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Title: Experimental treatments for cocaine toxicity: A difficult transition to the bedside

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Abbreviations:
- BChE: butyrylcholinesterase,
- BE: benzoylecgonine
- CNS: central nervous system
- CocH: cocaine hydrolase
- CocE: bacterial cocaine esterase
- DMCocE: Double mutant bacterial cocaine esterase
- EME: ecgonine methyl ester
- GABA: gamma-aminobutyric acid
  i.v.: intravenous
  i.p.: intraperitoneal
- TSPO: translocator protein

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Abstract

Cocaine is a commonly abused illicit drug that causes significant morbidity and mortality. Although there is no true antidote to cocaine toxicity, current management strategies address the life-threatening systemic effects, namely hyperthermia, vasospasm, and severe hypertension. Clinicians rely on rapid cooling, benzodiazepines, and alpha adrenergic antagonists for management, with years of proven benefit. Experimental agents have been developed to more effectively treat acute toxicity. Pharmacodynamic approaches include antipsychotics that are thought to interfere with cocaine’s actions at several neurotransmitter receptors. These medications may worsen the consequences of cocaine toxicity though as they can interfere with heat dissipation, cause arrhythmias and lower the seizure threshold. Pharmacokinetic approaches employ cocaine metabolizing enzymes, such as butyrylcholinesterase (BChE), cocaine hydrolase (CocH), and bacterial cocaine esterase (CocE). Experimental models with these therapies improve survival, primarily when administered prior to cocaine, though newer evidence demonstrates beneficial effects shortly after cocaine toxicity has manifested. CocE, being a foreign protein, can induce an immune response with antibody formation. When enzyme administration is combined with vaccination against the cocaine molecule, improvement in cocaine-induced locomotor activity is observed. Finally, lipid emulsion rescue has been described in human case reports as an effective treatment in patients with hemodynamic compromise due to cocaine, which correlates well with its documented benefit in toxicity due to other local anesthetics. A pharmaceutical developed from these concepts will need to be expedient in onset and effective with minimal adverse effects, while at the same time being economical.
BACKGROUND

For at least 30 years, cocaine has remained a major public health concern. In 2010, there were 1.5 million cocaine users in the US alone (Substance and Mental Health Services, 2011). The molecular actions of cocaine are numerous and defy a simple treatment to mitigate its toxic effects. Cocaine use predisposes to diffuse central nervous system (CNS) excitation. It inhibits the transporter proteins responsible for the reuptake of epinephrine, norepinephrine, serotonin, and dopamine into presynaptic neurons allowing repeated activation of the postsynaptic neuron through alpha and beta adrenergic, serotonergic, and dopaminergic receptors (Williams, 1988). Cocaine’s toxic effects cannot simply be explained by reuptake inhibition though, as other agents with similar effects on reuptake do not cause the same clinical manifestations as cocaine toxicity. Concentrations of glutamate and aspartate, excitatory amino acids, increase significantly in animals exposed to cocaine and may play a crucial role in acute toxicity and neuromodulation resulting in addiction (Smith, 1995; Kasanetz, 2013). Morbidity and mortality largely result from acute cardiovascular and neurologic complications. Hyperthermia, vasospasm, and severe hypertension are produced by catecholamine excess and psychomotor agitation. General management with rapid cooling and fast acting benzodiazepines is usually sufficient to decrease the risk of permanent disability or death. Alpha adrenergic antagonists and the potential use of calcium channel antagonists and sedatives have proven clinical utility when the first-line measures are inadequate. The numerous biochemical actions of cocaine with effects on various cellular receptors make development of an antidote difficult. Newer agents such as antipsychotics that antagonize dopamine receptors, enzymes metabolizing cocaine, and
vaccines against cocaine have been developed. Preliminary results hold promise, though significant barriers may prevent these therapies from achieving practical utility in acutely cocaine-toxic patients. In this paper we will review several recent advances in the treatment of acute cocaine toxicity and discuss the difficulties facing their clinical implementation.

CURRENT CLINICAL MANAGEMENT

Cooling

Among the most dangerous effects of cocaine toxicity is its ability to raise core temperature and cause life-threatening hyperthermia (Roberts, 1984; Daras, 1995). Emphasizing the dangerous relationship between cocaine-induced hyperthermia and mortality, there is a 33% increase in mean cocaine-related mortality on days where the ambient temperature is above 88°F (Marzuk, 1998). In addition to protein denaturation that occurs at elevated body temperatures, the cardiovascular system, which is likewise being stimulated by the sympathomimetic effects of cocaine, is further taxed to maintain cardiac output in the face of temperature-induced vasodilation. In this setting, rapid resolution of hyperthermia is of utmost importance. In a canine model of cocaine toxicity, limiting hyperthermia by reducing the ambient temperature to -5°C was more protective against mortality than prevention of acidosis with sodium bicarbonate, prevention of convulsions with antiepileptics, or inhibition of dopamine with a dopamine antagonist. Cocaine administration caused dogs to become more hypothermic at -5°C than a control group indicating that cocaine may have an effect in enhancing the response to hypothermia, which is actually protective (Catravas, 1981). In humans,
cocaine-induced hyperthermia is mediated by increased locomotor activity (Rosenberg, 1986). As the ambient temperature rises, cocaine augments elevations in core temperature, attenuates cutaneous vascular conductance and sweating, and decreases the perception of elevated temperature (Crandall, 2002). Rats given i.v. cocaine have increases in brain temperature that do not correlate with temporal muscle temperature (Kiyatkin, 2013). Patients with cocaine-induced hyperthermia often recover if rapidly cooled (Menaker, 2011), while the risks of prolonged elevations of core body temperature include death and permanent neurologic disability. Ice water immersion and paralysis are useful (Roberts, 1984; Rosenberg, 1986) and data suggest cold water immersion is the most practical treatment modality, effectuating rapid cooling at a rate of about 0.2°C/minute (Armstrong, 1996).

Benzodiazepines

Generalized suppression of central nervous system activity antagonizes the sympathomimetic effects of cocaine. In animal models of cocaine toxicity, sedation with a benzodiazepine increases the mean lethal and convulsive doses of cocaine (Guinn, 1980) and improves survival (Guinn, 1980; Catravas, 1981; Yuksel, 2013). Through their action on the gamma-aminobutyric acid (GABA) receptors in the amygdala and reticular activating system, benzodiazepines function as anxiolytics, sedatives, and antiepileptics. Additionally, benzodiazepines may enhance the effect of endogenous adenosine on the myocardium by inhibiting the nucleoside transporter responsible for adenosine reuptake with resultant coronary vasodilation from A2A receptor agonism.
Benozodiazepines also relieve tachycardia, hypertension, and vasoconstriction, thereby decreasing the metabolic demands of the myocardium. Finally, when high doses of ligands to the translocator protein (TSPO), formerly known as the peripheral benzodiazepine receptor, are administered in vivo to rabbits and ex vivo to rat and rabbit hearts, the area of myocardial infarction is decreased after an ischemic stress. The mechanism of protection is potentially due to reduced cardiac mitochondrial membrane permeability that results in decreased apoptosis and prevents release of mitochondrial cytochrome c (Leducq, 2003; Obame, 2007). Success using short-onset benzodiazepines such as midazolam or diazepam has been a cornerstone of the treatment for acute cocaine toxicity since the 1980s. Large human trials assessing their efficacy are lacking, but recent meta-analysis data demonstrate a 51.7% improvement in survival in cocaine poisoned animals treated with benzodiazepines compared to placebo (Heard, 2011). In humans a beneficial effect of benzodiazepine treatment is best demonstrated for patients with cocaine-related chest pain. In randomized trials patients treated with a parenteral benzodiazepine plus sublingual nitroglycerin had more rapid and substantial improvement in their subjective pain scores than those receiving nitroglycerin alone (Honderick, 2003). Also those who received benzodiazepines alone did no worse than those treated with only nitroglycerin (Baumann, 2000).

Adrenergic receptor antagonists
Cocaine inhibits norepinephrine reuptake in central presynaptic nerves. Excess norepinephrine causes stimulation of both alpha and beta adrenergic receptors. Studies of beta adrenergic antagonists in acute cocaine toxicity have shown decreases in the mean convulsive and mean lethal cocaine doses in animals (Guinn, 1980) and worsened coronary vasoconstriction in humans (Lange, 1990). Clinically, the use of a beta adrenergic antagonist in an acutely cocaine toxic patient has resulted in death (Fareed, 2007). Alternatively, alpha adrenergic antagonists, such as phentolamine, can mitigate the vasoconstrictive effects of cocaine toxicity suggesting the mechanism is cocaine-induced elevation in alpha adrenergic tone (Lange, 1989). Mean arterial pressure and coronary vasospasm can be relieved reducing afterload and improve myocardial perfusion. The clinical use of phentolamine has resulted in the resolution of chest pain and electrocardiographic changes consistent with coronary ischemia (Hollander, 1992).

Finally, calcium channel antagonists and neuromuscular blockers have been used to treat refractory cases of cocaine toxicity. Myocardial injury due to cocaine-induced vasoconstriction was decreased with verapamil in a clinical trial (Negus, 1994). Though little clinical evidence exists supporting use in acute cocaine toxicity, the mechanism of action of calcium channel antagonists makes them a reasonable second-line agent. Neuromuscular blockade is the last resort in the treatment of hyperthermia and agitated delirium associated with cocaine toxicity. Following paralysis, locomotor activity is abolished and behavior is controlled allowing passive and active cooling and administration of benzodiazepines.
THERAPIES UNDER DEVELOPMENT

PHARMACODYNAMIC APPROACHES

Treatments that antagonize receptors stimulated by cocaine can be categorized as pharmacodynamic approaches to the treatment of cocaine toxicity. Among the antagonists being explored are antipsychotics that affect multiple receptors where cocaine has actions.

Antipsychotics

The use of atypical antipsychotics in cocaine toxicity exploits their mechanisms as dopamine, serotonin, and muscarinic inhibitors. Animal studies show antipsychotics as a class increase survival by 27% over placebo (Heard, 2011). Olanzapine, specifically, is an antagonist at the dopamine D1, D2, muscarinic, and serotonin 5HT2A receptors. In mice pretreated with olanzapine, only 10.5% developed irreversible cocaine toxicity (and were euthanized) compared to 46.2% of those pretreated with placebo (Heard, 2009). Ziprasidone, an antagonist at dopamine and serotonin receptors, reduces cocaine induced lethality in pretreated mice by 51% (Cleveland, 2005), though in a more recent investigation using similar doses, ziprasidone failed to prevent lethality, but did delay the onset of seizure (Cleveland, 2007). There are concerns whether antipsychotics should be used at all in the setting of cocaine toxicity (Wu, 2008).
Conflicting data exist regarding antipsychotics that may be agent and or species specific. In dogs, pimozide showed no benefit in convulsions or lethality compared to controls, while a group treated with chlorpromazine had improved mortality, and a slight increase in the mean convulsive dose (Catravas, 1981). In a small cynomologus monkey trial, there was an increased mean convulsive dose and fewer convulsions in those treated with chlorpromazine compared to controls, but a greater proportion of subjects with convulsions compared to those treated with diazepam (Guinn, 1980). Additionally, haloperidol pretreatment in rats did not improve cocaine-induced mortality (Witkin, 1989). Associated anticholinergic effects causing impaired heat dissipation, decreased seizure threshold, and prolongation of the QT interval are all potentially catastrophic to a cocaine-toxic patient. We conclude, for now, that data are insufficient to support the use of antipsychotics for patients with cocaine toxicity.

PHARMAKOKINETIC APPROACHES

Pharmacokinetic approaches to the treatment of cocaine overdose aim to prevent its entry into, enhance its diffusion from, and mitigate subsequent action within the CNS. This mechanism aims to neutralize or metabolize cocaine rather than countering its clinical effects. Examples of this approach are the use of cocaine metabolizing enzymes, vaccines, and lipid emulsion.

Enzymes
Cocaine metabolism is complex. In addition to spontaneous hydrolysis, in humans, liver carboxylesterase hydrolyzes the methyl ester of approximately 45% of cocaine to form benzoylecgonine (BE) and butyrylcholinesterase (BChE) hydrolyzes the benzoyl ester of 45% of cocaine to produce ecgonine methyl ester (EME). About 5% of cocaine also undergoes N-demethylation by BChE to form norcocaine (see Figure)(Dean, 1991). In isolated cerebral arteries from cats and fetal sheep, BE was a more potent vasoconstrictor than cocaine, norepinephrine, and norcocaine. EME actually demonstrated vasodilatory properties and was protective in mice (Madden, 1990). Norcocaine easily crosses the blood brain barrier, while BE and EME are more restricted. Findings of BE in the brains of cocaine users days after last exposure, together with cocaine’s short half-life and clinical effects that last hours suggest that cerebrovascular effects may be due to BE (Madden, 1990).

Three enzyme types have been studied as potential antidotal therapies to acute cocaine toxicity. Wild-type human BChE, also referred to as pseudocholinesterase, hydrolyses cocaine to EME (Misra, 1975). In humans, decreased BChE activity is associated with life threatening reactions to cocaine and it has been postulated that phenotypes with low BChE activity are more susceptible to cocaine (Hoffman, 1992). In rats pretreated with BChE then exposed to cocaine, blood pressure elevation was mitigated and the lethal dose was increased. In rats administered cocaine 80 mg/kg then given BChE three minutes later, a smaller proportion suffered convulsions or expired in a dose dependent manner than controls (Lynch, 1997). After cocaine administration, a pretreated rat had significantly decreased plasma concentrations of cocaine, BE, and norcocaine, and significant increases in EME compared to a control (Mattes, 1997). Similar results are
reported in pretreated squirrel monkeys in vivo and human plasma in vitro (Carmona, 2000). Interestingly, rat brain concentrations of cocaine and BE were not altered by BChE, though brain EME concentrations were increased in a dose dependent manner after BChE pretreatment (Carmona, 2005).

A major limitation of native BChE is the inherent inefficiency of the enzyme; $k_{cat} = 0.07/sec$ and $K_m = 4.5$ microM. It would require massive doses in order to detoxify cocaine in a human (Sun, 2002a). Guided by molecular modeling, two amino acid substitutions, Ala328Trp/Tyr332Ala, were introduced into wild-type BChE in order to allow better orientation of (-)-cocaine for enzymatic hydrolysis after it has bound to the enzyme active site. The recombinant enzyme, CocH, is also primarily tetrameric, similar to wild-type BChE, is not rapidly degraded as are monomeric or dimeric enzymes, and has a 40-fold increase in catalytic activity. CocH has a $k_{cat} = 2.6/sec$ and $K_m = 18$ microM. Following CocH pretreatment, decreased cocaine concentrations were found in rat tissue and increased locomotor activity induced by cocaine was abolished in mice (Sun, 2002a). Rats pretreated with CocH showed no major change in the concentration of BE generated, but EME concentration was 8 fold greater than controls (Sun, 2002b). When rats with cocaine-induced hypertension were treated with 3 mg/kg CocH, after an average of 108 seconds following cocaine administration, they had rapid reversal of blood pressure abnormalities (Gao, 2004). Development of additional mutants of CocH, such as A199S/S287G/A328W/Y332G and A199S/F227A/S287G/A328W/Y332G, have yielded catalytic efficiency with hundreds to thousands times that of native BChE (Zheng, 2008). Investigators have fused A199S/S287G/A328W/Y332G with albumin (Albu-CocH) to provide a longer half-life. When given as pretreatment or as a rescue
after 100 mg/kg cocaine administered, Albu-CocH resulted in improved mortality and prevention or resolution of convulsions. When given after cocaine, brain cocaine concentrations in treated rats were four fold less compared with controls (Brimijoin, 2008).

A CocE found in *Rhodococcus* spp. catalyzes cocaine hydrolysis with a $k_{\text{cat}} = 7.8/\text{sec}$ and $K_m = 0.64\ \mu\text{M}$. CocE is effective in preventing convulsions and mortality and rescues mice from convulsions when given after a lethal dose of cocaine (Ko, 2009). CocE (1 mg i.v.) given to rats 1 minute after cocaine administration produced a 10-fold rightward shift in the cocaine-toxicity dose response curve. Notably, when CocE is administered to rats up to six minutes after cocaine there is still a significantly reduced mortality rate (Cooper, 2006). An immune response was noted with repeated administrations of CocE though and as anti-CocE antibodies increased, the clinical response to treatment declined (Ko, 2009). Double mutant CocE (T172R/G173Q) (DMCocE) given to rhesus monkeys 10 minutes after cocaine improved mean arterial pressure, heart rate, and locomotor activity, even as anti-DMCocE antibody titers increased in the animals following repeated administrations (Collins, 2011; Collins, 2012). Effective enzymatic therapy for acute cocaine toxicity has the potential to be curative though significant caveats to its administration will apply. More than 40% of patients who present to the Emergency Department with cocaine toxicity do so more than 1 hour after cocaine use (Gitter, 1991). More concerning is another analysis that shows patients suffering an acute myocardial infarction after cocaine use presented after more than 18 hours (Amin, 1990). It is unknown whether enzymatic therapy will be effective in these late-presenters. Pharmacoeconomically, enzymatic therapy will be
costly. Unless there is significant benefit of enzymatic treatment in terms of patient mortality, major adverse events, or reductions in hospital resource utilization compared to current clinical management, it will be difficult to justify the significant cost. Given these hurdles, it is difficult to imagine enzymatic therapy supplanting cooling and benzodiazepines in the treatment of cocaine toxic patients.

Vaccine and enzyme combinations

Vaccines that actively immunize against cocaine can result in innate production of anti-cocaine antibodies that yield immune mediated degradation of the cocaine molecule. While more suited to treat cocaine addiction by preventing the entry of cocaine into the CNS and the resultant reinforcing effects, it has also shown some promise in acute toxicity reducing sequelae in mice and humans (Fox, 1996; Martell, 2009). Anti-cocaine antibody binding allows for rapid sequestration of the toxin in plasma. As discussed above, enzymatic degradation enhances elimination of active cocaine, in combination, it is believed that enzymatic treatment and prior vaccination work synergistically to prevent cocaine toxicity. Data show higher plasma cocaine and cocaine metabolite concentrations in mice treated with vaccine and CocH suggesting endogenously produced antibodies trap cocaine in the plasma, possibly preventing entry into the CNS, and allow greater metabolism by CocH (Brimojoin, 2013). When the administration of cocaine vaccine (8100-1 KLH SNC vaccine) (norcocaine hapten-conjugated keyhole limpet hemocyanin) is compared with pretreatment with a quadruple mutant CocH, (A199S/S287G/A328W/Y332G), each agent alone was not sufficient to prevent
decreased grip strength or increased locomotor activity in cocaine-toxic mice (Gao, 2013; Carroll, 2012). Combination treatment of CocH and vaccine resulted in no loss of grip strength and greatly reduced locomotor activity (Carroll, 2012). Further, this combination afforded almost total protection from alanine aminotransferase (ALT) elevation, suggesting that the liver cells were protected from injury, when hepatotoxic doses (120 mg/kg i.p.) were administered (Gao, 2013). The protection from ALT elevation was equivalent to that when cocaine antibody was given suggesting that the mice who received the vaccine went on to produce antibody and reaped the same benefit. Of note, cocaine-induced hepatotoxicity is specific to rodents and does not typically occur in humans. Mice treated with adeno-associated viral vector, pAAVio-CASI-CocH C-W-SV40, encoding cDNA for C-terminally truncated CocH developed significant CocH activity and normal serum ALT after treatment with cocaine 120 mg/kg i.p. compared with mean ALT concentration of 18,000 units/mL in untreated subjects three months after vector administration (Gao, 2013). The use of an effective vaccine against cocaine has the potential to reduce toxicity substantially, though issues regarding bioethics and public health resource utilization must be considered. Would this vaccine be offered broadly or to those who abuse and are psychologically addicted to cocaine? Could it become mandated in some cases and what effects would that have on patient autonomy? Finally there is the potential for riskier behavior: some may try to overcome the vaccine with higher doses while others may experiment with cocaine with the perception that there is an easy and effective treatment (Young, 2012). Significant more development of this modality and the evaluation of bioethical issues surrounding its use are required before this is a reasonable treatment option.
Lipid Emulsion

Use of an intravenous 20% lipid emulsion was initially described as a rescue therapy for toxicity to local anesthetics (Weinberg, 1998; Rosenblatt, 2006), though it has now shown benefit in refractory cases of various overdoses (Jamaty, 2010). Case reports describe the effective use of intravenous lipid emulsion bolus followed by infusion in patients with hemodynamic compromise secondary to cocaine toxicity (Jakkala-Saibaba, 2011; Arora, 2013). The precise mechanism of lipid emulsion in overdose is not fully elucidated. Theories including the formation of a “lipid sink” with sequestration of a lipophilic xenobiotic, such as cocaine, in the plasma, creating a gradient off the target organs, and possibly enhancing elimination have been proposed (Weinberg, 1998). The partition coefficient (log P) and the volume of distribution are properties of chemicals found to be predictive of in vitro reductions of drug concentrations after lipid emulsion treatment. The more positive the log P and the greater the volume of distribution, the more likely a drug is to be highly lipid soluble and therefore more likely that lipid emulsion will be effective (French, 2011). The distribution constant (log D) correlates well with the log P and is a more precise estimate of lipid solubility as it takes pH into account (Samuels, 2012). Cocaine has a log D of 1.14 (Wilson, 2004) and volume of distribution of 1.96 L/kg (Chow, 1985), suggesting that lipid emulsion may be helpful in cases refractory to conventional management. Additionally, lipid emulsion is a component common in parenteral feeding preparations, is already present in many hospitals, and its cost is almost negligible relative to innovative pharmaceuticals. While it has been used clinically, the paucity of evidence precludes lipid emulsion from being
considered a conventional therapy, though its use is far more available to the clinician at the bedside. Lipid emulsion treatment for toxic exposures is in its infancy and there remain significant questions regarding its efficacy and potential harm. Concerns include impairment of therapeutic medications via the same mechanism as inactivation of the toxin (log D for diazepam and midazolam is 3.86 and 3.68 respectively (Wilson, 2004)), inducement of pancreatitis, and interference with the laboratory analysis of serum constituents such as lactate. Lipid emulsion remains an investigational final treatment option available to providers when patients are acutely decompensating.

SUMMARY

The perfect cocaine antidote must be easily deliverable to a patient manifesting signs and symptoms of severe cocaine toxicity, namely cerebral, coronary or peripheral vasoconstriction, or life threatening hyperthermia. This substance would rapidly halt the actions of cocaine centrally by neutralizing cocaine in the plasma before it has traversed the blood brain barrier, traversing the barrier itself, or creating a diffusion gradient to pull cocaine from the CNS into the plasma. This substance should perform better than symptomatic treatments to such a great degree that this product would be economically viable against generic benzodiazepines. This ideal has proven elusive though, due to the complexity of cocaine’s pathophysiologic effects.

The preponderance of preclinical studies evaluating antidotal therapies for cocaine are elegant experiments that help further elucidate cocaine’s actions at receptors and the ability of enzymes to catalyze its hydrolysis. The majority are proof of concept studies
that pretreat subjects with the investigational agent before administration of cocaine. Excitement for a potential contender is enhanced by the studies that show clinical improvement with a delay of several minutes between cocaine and antidote administration. Currently, ten minutes is the longest delay to treatment with retained benefit. Several potentially harmful active metabolites of cocaine, such as norcocaine and BE, may be present in greater concentrations relative to cocaine by the time a patient develops symptoms, presents to an emergency department, and is treated. The efficacy of experimental treatments on these metabolites or when given after a delay between cocaine administration and treatment is unknown. With regards to non-human derived proteins, antibody formation and the resultant immune response will have to be considered as an acutely cocaine-toxic patient may be extremely susceptible to significant immune mediated reactions. This is not likely an issue the first time a patient is treated, but the addictive nature of the drug suggests that patients may require treatment several times. These patients are also those from whom an accurate history of prior treatments would be very difficult to obtain. Other modalities such as antipsychotics predispose to anticholinergic effects that are potentially additive to the most severe risks of cocaine toxicity, namely hyperthermia, arrhythmia, and seizures. The last issue in the development of new pharmaceuticals is their potentially exorbitant cost, especially for enzymes or other complex proteins. Any new antidotal therapy would have to be far more efficacious than generic benzodiazepines and phentolamine to be a cost-effective care strategy. Given these cost issues, clinical studies proving efficacy will need to be powered to show superiority to current treatment modalities, which will require more patients than studies performed to show non-inferiority.
CONCLUSION

Cocaine toxicity remains a significant cause of death and permanent disability. Cooling, high dose, rapid-acting benzodiazepines, and adrenergic antagonists are the foundation of current clinical management. Lipid emulsion has been effective in managing refractory cases and may be an economical rescue treatment for patients with severe cocaine toxicity. Experimental agents hold promise, though there are many issues to contend with before these are available at the bedside. These agents must not predispose the patient to arrhythmia or interfere with normal neurotransmitter function. They also need to be effective after a significant delay between cocaine exposure and presentation. Immunogenicity must be minimal, as such critically ill patients would fare poorly with additional anaphylactoid or anaphylactic reactions. Even considering the significant and numerous hurdles, the ideal agent may be on the horizon and for that we can wait and hope. For now, years of treating cocaine toxicity have supported the safe and effective use of cooling and benzodiazepines in these critically ill patients.
Authorship Contribution

Wrote or contributed to the writing of the manuscript: Connors, Hoffman
References


Footnotes

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Legend for Figure

Three primary pathways of cocaine metabolism and the relative production of each metabolite.
Figure 1

Cocaine (Benzoylmethylecgonine) → Ecgonine Methyl Ester

- Butyrylcholinesterase
- Spontaneous hydrolysis or via liver Carboxylesterase

Norcocaine → Benzoylecgonine

5% → 45%