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Selected Topics: Toxicology

SUCCESSFUL TREATMENT OF ANTIHYPERTENSIVE OVERDOSE USING INTRAVENOUS ANGIOTENSIN II

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☐ **Abstract—Background: Despite multiple treatment options, antihypertensive overdose remains a cause of significant morbidity and mortality. Intravenous angiotensin II (AG II) is approved for use in vasodilatory shock. We describe 2 cases of refractory shock from antihypertensive overdose that were successfully treated using AG II. Case Reports: A 24-year-old female presented after an overdose of multiple antihypertensive medications, including an angiotensin converting enzyme inhibitor (ACEI). She developed hypotension that was refractory to norepinephrine, epinephrine, and vasopressin, with a mean arterial pressure (MAP) of 57 mm Hg 9 h after emergency department arrival. Fifteen minutes after starting AG II at 10 ng/kg/min, her heart rate and MAP rose by 7 beats/min and 12 mm Hg, respectively. Her hemodynamic parameters continued to improve thereafter. She developed acute kidney injury, which resolved prior to discharge. The second patient, a 65-year-old male, presented after an overdose of multiple antihypertensive medications, including an ACEI. Despite norepinephrine, epinephrine, and hyperinsulinemia-euglycemia, he remained bradycardic and hypotensive, with a heart rate of 47 beats/min and MAP of 59 mm Hg. Thirty minutes after starting AG II at 10 ng/kg/min, his heart rate was 61 beats/min and MAP was 66 mm Hg. He recovered without apparent sequelae. Why Should an Emergency Physician Be Aware of This?: Antihypertensive overdose can lead to shock refractory to catecholamine and vasopressin therapy. Our experience suggests that AG II is efficacious in antihypertensive overdose and may be particularly efficacious in instances of ACEI overdose. However, further study is required to confirm the appropriate indication(s).**

☐ **Keywords—drug overdose; angiotensin II; antihypertensive agents; toxicology**

INTRODUCTION

Overdose of antihypertensive agents is a leading cause of calls to poison centers, with more than 100,000 exposures and 201 deaths reported in 2016 (1). In overdose, antihypertensives can be both vasodilatory and cardiotoxic (2). In addition to conventional therapy with i.v. fluids and vasopressors, hyperinsulinemia-euglycemia (HIE) is recommended in overdoses of calcium channel blockers and β-blockers (3). Nonetheless, HIE is labor-intensive, requiring a concurrent dextrose infusion as well as frequent blood glucose and chemistry checks, and may not be implemented when recommended by a poison center (4–6). There is a need for additional treatment modalities, especially when current therapy proves to be ineffective.

Intravenous AG II has been used successfully to treat shock due to ACEI (7–9) and combined ACEI/calcium channel blocker overdose (10). These cases were treated

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using a bovine formulation of AG II, which had poor long-term stability and was voluntarily withdrawn from the market in 2009 "for reasons unrelated to safety" (11,12). A human formulation of AG II, which differs from the bovine formulation by one of eight amino acids, was U.S. Food and Drug Administration–approved for use in 2017 for vasodilatory shock, regardless of cause, based upon the ATHOS-3 (Phase 3 Angiotensin II for the Treatment of High-Output Shock) clinical trial that predominantly enrolled patients with septic shock (13). Here, we present 2 cases of refractory shock after multiple-agent antihypertensive overdose that were successfully treated using AG II. To our knowledge, this is the first report using the current formulation of AG II to treat antihypertensive overdose. Consent for publication was obtained from patients or their immediate family.

CASE REPORTS

Case 1

A 24-year-old female with a medical history of dilated cardiomyopathy (baseline ejection fraction [EF] of 25%) and hypertension was found down at her home approximately 2 h after intentionally ingesting her prescribed medications in a suicide attempt. Her home medications included amlodipine, carvedilol, lisinopril, spironolactone, hydralazine, isosorbide mononitrate, furosemide, and aspirin. Medications were scattered around her room, and a definitive pill count was not possible. She stated to emergency medical services (EMS) that she had taken "all the meds I could." Her initial vital signs were blood pressure (BP) 76/43 mm Hg, heart rate (HR) 60 beats/min, respiratory rate (RR) 26 breaths/min, and pulse oximetry (SpO_2) 85% on room air. EMS administered 500 mL normal saline en route to the hospital.

Vital signs in the ED were temperature 35.0°C, via indwelling urinary catheter, BP 86/50 mm Hg, HR 62 beats/min, RR 12 breaths/min, and SpO_2 96% on oxygen via nonrebreather mask. She was lethargic, thought to be due to global hypoperfusion. An electrocardiogram (ECG) showed normal sinus rhythm with a QRS interval of 94 ms, QTc interval of 447 ms, and prominent U waves. She was intubated for airway protection. Fifty grams of activated charcoal and 1 L normal saline were administered; her BP rose to 99/47 mm Hg. Laboratory studies demonstrated a serum potassium of 2.5 mmol/L (reference range 3.5–5.1 mmol/L) and creatinine 1.3 mg/dL (reference range 0.5–0.9 mg/dL). The remainder of her chemistry, hepatic function panel, complete blood count, and thyroid studies were within normal limits. Serum acetaminophen, salicylates, and ethanol concentrations were undetectable. A routine urine drug screen was negative for amphetamines, barbiturates, cocaine, opiates, methadone, oxycodone, phencyclidine, tetrahydrocannabinol, and benzodiazepines.

Approximately 3 h after arrival to the ED, her BP fell to 64/50 mm Hg with a heart rate of 68 beats/min. There was no improvement with an additional 1 L normal saline (total of 2.5 L). Norepinephrine (up to 30 μg/min), vasopressin (0.04 U/min), and epinephrine (up to 10 μg/min) were sequentially initiated and titrated over the subsequent 6 h, however, she remained hypotensive (Figure 1). Five

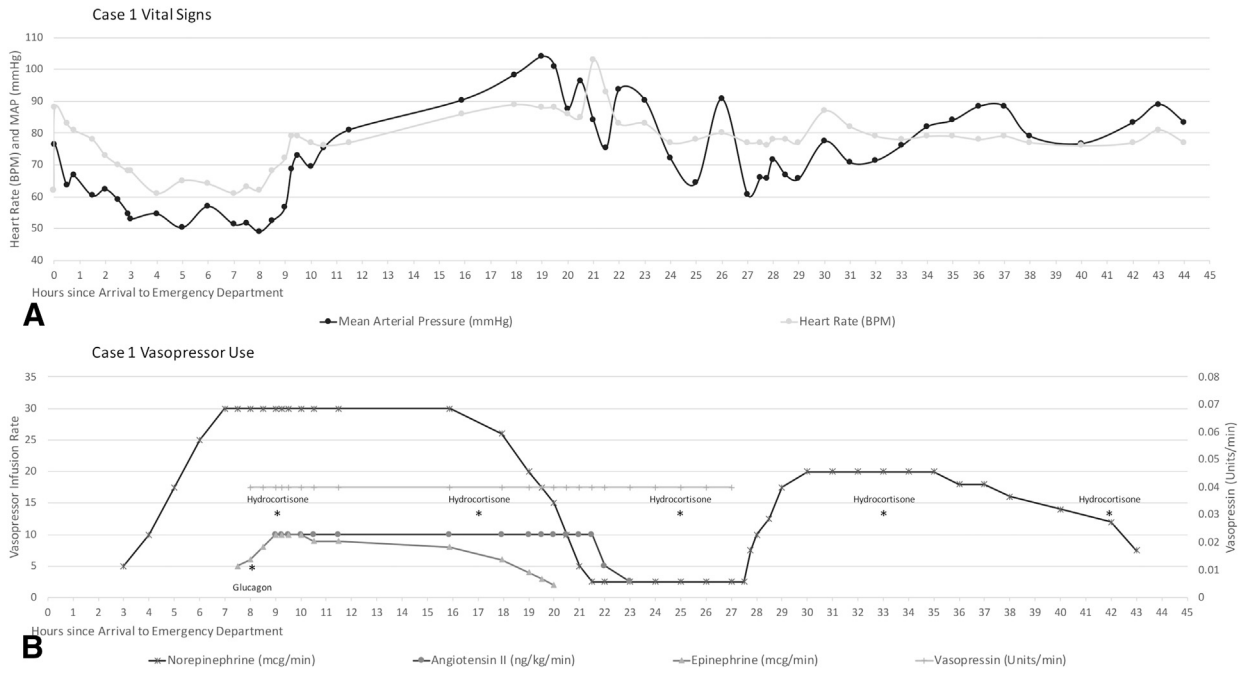

Figure 1. (A) Vital signs and (B) vasopressor infusions for case 1.

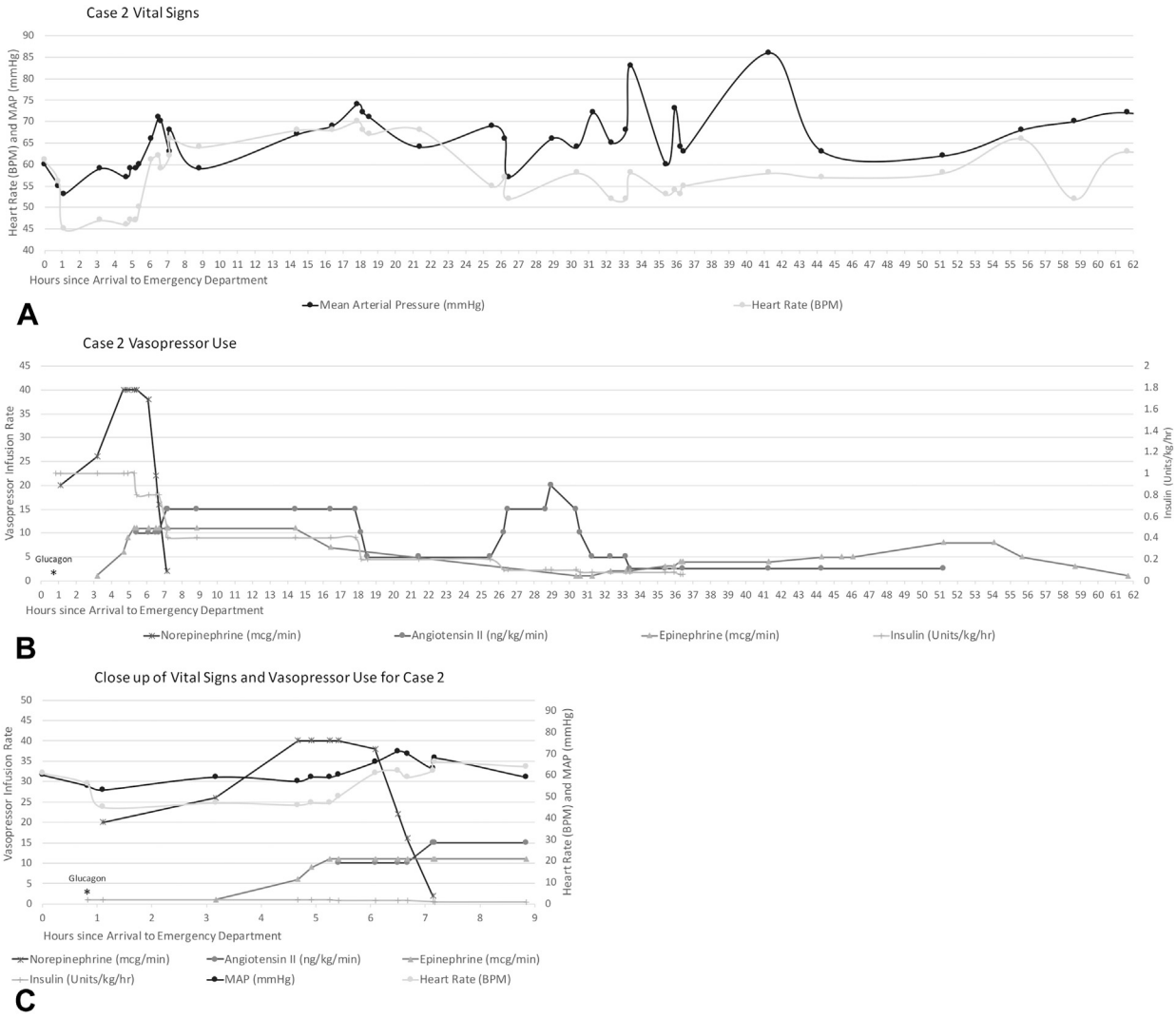

Figure 2. (A) Vital signs and (B) vasopressor infusions for case 2. (C) Close-up of the first 9 h after emergency department arrival.

milligrams i.v. glucagon was administered without any improvement. Approximately 9 h post ingestion she was started on hydrocortisone sodium succinate (100 mg every 8 h) and AG II (10 ng/kg/min).

Within 15 min of initiating AG II, her MAP rose by 12 mm Hg. One hour after starting AG II her BP was 108/50 mm Hg. A transthoracic echocardiogram demonstrated an EF of 40%, increased from her baseline of 25%. Over the next 24 h she was weaned from epinephrine, AG II, vasopressin, and norepinephrine, in that order. She developed significant hypertension and was placed on a nicardipine infusion, while all seven of her antihypertensive medications were cautiously restarted. She suffered acute kidney injury, with a peak creatinine of 1.76 mg/dL on hospital day 2, returning to 0.74 mg/dL on day 5, and was discharged to a psychiatric facility.

Case 2

A 65-year-old male with a medical history of hypertension, congestive heart failure, benign prostatic hyperplasia, and major depressive disorder was brought to the ED after an intentional overdose of his antihypertensive medications in a suicide attempt. He reported taking sixty 12.5-mg carvedilol tablets, thirty 10-mg amlodipine tablets, and an unknown number of lisinopril/hydrochlorothiazide 20/25 mg combination tablets approximately 18 h earlier. Upon examination he was awake and alert, with a BP of 74/42 mm Hg and HR of 49 beats/min. An ECG showed sinus bradycardia with a first-degree atrioventricular block, QRS interval of 168 ms and QTc interval of 447 ms. A baseline ECG was not available for comparison. His initial chemistry was within normal limits except for a serum creatinine of 2.8 mg/dL with

an unknown baseline. Serum acetaminophen, salicylates, and ethanol concentrations were undetectable.

Two liters of normal saline and 2 mg i.v. glucagon were administered without a significant change in his vital signs. He was started on norepinephrine (up to 40 μg/min), HIE (i.v. bolus of 1 U/kg followed by infusion at 1 U/kg/h), and epinephrine (11 μg/min) (Figure 2). Five hours after arrival he remained bradycardic and hypotensive, with a heart rate of 47 beats/min and MAP of 59 mm Hg; AG II therapy was initiated at 10 ng/kg/min.

Thirty minutes after starting AG II, his HR improved to 61 beats/min and MAP rose to 66 mm Hg. Over the next hour, norepinephrine was titrated off. A transthoracic echocardiogram demonstrated an EF of 45–50% with grade I diastolic dysfunction, and abnormal septal motion consistent with a bundle branch block; there was no prior study available for comparison. Finally, on hospital day 3, HIE, AG II, and epinephrine were discontinued, in that order. He was discharged to a psychiatric facility without apparent complications.

DISCUSSION

AG II is an octapeptide with a half-life of seconds to minutes in vivo (14). Its most well-described downstream effect is increased aldosterone secretion; however, AG II raises blood pressure by multiple additional mechanisms, including antidiuretic hormone secretion, vasoconstriction via a G-protein coupled receptor, and enhanced catecholamine release (14). It may also have positive inotropic and chronotropic effects (13). AG II is generally well tolerated, with a low frequency of adverse events; in the ATHOS-3 trial, the overall incidence of adverse events and serious adverse events was statistically similar between the AG II and placebo arms (15). The medication has been used historically in a number of scenarios, including in the treatment of pulmonary, hepatic, renal, and cardiovascular diseases, as well as metabolic and endocrine disorders, and has been shown to restore blood pressure in patients with catecholamine-refractory hypotension (15,16). Importantly, AG II has been shown to be effective in reversing shock associated with ACEI overdose (7–9). From a mechanistic viewpoint, AG II is a rational choice when treating ACEI overdose, as it acts downstream from ACE to directly replace a deficiency of endogenous AG II (17,18). As our experience demonstrates, AG II may be efficacious in overdose of other types of antihypertensive agents.

Patients treated therapeutically with ACE inhibition experience a reduction in blood pressure from both a

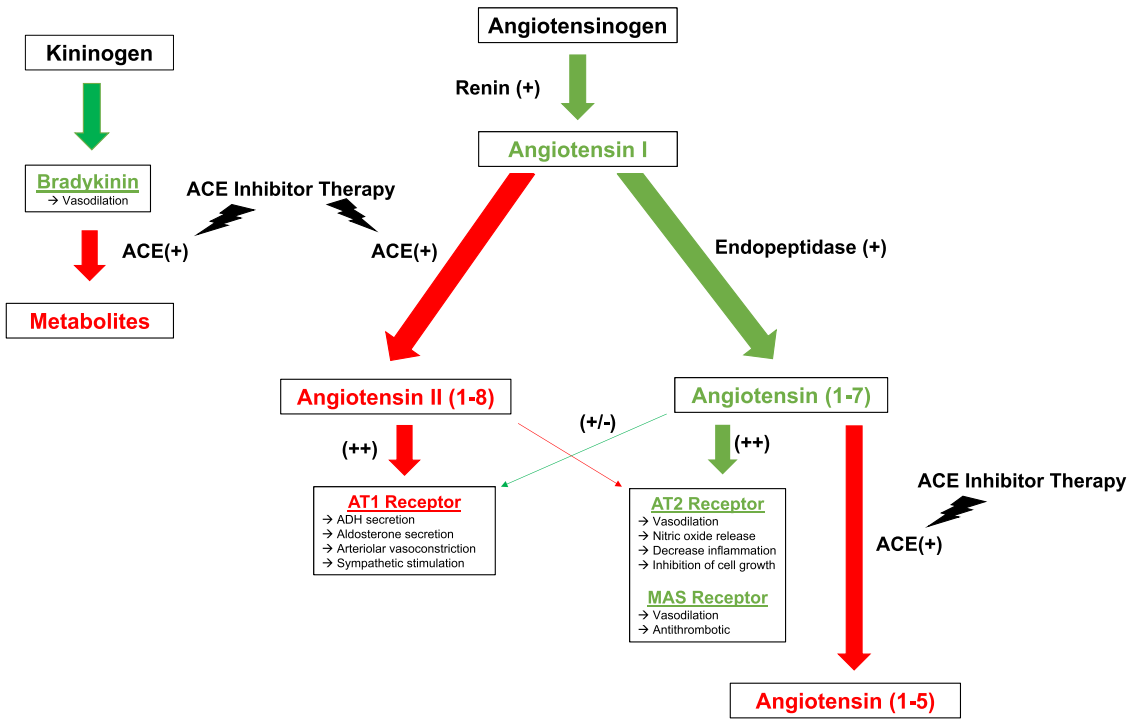

Figure 3. Proposed mechanism of angiotensin metabolism in the setting of angiotensin converting enzyme (ACE) inhibition. Angiotensin I is converted to angiotensin II by ACE. Because of ACE inhibition, angiotensin I is preferentially converted to angiotensin 1–7 (AT 1–7). The conversion of AT 1–7 to angiotensin 1–5 by ACE is also inhibited by ACE inhibition. Vasodilatory effects of AT 1–7 are increased due to the increased production and decreased catabolism of AT 1–7. Likewise, bradykinin catabolism is mediated by ACE and decreased by ACE inhibition. Bradykinin has vasodilatory properties. The combined effect of decreased AT II, increased AT 1–7 and increased bradykinin contribute to decreased arteriolar tone. ACE, angiotensin-converting enzyme; AT, angiotensin; ATR, angiotensin II receptor. Reproduced from Chawla et al., with permission (19).

decrease in AG II and an excess of the vasodilatory mediators normally metabolized by ACE (Figure 3) (19). ACE inhibition dysregulates the renin–angiotensin–aldosterone system, preventing cleavage of angiotensin I (AG I) to AG II and resulting in an excess of AG I (20). There is additionally an increase in bradykinin and angiotensin 1–7, which are vasodilatory (21,22). The relative levels of the precursors and products of ACE (AG I and AG II, respectively), as well as the ratio of AG I/II, are reflective of ACE functionality (23).

In the ATHOS-3 study, the AG I/AG II ratio was predictive of both blood pressure response and mortality (24). Accordingly, it has been suggested that patients with a high AG I/AG II ratio, reflecting ACE dysfunction, would benefit from AG II administration (25). Deficiency of AG II in the setting of ACE dysfunction is well described, and may underlie the principle mechanisms by which AG II is effective in sepsis (25,26). Similar mechanisms are likely to be present in ACEI overdose and might be contributory when patients on ACEI therapy overdose on other antihypertensive agents. Nonetheless, the exact mechanisms by which AG II may be useful in reversing the effects of other classes of antihypertensive medications has yet to be fully elucidated.

Our report has a number of limitations, most importantly the lack of drug levels to confirm the agent(s) ingested. Both patients described herein were prescribed multiple antihypertensive agents. It is unclear which of these were ingested and at what dose. We also suspect that our second patient's time of ingestion was much closer to his ED arrival than reported. Nonetheless, both described a massive multi-agent overdose of their antihypertensive medications, with observed development of profound hypotension, which was refractory to i.v. fluids, glucagon, catecholamines, and vasopressin (as well as hydrocortisone in case 1 and HIE in case 2). Further supporting an overdose was a lack of compensatory tachycardia. Neither patient had an objective evaluation of cardiac function (i.e., echocardiogram or pulmonary artery catheter) at the time when catecholamines and AG II were initiated, making it difficult to conclude whether shock was vasodilatory, cardiogenic, or mixed. In addition, the patient described in case 1 received hydrocortisone, which has been shown to hasten resolution of septic shock (27). Although this could confound results, we note that the resolution of shock noted in the CORTICUS (Corticosteroid Therapy of Septic Shock) trial was measured on the scale of days, not hours, as we observed. Finally, as with all case reports, a comparator patient population was not present. Therefore, we cannot be certain that our patients would not have improved with standard therapy instead of the addition of AG II.

In future reports, it would be helpful to obtain drug levels and serial objective measurements of cardiac function throughout the resuscitation. These data will allow clinicians to confirm the scenarios in which AG II may be effective, as well as its specific effect(s) on hemodynamics in the setting of antihypertensive overdose.

WHY SHOULD AN EMERGENCY PHYSICIAN BE AWARE OF THIS?

To our knowledge, this is the first documented use of AG II for an antihypertensive overdose since its current form was approved for use. The patients presented here demonstrated hemodynamic responses similar to cases described prior to the withdrawal of bovine-derived AG II (7–9). Our patients had a rapid, profound, and sustained response to the medication, despite initial failure of multiple vasoactive and inotropic agents. Emergency physicians should be aware of multiple agents with which to stabilize patients in shock, particularly those patients that do not respond to first-line agents and conventional therapy, such as i.v. fluids and vasopressors. This case report highlights an additional agent to add to the armamentarium. Our experience suggests that AG II may have a role in the treatment of refractory shock due to overdose of multiple antihypertensive medications, including ACE inhibitors. Additional studies are required before fully elucidating both association of effect and causality.

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