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Case Report

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Metoprolol treatment of dual cocaine and bupropion cardiovascular and central nervous system toxicity

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Cardiovascular and central nervous system (CNS) toxicity, including tachydysrhythmia, agitation, and seizures, may arise from cocaine or bupropion use. We report acute toxicity from the concomitant use of cocaine and bupropion in a 25-year-old female. She arrived agitated and uncooperative, with a history of possible antecedent cocaine use. Her electrocardiogram demonstrated tachycardia at 130 beats/min, with a corrected QT interval of 579 ms. Two doses of 5 mg intravenous metoprolol were administered, which resolved the agitation, tachydysrhythmia, and corrected QT interval prolongation. Her comprehensive toxicology screen returned positive for both cocaine and bupropion. We believe clinicians should be aware of the potential for synergistic cardiovascular and CNS toxicity from concomitant cocaine and bupropion use. Metoprolol may represent an effective initial treatment. Unlike benzodiazepines, metoprolol directly counters the pharmacologic effects of stimulants without respiratory depression, sedation, or paradoxical agitation. A lipophilic beta-blocker, metoprolol has good penetration of the CNS and can counter stimulant-induced agitation.

Keywords Cocaine; Bupropion; Toxicity; Beta-blocker; Metoprolol

Capsule Summary

What is already known

Beta-blockers have been used to effectively treat cocaine-associated tachycardia and hypertension, but less is known regarding its use in the treatment of concomitant bupropion toxicity. Lipophilic beta-blockers have been shown to have a role in the treatment of agitation. The unopposed alpha stimulation phenomenon for beta-blocker use in the setting of cocaine toxicity is unpredictable, inconsistent, and based on a small number of cases.

What is new in the current study

A lipophilic beta-blocker, metoprolol, was used to definitively treat agitation and tachycardia in a cocaine-toxic patient. It was later discovered she had ingested a large amount of bupropion. Metoprolol reversed her agitation, tachycardia, and prolonged QT interval. In this study we investigate the use of beta-blockers for combined cocaine and bupropion cardiovascular and central nervous system toxicity.

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INTRODUCTION

Cardiovascular and central nervous system (CNS) toxicity from cocaine is unpredictable and may manifest as tachydysrhythmias, hypertension, acute myocardial infarction, agitation, and seizures.[1,2] Bupropion is a frequently-prescribed antidepressant and is a norepinephrine-dopamine reuptake inhibitor and nicotinic antagonist.[3] The chemical structure and toxicity of bupropion are similar to cocaine and amphetamines, and it has been associated with an increased risk of delayed-onset seizures.[3] Concomitant cocaine and bupropion toxicity may result in additive and synergistic effects.[4] Benzodiazepines have been recommended as initial treatment to counter cocaine- and bupropion-induced CNS-mediated hyperadrenergic symptoms.[1,2] However, benzodiazepines may be unreliable for this indication.[1] Multiple, escalating doses of benzodiazepines may be required, which increases risk of sedation with respiratory depression. Beta-blockers have been successfully used to counter cocaine toxicity.[1] In this case report, we describe concomitant cocaine and bupropion cardiovascular and CNS toxicity, and initial treatment with metoprolol.

CASE REPORT

A 25-year-old female was brought to the emergency department (ED) by ambulance for agitated behavior in a hotel room. The accompanying paramedics stated an acquaintance of the patient on scene mentioned antecedent cocaine use, but that the patient was unable to provide any further history en route to the ED. Prehospital vital signs were recorded as systolic blood pressure 126 mmHg, pulse rate 140 beats/min, respiratory rate 20 breaths/min, and her blood glucose was 124 mg/dL. She was immediately triaged to a treatment room and connected to continuous cardiovascular and pulse oximetry monitoring. Initial vital signs were: blood pressure 137/78 mmHg, pulse rate 140 beats/min, respiratory rate 18 breaths/min, temperature 36.7°C, and pulse oximetry (SpO_2) 94% on room air. An electrocardiogram was performed at this time (Fig. 1) and demonstrated sinus tachycardia (130 beats/min) and prolonged corrected QT (QTc) interval (579 ms). The timeline for vital signs, medication, and events for her ED stay is detailed in Table 1.

Physical examination revealed a thin young female who was agitated, diaphoretic, uncooperative, and mumbling nonsensical words. Mydriasis was noted on examination of her pupils. Her cardiovascular examination revealed sinus tachycardia with no murmur, gallop, or rub on auscultation. Jugular venous distention was not present, and there was no edema noted in her extremities. Her pulmonary examination was clear to auscultation. The remainder of her directed physical examination was limited due to her agitated state and inability to follow direction. Suspecting cocaine-associated cardiovascular and CNS toxicity, the initial ED treatment team administered 5 mg of metoprolol intravenously (IV) 30 minutes after arrival. Metoprolol, a lipophilic beta 1-spe-

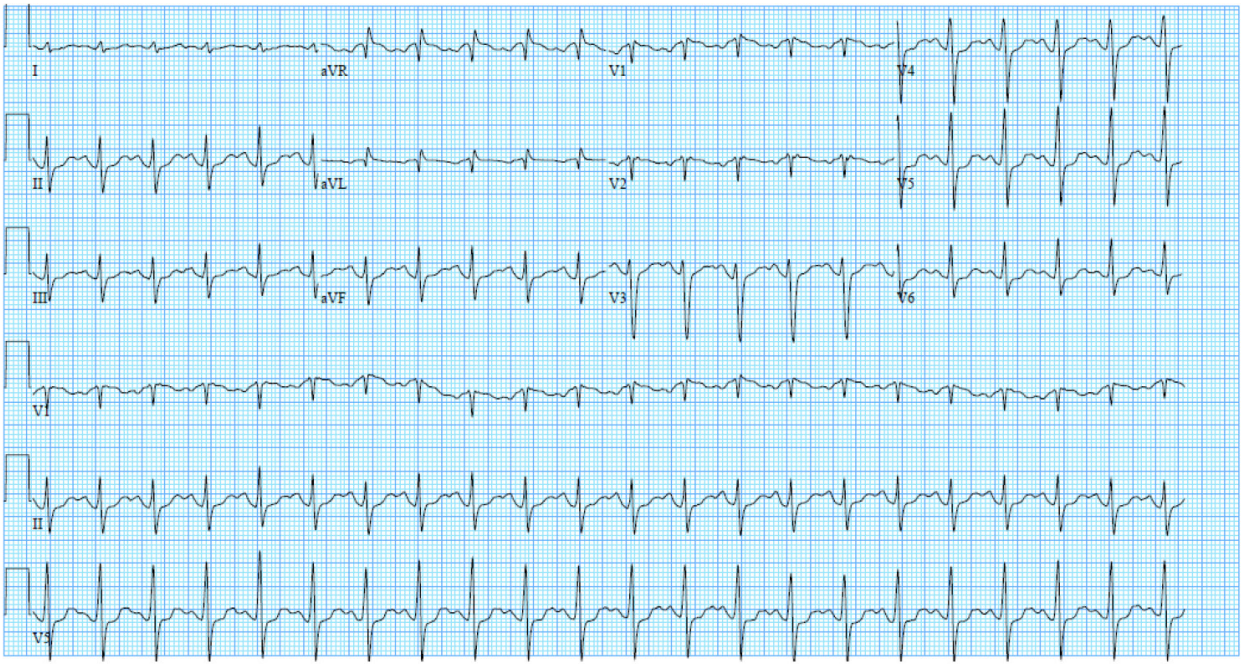

Fig. 1. Electrocardiogram performed shortly after arrival (rate, 130 beats/min; PR interval, 104 ms; QRS duration, 108 ms; corrected QT interval, 579 ms).

Table 1. Patient care timeline: vital signs, medications given, and events

Medication/event	Time	Blood pressure (mmHg)	Pulse (beats/min)	Respiration (breaths/min)	Temperature	SpO_2 (%)
Arrived	5:00	137/78	140	18	36.7°C	94
Metoprolol 5 mg IV	5:30	117/88	102	22	-	-
	5:31	109/82	95	24	-	100
Metoprolol 5 mg IV	6:01	114/89	90	21	-	100
	7:26	110/79	83	26	36.3°C	99
	10:30	112/77	89	15	36.5°C	100
	10:45	102/74	92	28	-	99
	11:35	-	90	-	-	99
	11:40	106/75	87	26	-	99
	11:52	-	85	18	-	99
	12:01	118/99	89	20	-	98
	12:25	-	88	19	-	100
	12:32	100/65	94	21	-	99
Increasing confusion	13:14	125/91	115	-	-	100
Seizure, lorazepam 1 mg IV	13:30	130/94	114	-	-	100
Intubation, etomidate 20 mg IV, rocuronium 100 mg IV	15:02	131/92	103	-	-	100
Propofol and fentanyl infusion IV	15:47	122/91	95	15	-	-
Sodium bicarbonate 50 mEq IV	16:31	118/85	89	15	36.1°C	100
Transferred to intensive care unit						

IV, intravenous; SpO_2, pulse oximetry.

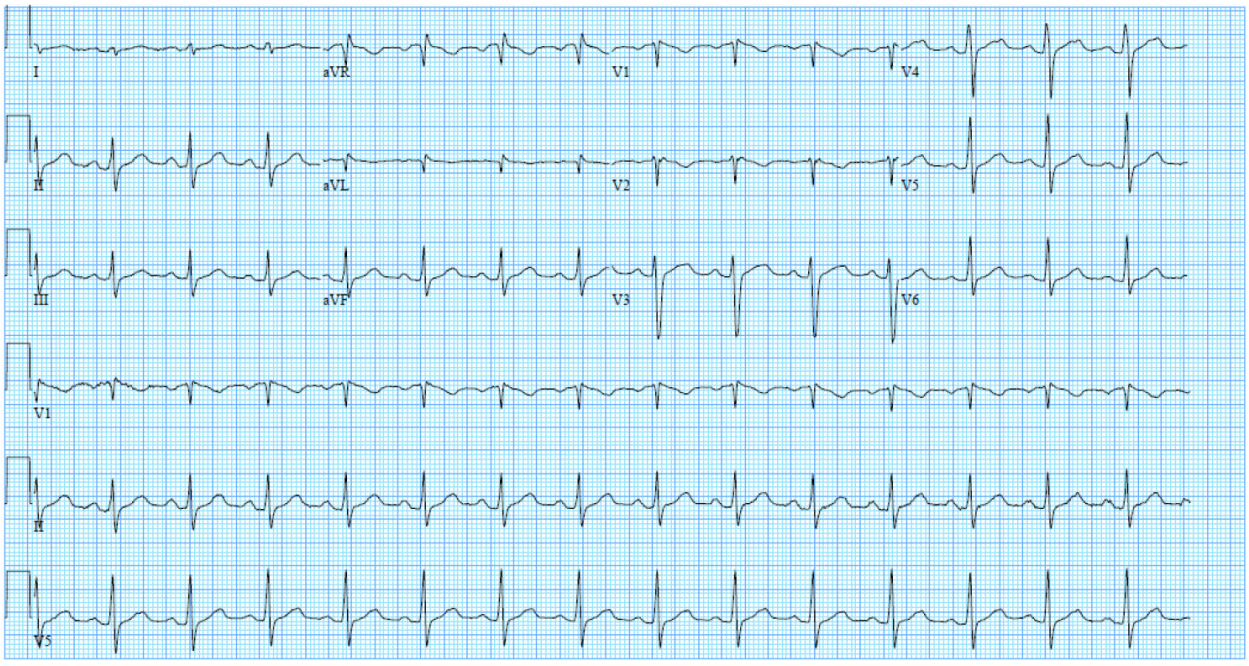

Fig. 2. Electrocardiogram performed 10 minutes after receiving metoprolol (rate, 89 beats/min; PR interval, 174 ms; QRS duration, 110 ms; corrected QT interval, 489 ms).

cific adrenoceptor antagonist, was specifically chosen because the patient was tachycardic but normotensive. Repeat vital signs recorded immediately after metoprolol administration were: blood pressure 117/88 mmHg, pulse rate 102 beats/min, respiratory rate 22 breaths/min, and SpO_2 100%. The patient became less agitated, with resolution of her diaphoresis over the next 10 minutes. A second dose of metoprolol 5 mg IV was administered 20 minutes later with complete resolution of her tachycardia, agitation, and

inability to speak coherently. At this point she became cooperative with further examination, questioning, and treatment.

A second electrocardiogram was then obtained (Fig. 2) and demonstrated normal sinus rhythm (89 beats/min) and marked improvement of the QTc interval (489 ms). Examination of her purse contents revealed an empty prescription bottle of bupropion. When confronted with these findings, she admitted to a suicide attempt hours earlier by taking the entire contents of the bottle. However, she refused to voluntarily drink activated charcoal. Laboratory results revealed normal complete blood count and chemistry panel. Ethanol, acetaminophen, and salicylate were not detected. A rapid qualitative urine drug screen was positive for cocaine and benzodiazepines. For the next six hours in the ED she remained calm and conversant, and received no further medications. Her vital signs remained stable. She was evaluated by the admitting Hospitalist, and participated in an interview with the on-call psychiatrist. She awaited the availability of an inpatient room on the general medicine service.

Approximately 8 hours after arrival she became more confused and pulled out her Foley catheter. Soft physical restraints were ordered at this time, but no sedatives were required. Her vital signs at this point were notable for increasing heart rate (115 beats/min) and blood pressure (125/91 mmHg). Fifteen minutes later she then was noted to exhibit tonic-clonic movements of her extremities with eyes deviated upward. Lorazepam 1 mg IV was administered with immediate resolution of her seizure. Two hours later, she experienced a second tonic-clonic seizure which resolved after one minute without treatment. She was then intubated for airway protection and to obtain a computed tomography scan of the brain, which was normal. She was placed on a propofol and fentanyl infusion. Widening of the QRS complex was then noted, and 50 mEq sodium bicarbonate IV was administered with subsequent resolution. Her tachycardia and hypertension normalized. She was then transferred to the intensive care unit. She was extubated 24 hours later, and discharged from the hospital two days later. Comprehensive quantitative toxicology studies were available one week later, with cocaine metabolite benzoylecgonine level >1,000 ng/mL, bupropion level 1,200 ng/mL (therapeutic range 50 to 100 ng/mL), and bupropion metabolite 4-hydroxybupropion level 10,000 ng/mL (therapeutic range 600 to 2,000 ng/mL) from serum samples drawn just after her arrival in the ED.

DISCUSSION

This case report is the first involving acute dual cocaine and bupropion cardiovascular and CNS toxicity successfully treated with only IV metoprolol, with reversal of prolonged QTc interval (Figs. 1, 2) and 8 hours of sedation. Cocaine inhibits re-uptake of monoamines at preganglionic sympathetic nerve endings, resulting in beta- and alpha-adrenergic stimulation with hypertension, tachycardia, and vasoconstriction.[2] Cocaine inhibits sodium influx into cells, increasing risk of dysrhythmia. Bupropion is a norepinephrine-dopamine reuptake inhibitor that also modulates vesicular monoamine transporter uptake.[2] Concomitant use of cocaine and bupropion results in additive and synergistic hyperadrenergic adverse effects, such as myocardial ischemia, which may occur at therapeutic doses.[5]

The use of benzodiazepines as first-line treatment for cocaine cardiovascular toxicity has been established for many years.[1,2] Based on a large systematic review of cocaine toxicity, benzodiazepines do not reliably mitigate hyperadrenergic symptoms, whereas beta-blockers are more efficacious.[1] In our case, the patient received IV lorazepam for her first seizure, but this did not affect her tachycardia and hypertension. The use of beta-blockers for treatment of cocaine toxicity has been hampered by the rare, inconsistent, and unpredictable phenomenon of "unopposed alpha-stimulation," whereupon blood pressure suddenly rises and/or coronary arterial vasoconstriction occurs after beta-blockers are administered.[1,2] This is based on a small number of cases yet has resulted in a relative contraindication that has existed in medical literature for over three decades.[2] In our case, there was no evidence of "unopposed alpha-stimulation" after metoprolol.

The patient's benzoylecgonine level was well over the range for potential lethal toxicity.[6] The quantitative levels of bupropion and 4-hydroxybupropion were greater than 10 times the therapeutic range and confirmed her ingestion occurred hours before her arrival.[7] The association of cocaine and bupropion overdose and seizures is well-documented.[8] Cocaine-induced seizures are usually immediate, whereas bupropion results in delayed onset, usually hours after ingestion. This may be explained by differences in cocaine- and bupropion-associated neurochemical pathways of increased excitation and decreased inhibition, which results in imbalance within the CNS then seizures.[9] We believe metoprolol not only improved the patient's agitation but may have had a prophylactic effect against cocaine-induced seizure. It is possible metoprolol also suppressed her bupropion-induced seizures, which occurred 7 then 8 hours later. Lipophilic beta-blockers, such as metoprolol and propranolol, have been shown to have anticonvulsant effects.[10] The half-life of metoprolol is 3 to 4 hours, and it is likely its effects abated after 8 hours, as illustrated by the sudden advent of tachycardia and hypertension preceding the two episodes of seizure (Table 1).[11]

The relationship between tachydysrhythmia, prolonged QTc in-

terval, and seizure has been established in past studies and is based on similarity between conductive tissue in the heart and brain.[12] The cardiac conduction system is comprised of specialized cells histologically resembling nerve tissue. Both systems are bidirectional and excitable from sodium inward and potassium outward currents, and this explains why anticonvulsant drugs, such as phenytoin, may influence cardiac rhythm and vice versa.[13] Imbalance of the autonomic nervous system has also been shown to increase risk of concomitant seizures and tachydysrhythmias.[8,9] Beta-blockers represent a mainstay of treatment for long QT syndrome, and metoprolol has been shown to reverse drug-induced QTc interval prolongation.[14,15]

We believe monotherapy with metoprolol for separate or combined cardiovascular and CNS toxicity from cocaine and/or bupropion may have a theoretical advantage over benzodiazepines for suppression of early-onset seizures. Continuation of metoprolol may also suppress later-onset seizures. Esmolol, a short-acting beta $_1$-blocker, is another option but is not lipophilic and may preclude any potential anticonvulsant effect. However, the combination of esmolol and low-dose benzodiazepines represents another treatment option for treatment of acute and delayed cardiovascular and CNS toxicity from concomitant cocaine and bupropion overdose. However, mainstay therapy for drug-induced seizures remains benzodiazepines in escalating doses, and this may need to be continued in the intensive care unit until the inciting drug is metabolized.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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