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Vasopressor-Refractory Shock From Clozapine Overdose Treated With Synthetic Angiotensin II Infusion

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Background: Clozapine is an atypical antipsychotic with potent alpha-adrenergic blocking properties when administered at high dosages, resulting in vasodilatory shock in overdose settings.

Case Summary: A 39-year-old man presented with profound catecholamine- and vasopressin-refractory vasodilatory shock following massive clozapine ingestion. Angiotensin II was initiated when the patient was requiring 2.2 µg/kg/min norepinephrine equivalents of vasopressor support, resulting in a prompt increase in the perfusion pressure. All vasopressors were liberated within 18 hours of angiotensin II initiation, and the patient was discharged with no deficits.

Conclusions: Synthetic angiotensin II may represent a therapeutic option for refractory hypotension resulting from high dosages of clozapine or other potent alpha-adrenergic blocking medications.

Key Words: angiotensin; hypotension; overdose; resuscitation; vasodilatory shock; vasopressor

Clozapine is an antipsychotic that possesses potent alpha-adrenergic antagonistic properties, particularly when used in high dosages. Previous cases have successfully used vasopressin in clozapine overdose settings, as vasodilatory shock from clozapine is usually refractory to catecholamine vasopressors due to significant clozapine-associated alpha-adrenergic receptor antagonism in the peripheral vasculature (1, 2). We report a case of massive clozapine ingestion resulting in vasodilatory shock refractory to high dosages of catecholamines and vasopressin, successfully treated with synthetic angiotensin II infusion.

CASE DESCRIPTION

A 39-year-old man (139 kg and 183 cm) with schizoaffective disorder on chronic clozapine presented with altered mental status and generalized weakness after being found unresponsive. Other past medical history included hypothyroidism controlled with levothyroxine and hyperlipidemia controlled with atorvastatin and fenofibrate. The caregiver reported no recent illnesses. On presentation, he was afebrile, had a blood pressure of 82/40 mm Hg, was briefly arousable and directable, but had rapid return to somnolence and stertorous breathing; the physical examination was otherwise unremarkable. He required immediate endotracheal intubation for progressively declining respiratory effort, altered mental status, and profound hypotension. Initial blood gases revealed near-normal acid-base status, lactate 2.8 mmol/L, and a central venous oxygen saturation of 71%. Bedside transthoracic echocardiogram showed hyperdynamic ventricles with grossly preserved ejecting function and no pericardial effusion.

Following appropriate crystalloid resuscitation, vasopressors were promptly initiated and required rapid uptitration in an attempt to achieve adequate perfusing pressure. In the setting of persistent hypotension despite continued escalation of vasopressors, he became progressively more acidotic, lactate concentration increased to 8 mmol/L, and he became oliguric. Aspartate and alanine aminotransferases as well as bilirubin were normal. Despite norepinephrine 1 µg/kg/min, epinephrine 1 µg/kg/min, vasopressin 0.08 U/min (total vasopressor dosage; 2.2 µg/kg/min norepinephrine equivalents [3]), and stress-dose corticosteroids, the mean arterial pressure (MAP) remained 50–55 mm Hg (**Fig. 1**). Approximately 8 hours from the onset of shock, angiotensin II was initiated at a rate of 20 ng/kg/min and the MAP promptly rose to 66 mm Hg within minutes. Subsequently, other vasopressors

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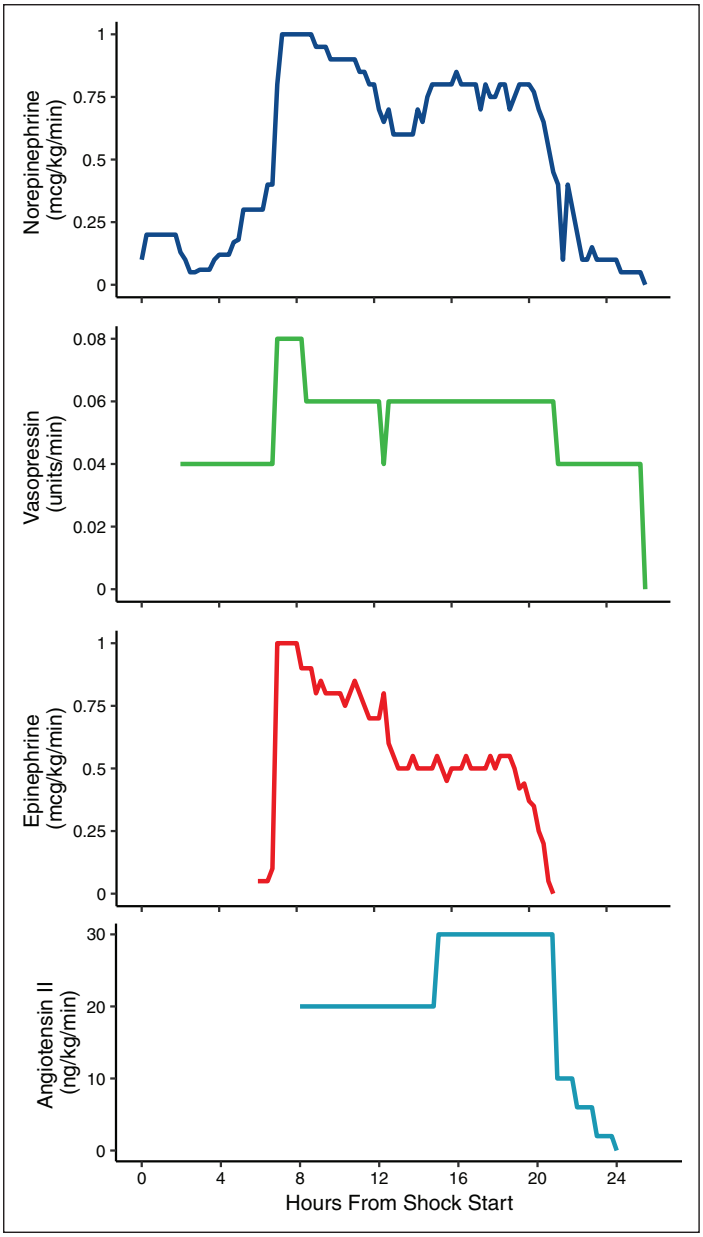

Figure 1. Vasopressor requirements.

were downtitrated to maintain a goal MAP greater than 65 mm Hg. Although an adequate MAP was maintained and vasopressors were being liberated, persistent oliguria, over tripling of serum creatinine to 3.6 mg/dL (baseline 1.1 mg/dL), and acidosis led to the decision to initiate renal replacement therapy with consultation of the Critical Care Nephrology service, approximately 6 hours following angiotensin II initiation. Approximately 8 hours following angiotensin II initiation, after norepinephrine and epinephrine were downtitrated to 0.8 and 0.55 μg/kg/min, respectively, the MAP began to decline, prompting increase in angiotensin II to 30 ng/kg/min, restoring stability in the MAP. Vasopressor requirements then continued to decline over the following 8 hours to norepinephrine 0.1 μg/kg/min and vasopressin 0.04 U/min, at which point angiotensin II was discontinued. Norepinephrine and vasopressin were stopped 2 hours later with self-maintenance of the MAP greater than 65 mm Hg, without the need to resume any vasopressor support. No adverse effects were noted.

Clozapine concentration collected at presentation returned at 3,912 ng/mL (normal 350–600 ng/mL). Toxicology panels all returned negative and no other etiologies of shock were identified. On hospital day 3, he remained hemodynamically stable off vasopressors, was separated from continuous renal replacement therapy, and was producing urine. On hospital day 5, the endotracheal tube was removed and the patient confirmed intentional ingestion of approximately 11 g clozapine. He was subsequently transferred to inpatient psychiatric care with recovered renal function.

DISCUSSION

Vasodilatory shock is the most common phenotype of presenting circulatory shock states in critically ill patients (4). The immediate objective during resuscitative efforts is to restore the perfusion pressure to maintain oxygenation of vital tissues and organs, by administration of intravascular fluids and vasopressors. Vasodilatory shock that is refractory to vasopressors is highly morbid, and in cases where norepinephrine dosing requirements reach 1 μg/kg/min, mortality is as high as 90% (5). Historically available vasopressors include catecholamines, which produce vasoconstriction by direct stimulation of alpha-adrenergic receptors in the vasculature and arginine vasopressin that produces vasoconstriction by stimulation of V_1 receptors in the vasculature.

Clozapine is a second-generation antipsychotic used for treatment of resistant schizophrenia. It has alpha-adrenergic antagonist activity, the degree of which is such that a boxed warning describes potentially life-threatening events, even after the first dose, as low as 12.5 mg. The steady-state half-life of clozapine is 12 hour, although in massive ingestion scenarios, saturation of metabolism can prolong the half-life beyond 20 hours (6). This may be an explanation for prolonged hypotension and acidosis in our patient. Additionally, with supratherapeutic concentrations, the effects of catecholamine vasopressors may be blunted due to clozapine's strong alpha-adrenergic antagonism and we hypothesize there may also be paradoxical hypotension with administration of epinephrine due to more complex and not well-studied factors (7). Although there are no data to support this with clozapine, this phenomenon has been observed in overdose situations of other antipsychotics that poses alpha-antagonistic properties (8). For these reasons, vasopressin has been used successfully to increase blood pressure in the setting of clozapine overdose as its vasoconstrictive effects are through direct stimulation of V_1 receptors (1, 2). In our case, despite very high-dose catecholamines, addition of vasopressin did not reverse shock, even at a higher 0.08 U/min dosage, leading to the need for an alternative mechanism for vasoconstriction.

Angiotensin II (Giapreza; La Jolla Pharmaceuticals, San Diego, CA) is a recently approved synthetic analogue of the endogenous human peptide that is naturally produced by cleavage of angiotensin I by the angiotensin-converting enzyme (3). Angiotensin II directly stimulates G-protein-coupled angiotensin type-1 receptors in the peripheral vasculature, resulting in myosin phosphorylation, and thereby contraction of vascular smooth muscle cells. The net result is an increase in systemic blood pressure, irrespective of adrenergic or vasopressin receptor activity. Angiotensin

II has been shown in phase 3 and a postapproval real-world use evaluation to restore rapidly systemic blood pressure and reduce vasopressor needs in patients with vasopressor-refractory vasodilatory shock (3, 9).

CONCLUSIONS

Pharmacologically, angiotensin II is an attractive agent for use in clozapine overdose due to its potent vasoconstricting effects, independent of adrenergic or vasopressinergic stimulation. Indeed, in our case, low-dose angiotensin II increased MAP promptly in vasodilatory shock that was refractory to high-dose catecholamines and high-dose vasopressin.

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The patient and/or their decision maker signed Minnesota Research Authorization consenting for purposes of research publication.

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