeochromocytoma. Urinary and plasma catecholamine

levels may increase two- to nine-fold within 24 h of ceasing the drug [9, 10, 14].

There is one previous report of clonidine withdrawal syndrome following cessation of intrathecal infusion [15]. The patient was a 49-year-old male with an intrathecal pump, infusing clonidine (30 mcg/h), morphine (150 mcg/h) and bupivacaine for cancer pain. The catheter was removed with a view to revision and replacement with a more permanent catheter. Two hours after cessation of the epidural clonidine, the patient developed anxiety, agitation, hypertension, sinus tachycardia and a new left bundle branch block (LBBB) on 12-lead ECG. Symptoms improved over the next 12 h with oral and transdermal clonidine replacement and intravenous midazolam. The LBBB on ECG resolved and there was no rise in cardiac markers. This patient did not develop pulmonary oedema or myocardial injury.

Our patient developed severe hypertension and left ventricular failure with acute pulmonary oedema. Clonidine replacement therapy is the primary goal in controlling the hypertensive crisis. We initially administered intravenous clonidine and subsequently changed this to oral when his clinical condition stabilized. In the acute hypertensive phase, we also treated our patient with intravenous GTN infusion for vasodilation and benzodiazepines to reduce anxiety and agitation. Hypertension may also be treated with direct acting vasodilators such as sodium nitroprusside or alpha-receptor antagonists such as phentolamine [9, 16].

Of note, in our patient, the acute left ventricular (LV) dysfunction resulting in pulmonary oedema responded well to non-invasive positive pressure ventilation. This was reversible on a follow-up echocardiography suggesting that it may have been a catecholamine-mediated cardiomyopathy. In particular, our patient met criteria indicative of takotsubo–type cardiomyopathy [17, 18]. He had an acute stress with catecholamine surge, his ECG showed non-specific ST-segment changes, there was a slight elevation in cardiac markers, there were no significant coronary lesions, echocardiogram had a characteristic appearance of the reverse takotsubo pattern, with hypokinesis of all segments except for vigorous contractions of the apex and mid- to apical septum consistent with a 'reverse takotsubo cardiomyopathy' [19] and he had a complete recovery of his cardiac function.

'Takotsubo' or 'stress-induced' cardiomyopathy is postulated to be the result of high serum catecholamine concentration resulting from stress. Serum catecholamine concentration may be up to two to three times higher in patients with takotsubo cardiomyopathy compared to patients with myocardial infarction [17, 20]. We postulate that as our patient was withdrawing from clonidine, he most likely had high serum catecholamine concentrations which precipitated the takotsubo cardiomyopathy variant. Management of takotsubo cardiomyopathy is primarily supportive with the aim to also rule out significant coronary stenosis and ischaemia as a cause of heart failure [17].

Conclusion

To our knowledge, this is the first case report of 'stress-induced' cardiomyopathy associated with clonidine withdrawal and hypertensive crisis in a patient with intrathecal clonidine pump failure. The symptoms and signs of clonidine withdrawal are most likely due to a catecholamine storm similar to that seen with phaeochromocytoma.

In cases of intrathecal dosing, the onset of withdrawal may be faster and potentially more severe than that seen with withdrawal of oral clonidine therapy. The principles of management include supportive care and replacement of clonidine in adequate doses titrated to clinical effect.

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