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Pharmacology and Therapeutic Applications of Cocaine

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SINCE COCAINE'S INTRODUCTION to Western medicine (1884) as the first local anesthetic, it remains a unique drug combining local anesthesia with intense vasoconstriction. Its early use led to numerous reports of toxicity and addiction, because of a lack of appreciation of its potency, and the consequences of unlimited access to it, by physicians and general public alike.[1–4] A century of clinical experience has led to the evolution of guidelines for safe and effective use,[5–7] and strict legal controls over availability and distribution.[2]

However, illicit abuse of cocaine has reached epidemic proportions in the last 15 years.[8] This has produced both enormous social, economic, and political dilemmas, and an increasing awareness of associated medical hazards.[8–11] In 1973, the second report of the National Commission on Marihuana and Drug Abuse, on the basis of statements made by the American Medical Association's Department of Drugs and from the American Association of Ophthalmologists, concluded that cocaine possessed no unique pharmacologic properties.[12] Consequently, the medical profession was surveyed to determine its benefits. Not only was it considered invaluable, but it appeared to have a reasonable safety record.[13,14] Coupled with increased governmental interest in cocaine's use has come a resurgence of research into its pharmacologic and physiologic properties. Using earlier observations as a foundation, this review will focus on contemporary clinical and scientific knowledge, and discuss uses of cocaine in medicine, particularly as they pertain to anesthetic practice.

Historical Aspects

On discovering the New World, the Spanish Conquistadors found in Peru an Incan civilization that attached enormous importance to the leaves of the plant, *Erythroxylon coca,* for religious, mystical, social, stimulant, and numerous medicinal purposes.[15–19] They most noted the drug's capacity to increase stamina, and to alleviate hunger and thirst. Although it has been conjectured that coca may have served as an analgesic during skull trephination, an operation historically practiced in Peru and Bolivia, evidence of its use as a local anesthetic for this procedure is lacking.[16]

Centuries later, in 1859, Albert Niemann characterized the active coca alkaloid, and named it "cocaine." In 1860, Wohler commented that

> "Cocaine has the remarkable action on the nerves of the tongue that the place of contact after a few moments becomes anesthetized and almost insensitive."[1]

Despite numerous suggestions of cocaine's potential as a local anesthetic, it was not until 1884 that Carl Köller demonstrated the critical link between the observed anesthetic effects of cocaine and its application to clinical

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ophthalmic practice.[1,4,20] This new form of anesthesia rapidly spread to other surgical disciplines.[1,20–23]

Cocaine's dangers were promptly recognized. It could create crippling dependence and psychosis.[24] By 1891, 200 reports of systemic cocaine intoxication, including 13 deaths, were reported.[25]

In 1924, an American Medical Association committee reviewed 26 of 43 deaths under local anesthesia, attributable to cocaine.[5] Guidelines for its safe use were recommended. Cocaine paste (a concentrated "mud" of crystals dissolved in epinephrine) was condemned as toxic.

Pharmacology

The cocaine alkaloid, benzoylmethylecgonine, is an ester of benzoic acid. It constitutes up to 1.8% dry weight of the leaves of *Erythroxylon coca* and related species.[26] Ecgonine, like atropine and scopolamine, is a tropane derivative. Commercially, the coca alkaloids are hydrolyzed to obtain ecgonine, which is then benzoylated and methylated to the base, cocaine.[27] Conversion to the hydrochloride salt produces a powdery, white crystalline, water-soluble substance, with a pK_a of 8.6, which decomposes on heating and thus cannot be autoclaved. The illicit lipid-soluble preparation, "crack" (cocaine free-base), is inexpensively manufactured by mixing the hydrochloride salt with an alkali. Crack is more stable on heating, vaporizes readily, and has high bioavailability when smoked.[28]

Absorption

Clinical evidence of systemic absorption through mucous membranes was noted as early as 1919.[29] Following the development of a colorimetric assay for cocaine, Campbell and Adriani demonstrated substantial absorption of cocaine from the upper respiratory tract within minutes of application, being maximal through tracheal and laryngeal mucosa.[30,31] Peak plasma levels appeared proportional to dose, regardless of concentration.

In 1975, a more specific and sensitive assay for cocaine was developed by Jatlow and Bailey, making it possible, for the first time, to measure plasma concentrations as low as 5 ng/ml (100-fold less than detectable by the colorimetric method), enabling comprehensive pharmacokinetic studies.[32] In a clinical study, topical intranasal cocaine (1.5 mg/kg) was rapidly absorbed, with peak plasma concentrations (120–474 ng/ml) occurring within 30–60 minutes (fig. 1).[33] Cocaine was still detectable on nasal mucosa 3 h after application, and in plasma for up to 6 h. Higher peak plasma concentrations occurred in those patients with significant cardiac disease.[33] The bioavailability of topical intranasal cocaine (as measured by the area under the plasma concentration–time curve), was estimated to be 4 to 6 times less than reported for an equivalent intravenous dose (0.19–2.0 mg/kg).[34] Peak

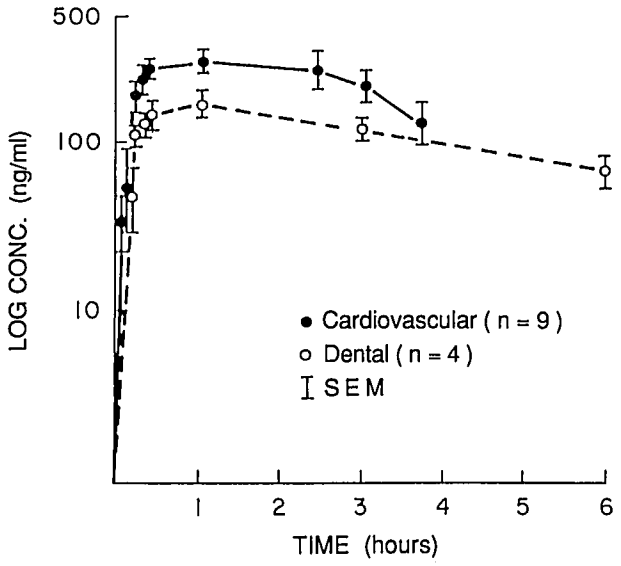

FIG. 1. Plasma concentrations of cocaine after topical application (1.5 mg · kg^{-1}) to the nasal mucosa in patients undergoing open heart or dental surgery. (Reproduced with permission.[33])

plasma concentration was proportional to the dose administered. The time to peak concentration lengthened with increasing doses (fig. 2). Via potent vasoconstriction, cocaine may limit its own absorption. Appearing in the systemic circulation slowly enough for efficient plasma metabolism, its apparent bioavailability may be decreased. Fluctuating degrees of local vasoconstriction may explain the intersubject variability in rate of absorption seen.[34] Although delayed, oral cocaine produced plasma levels and psychologic effects similar to those after nasal application.[35] Therefore, the amount of cocaine swallowed after intranasal application must be considered when estimating total dose administered.

Clearance and Metabolism

Several studies indicate that cocaine has a biologic half-life of 0.5–1.5 h, a volume of distribution of 2.0 l/kg, and a systemic clearance of 2 l/min.[36] Only 1–5% of cocaine is cleared unmetabolized in urine, where it may be detected for only 3–6 h after use. However, its two major metabolites, ecgonine methyl ester (EME) and benzoylecgonine, have biologic half-lives of approximately 4 and 6 h, respectively (fig. 3). These compounds constitute over 80% of cocaine's metabolites and are detected in urine for 14–60 h after cocaine administration.[36,37]

Esterases play a major role in the metabolism of cocaine. Rapid hydrolysis by plasma and liver esterases to EME and benzoic acid is clearly established. In man, plasma cholinesterase (pseudocholinesterase) hydrolyzes cocaine.[38–40] Jatlow *et al.*[39] demonstrated that plasma from subjects homozygous for atypical cholinesterase, with low

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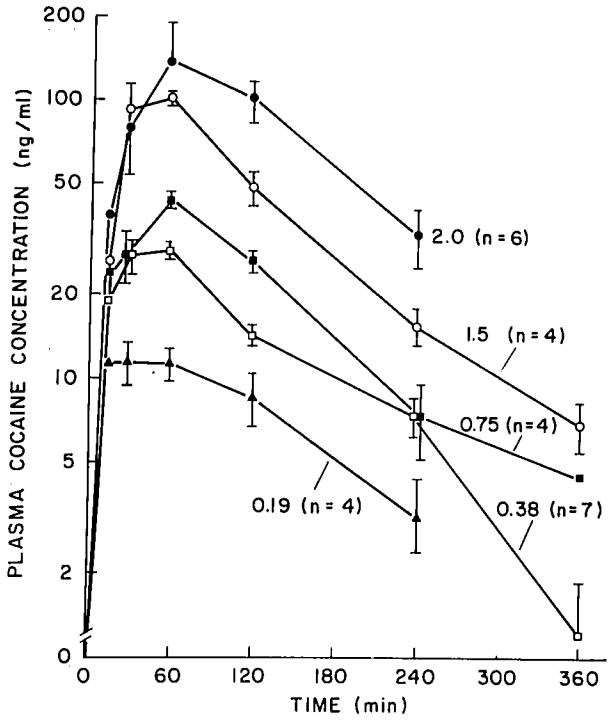

FIG. 2. Time course of plasma cocaine levels following various doses (0.38–2.0 mg · kg^{-1}) of intranasal cocaine. Points are mean ± SE. (Reproduced with permission.[34])

dibucaine numbers and a history of succinylcholine sensitivity, had impaired *in vitro* decay of cocaine (fig. 4).[39] Plasma from heterozygotes metabolized cocaine at an intermediate rate. Acquired deficiencies of the enzyme (pregnancy, plasmapheresis, liver disease, malnutrition), and anticholinesterase medications (echothiophate eyedrops, neostigmine) also may result in impaired plasma hydrolysis.

Liver esterases hydrolyzing cocaine to EME and benzoic acid had lower affinity, but greater capacity, for cocaine

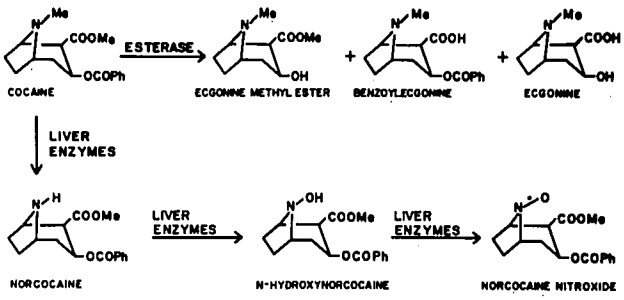

FIG. 3. Proposed metabolic pathways for hydrolysis and oxidation of cocaine. N-hydroxynorcocaine and norcocaine nitroxide have been found in animal studies. It has been suggested that these metabolites play a role in hepatotoxicity of cocaine in certain animal species. (Reproduced with permission.[37])

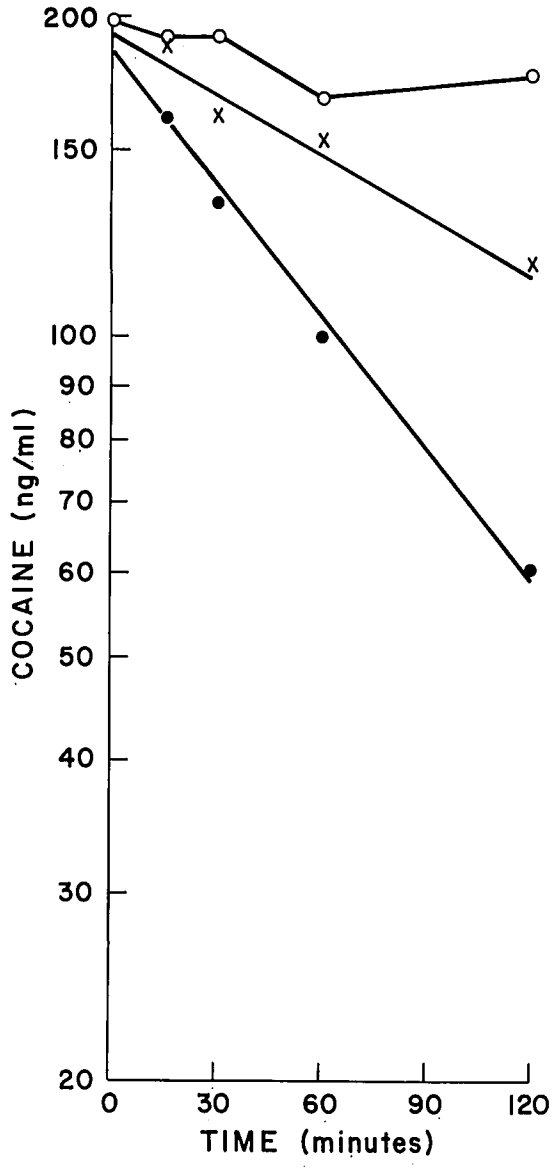

FIG. 4. Cocaine hydrolysis in plasma (●—●) of a normal control (dibucaine number = 83) *in vitro*. In a homozygous individual who is succinylcholine sensitive (dibucaine number = 15), little if any cocaine is hydrolyzed (O—O). In a heterozygous individual (X—X) (dibucaine number = 55), the extent of hydrolysis is less than in the normal patient but greater than in the homozygous subject with a low dibucaine number. (Reproduced with permission.[39])

substrate.[39] Under normal circumstances both plasma and liver enzymes contribute equally to cocaine hydrolysis. The Michaelis constant (K_m) values of 50 and 1,000 μM/l for plasma and liver esterases suggest that enzyme saturation would be unusual for doses less than 2 mg/kg.[40]

The metabolic pathway for cocaine's second major metabolite, benzoylecgonine, is unclear. Although nonenzymatic hydrolysis of cocaine at physiologic *p*H and tem-

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perature could account for most benzoylecgonine excreted, an enzymatic process cannot be excluded.[40,41]

Minor, but significant, oxidative metabolism of cocaine to norcocaine occurs in the liver (fig. 3).[38] Norcocaine is the only metabolite of cocaine with significant pharmacologic activity. It has been detected in primate brain, where it appeared equipotent to cocaine in inhibiting neural reuptake of norepinephrine.[42]

Oxidative metabolism of cocaine in the liver also produces substances capable of inducing severe hepatic necrosis; this has been observed in mice, with and without hepatic enzyme induction.[37,43-44] To date, all reported cases of cocaine-induced liver damage in man have been associated with concurrent multiple drug abuse, particularly of heroin.[45,46] However, if metabolic pathways were altered quantitatively or qualitatively, such as in individuals with atypical cholinesterases, with administration of microsomal enzyme inducers or plasma esterase inhibitors, or after exposure to massive doses of cocaine,[36,44] increased oxidative metabolism could augment the risk of hepatotoxicity from cocaine.

Altered metabolism and/or impaired clearance of cocaine metabolites may occur in the fetus and newborn. Following maternal cocaine use in pregnancy, benzoylecgonine was found to persist for 4–5 days in the neonate.[47] It has been proposed that significant metabolism, with prolonged exposure, to centrally acting norcocaine may occur in the fetus.

Mechanisms of Action

Cocaine has complex and incompletely understood actions on nerve conduction, and on autonomic sympathetic and central nervous system function. Actions are consequent to additive effects on many neurotransmitter systems and altered neural conduction. Several types of binding sites for cocaine have now been demonstrated in both central and peripheral nervous systems.[48]

Local Anesthetic Effects

Although the precise mechanism of local anesthetic action remains unresolved, cocaine, like many local anesthetics, prevents conduction in nerve fibers by reversibly blocking membrane sodium channels and preventing the transient rise in sodium conductance fundamental to the generation of the action potential.[49-51] Cocaine binds to receptor sites on a specific membrane-bound protein deep within the sodium channel. Binding is strongly voltage-dependent, being favored by depolarization ("use-dependent blockade"), and is relatively prolonged.[52]

In 1918, Sollman observed a more rapid onset of anesthesia after the addition of sodium bicarbonate to cocaine. At alkaline *p*H, cocaine's non-ionized base predominates, allowing better access to internal receptors.[49,53] Local infection, with acid formation, can prevent the onset of adequate anesthesia. However, the cation is the more active form, while the non-ionized base merely aids nerve penetration. Acidosis can prolong an established block, as the cation will be trapped intracellularly.[54]

Cocaine, similar to other local anesthetics, directly affects excitable tissues, including the myocardium. Local anesthetics decrease the rate of depolarization and amplitude of the action potential, slow conduction speed, and increase the effective refractory period. In addition, action potential duration decreases, spontaneous pacemaker activity is depressed, and there is a negative inotropic effect.[55] Cocaine's sympathomimetic properties usually mask these antidysrhythmic and myocardial depressant effects.

Sympathomimetic Actions

Cocaine's sympathomimetic actions make it unique among local anesthetics. Frohlich and Loewi, in 1910, described its ability to sensitize various tissues to the effect of catecholamines. Trendelenburg[56] confirmed that it delayed norepinephrine inactivation. Herrting *et al.*,[57] Muscholl,[58] and MacMillan[59] demonstrated that cocaine actually blocked the re-uptake of norepinephrine and epinephrine into sympathetic nerve endings. Other agents also block this active re-uptake process in either the peripheral or central nervous system, including the tricyclic antidepressants, ketamine, and the anticholinergic, benztropine.[60,61] However, cocaine has effects on behavior and catecholamine metabolism not seen with these other inhibitors of norepinephrine re-uptake. Many investigators believed that re-uptake blockade alone could not account for the extent of cocaine's adrenergic actions, nor its potentiation of methoxamine, which is not a substrate for amine re-uptake.[62-64] Cocaine also may act postsynaptically to produce a change in effector cells, making them capable of generating an increased maximal response. Cocaine also may enhance calcium influx, change the numbers or sensitivity of receptors, or otherwise alter the link between receptor occupation and cell response.[62,64,65]

A functional coupling may exist between amine–re-uptake and presynaptic autoreceptor mechanisms. Re-uptake blockers, such as cocaine, prevent the regulation of neurotransmitter release by exogenous agonists of presynaptic receptors (*e.g.*, clonidine).[66,67] The presynaptic α_2-adrenergic mechanism for inhibition of norepinephrine release appears most effective at low stimulation frequencies.[68] Wilkerson's demonstration[69] that intravenous cocaine produced a several-fold greater rise of blood pressure in nonanesthetized, as compared with anesthetized, dogs, may be explained by several mechanisms. In the awake animals, increased central sympathetic outflow and high peripheral stimulation frequencies decreased presynaptic

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regulation of neurotransmitter release, and monoamine re-uptake blockade. These actions result in both increasing neurotransmitter binding postsynaptically and decreasing negative feedback mechanisms presynaptically. Muscarinic receptors are also blocked by cocaine *in vitro;* their inhibition could functionally enhance cocaine's sympathomimetic actions.[70] Further investigation of these areas may produce a cohesive theory of the many facets of cocaine's sympathomimetic effects.

Cocaine's effects on sympathetic function are stereospecific. Work done before 1925 demonstrated that the dextro-isomer of cocaine, pseudococaine, is a better local anesthetic than cocaine, and several-fold less toxic, with no euphoric effect.[24] It has minimal effect on amine reuptake.[71]

Central Nervous System Effects

In the central nervous system, cocaine affects both neuronal conduction and the function at synapses involving the monoamine neurotransmitters norepinephrine, dopamine, and serotonin, as well as tryptophan and acetylcholine.[72,73] These central electrical and neurochemical effects are interdependent. Cocaine causes brief but intense behavioral stimulation, with euphoria and arousal, and thus is a potent behavioral reinforcer. It has a biphasic action on seizure threshold, being anticonvulsant at lower doses, but convulsant at higher doses.[73]

Considerable evidence links its stimulant properties to effects on monoamines.[73] Central catecholamine turnover amplifies cocaine's peripheral actions by increasing sympathetic outflow. Euphoria may be mediated by acute activation of dopaminergic mesolimbic and mesocortical reward systems.[72] Intact limbic dopaminergic systems are certainly required for the reinforcing properties of cocaine in animals.[70]

The precise site and mechanism of cocaine-induced seizures is unclear. High doses of local anesthetics may selectively block inhibitory pathways in the cerebral cortex, contributing to an excitatory state.[73] However, seizures appear to originate in subcortical areas; the initial reaction to cocaine is often a series of spindle bursts or spike discharges originating in the amygdala or other limbic structures.[50,73,74] Altered turnover of catecholamines and serotonin modulates cocaine's convulsant properties.[73]

Actions of Cocaine

An awake individual's response to cocaine is dependent on dosage, duration of exposure, mode of administration, concurrent medications, predisposition, and environmental setting.[5–8,27,28] The neuropharmacologic and cardiovascular effects of cocaine resemble those of the amphetamines.[72,75] The acute effects are generally brief and intense. In experienced subjects, low doses of intranasal (25 mg), and intravenous (10 mg), cocaine produced noticeable hemodynamic and psychologic effects.[76] With increasing dose, a wider range of symptoms and signs occurs. Occasional early bradycardia may be due to central vagal stimulation.[49] More commonly, sympathetic stimulation results in tachycardia, increased myocardial contractility, vasoconstriction, bronchodilatation, pupillary dilatation, and muscle tremors.[24,49,75,76] Temperature may rise, with stimulation of the thermoregulatory center, increased muscle activity, and decreased cutaneous blood flow. Arousal and euphoria may be followed by dysphoria, anxiety, somnolence, and drug craving.[24,71,76]

The effects of cocaine appear proportional to the *rate* of change of plasma concentration, rather than the absolute level.[33,77] After a single dose, psychologic and cardiovascular effects decline more rapidly than cocaine plasma levels; "acute tolerance" may occur at a receptor level, or be due to redistribution of cocaine from brain to fatty tissue.[77–79] Other peripheral effects of cocaine have been described. For example, cocaine enhances the immune response, increasing natural killer cell activity *in vivo,* and has been shown *in vitro* to enhance platelet aggregation.[80,81]

Clinical Use of Cocaine

Topical Use

After 1924, cocaine was considered safe only for topical use.[5] However, repetitive corneal application results in pits and irregularities, whereas use in the urinary tract was associated with toxicity due to rapid absorption through injured mucosa.[5,13,14,20,82] Today, its primary use is as a topical anesthetic of the upper respiratory tract. Recently, it has been used to provide anesthesia for laser vaporization of the uterine cervix, although little is known about the extent of absorption from this site.[83]

Currently recommended pharmaceutical preparations for topical application are hydrochloride solutions of 2–10% strength. Despite their potential for toxicity, solutions and pastes up to 25% concentration retain popularity, because of claims of more rapid onset, longer duration of action, and better hemostasis. Although injected cocaine as dilute as 0.02% will block terminal sensory fibers, topical anesthesia requires higher concentrations. On the tongue, topical cocaine (4%) has a 4-min latency and 10-min duration; a 20% solution, with epinephrine, acts within 20 s, and anesthesia lasts nearly an hour.[54]

Various additives have been tried in attempts to increase efficacy and decrease absorption. Bicarbonate, originally thought to do this, may actually decrease both latency and duration of topical cocaine, resulting in rapid absorption and early peaking of plasma concentrations.[53,54,84,85]

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In 1903, Braun[86] demonstrated that epinephrine reinforced the anesthetic effects of cocaine. It was also believed to delay systemic absorption of topical cocaine.[26] Since that time, the addition of epinephrine to cocaine has remained highly controversial.[5–7,56,87] Experimental and clinical work indicates that systemic epinephrine potentiates the sympathomimetic effects of cocaine and may precipitate serious dysrhythmias.[5,26,56,88] However, surveys suggest that 30% of responding otolaryngologists, and 70% of plastic surgeons, still routinely use epinephrine with cocaine to improve operating conditions and hemostasis.[13,14] Many commonly use additional submucosal lidocaine with 1:200,000 epinephrine. Although epinephrine was associated with more adverse reactions in one survey,[14] there was no evidence in another.[13]

In 1958, Campbell and Adriani[31] could show no difference in cocaine plasma levels after topical cocaine with or without epinephrine, nor in duration of anesthesia. Recent studies, using more sensitive assays, suggest that epinephrine may significantly reduce cocaine absorption, but unreliably. In a group of patients undergoing nasal surgery, epinephrine added to 4% cocaine solution significantly decreased mucosal absorption and peak blood levels, but had no effect on the peak when added to 25% paste, although blood levels *remained* unusually high (1,000 ng/ml) for 3 h (after which levels were not measured).[81,89] Similarly, epinephrine substantially decreased the nasal absorption of a 1% cocaine–bicarbonate solution (mean plasma cocaine concentrations 990 ng/ml without, and 310 ng/ml with, epinephrine) on average.[90] However, 3 of 15 patients receiving a cocaine-bicarbonate-epinephrine mix developed significant bradycardia, accompanied in one case by ventricular extrasystoles, within 3 min of application. Of these, two patients had unusually rapid absorption of cocaine, described as "idiosyncratic," having the study's highest recorded plasma cocaine levels at 10 min (2,250 and 1,680 ng/ml). These studies suggest that epinephrine substantially reduces the absorption of dilute cocaine solutions applied topically, but does so inconsistently. Table 1 shows the wide range of plasma levels of cocaine achieved in clinical studies, following topical intranasal application of cocaine with or without epinephrine.

Late absorption of cocaine, in the presence of epi-

TABLE 1. Clinical Studies of Intranasal Cocaine Absorption 1976–1988

Author	Cocaine Prep	Dose (mg)	Additives	n	Peak Plasma Levels, Mean ± SD (ng/ml)	Time to Peak (min)	Comments
Van Dyke *et al.* (1976)	10% soln.	1.5 mg/kg	—	9	308 ± 33	60	CV group.
				4	148 ± 19	60	Dental group. Cocaine detectable at 6 hr (59 ± 23)
Miller *et al.* (1977)	10% soln.	~250	*	6	116	60	*1% lidocaine with 1:100,000 epi (10 ml) injected submucosally
	5% soln.	~125	*	2	60	30	Toxic symptoms at 10 min in one patient; blood level 350 ng/ml at 75 min. (No 10-min sample)
	5% soln.	~125	*	1	350	—	
Quiney (1986)	25% paste	500	Suprarenal extract	5	500	40	Sudden late rise observed in 1 patient (1,100 ng/ml at 60 min) after paste
	10% soln. (Moffet's)	200	Epi 1 mg $NaHCO_3$	4	180	10	At 60 min only 5% applied dose absorbed, for paste and solution.
Lips *et al.* (1987)	25% paste	250	—	5	2000 ± 1500	18	Very high bioavailability, as measured by area under curve, for paste
	25% paste	250	Epi 1 mg	5	1600 ± 1400	32	
	4% soln.	160	—	5	500 ± 300	22	Peristent high blood levels for paste with epinephrine
	4% soln.	160	Epi 2 mg	5	30 ± 3	32	No toxic features observed
Bromley and Hayward (1988)	1% soln.	200	$NaHCO_3$	15	990 ± 411	10	Three patients in cocaine with epinephrine group developed bradycardia; two of these had the highest plasma levels at 10 min—2,250 and 1,680 ng/ml
	1% soln.	200	$NaHCO_3$ Epi† 1 mg	15	310 ± 680	10	

Epi, epinephrine.

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nephrine, has also been observed.[85] Van Dyke *et al.*[33] demonstrated that cocaine (without epinephrine) persisted on nasal mucosa for 6 hours. It is possible that sudden late absorption is possible after decay of epinephrine-induced vasoconstriction. Therefore, although epinephrine may limit the rate of absorption of cocaine, there is apparent variability in this effect, which could relate to other factors (*e.g.*, *p*H, cocaine concentration, presence of bicarbonate, status of mucosa), and it cannot be assumed to protect against toxicity in the clinical setting.

Epinephrine has been shown to improve hemostasis only when added to concentrated cocaine preparations.[89,91] This is difficult to explain, considering that epinephrine *does not* affect rate of absorption of the concentrated preparations. Other factors (*e.g.*, platelet function) may be involved in the hemostatic effect. Prospective studies evaluating the value of epinephrine have involved small numbers of patients and have not demonstrated any consistent benefit from adding it to those concentrations of cocaine recommended for clinical use (10% or less).

Cocaine and General Anesthesia

Topical cocaine is commonly applied to patients receiving a general anesthetic. Cocaine affects general anesthetic requirements and the arrhythmogenic properties of some anesthetic agents. In turn, general anesthesia modifies cocaine's sympathomimetic effects and toxicity. Stoelting *et al.*[92] demonstrated a dose-dependent increase in MAC value for halothane (by up to 27%) 3 h after its intravenous administration to dogs, possibly due to increased central nervous system (CNS) catecholamine turnover. Similarly, one anecdotal report attributed awareness during intubation to the prior use of topical cocaine.[93]

Mayer[5] considered that general anesthesia and cocaine led to increased toxicity. Orr and Jones[94] noted severe ventricular dysrhythmias, not observed with lidocaine spray, when cocaine was used for laryngoscopy during thiopental anesthesia. Anderton and Nassar[95] reported self-limiting atrial and ventricular extrasystoles at the commencement of nasal surgery, in 2 of 47 apprehensive young patients. They received only 35 mg topical cocaine during a halothane-based anesthetic.

In contrast, Evangelou and Adriani,[96] observing the effects of intratracheal cocaine (80 mg) in patients deeply anesthetized with cyclopropane, noted fewer dysrhythmias than generally seen. Barash *et al.*[97] could demonstrate no sympathomimetic effect due to nasal topical cocaine (1.5 mg/kg) in well-premedicated, extensively monitored, anesthetized patients presenting for cardiac surgery. Similarly, Lips *et al.*[89] detected no hemodynamic disturbance following intranasal cocaine (160–225 mg), administered after induction of general anesthesia, despite the use of epinephrine.

In all studies in which dysrhythmias were observed, patients were either unpremedicated or anxious, and cocaine was used before, or shortly after, induction of anesthesia and/or laryngoscopy, a procedure known to cause a rise in circulating epinephrine and norepinephrine.[98] In contrast, when cocaine was applied after a deep plane of general anesthesia was obtained, with ventilation well maintained, no cardiovascular effects of cocaine were seen. Thus, *endogenous* catecholamines also have an important role in determining cardiovascular responses to cocaine.

The volatile anesthetics may potentially augment any interaction between cocaine and catecholamines, by sensitizing the myocardium to their effects.[99] In dogs anesthetized with halothane (1%) and nitrous oxide (60%), cocaine (2 mg/kg) substantially lowered the minimal dysrhythmic dose of epinephrine.[100] Ketamine also markedly potentiates the cardiovascular toxicity of cocaine.[100] Alternatively, because deep levels of general anesthesia inhibit adrenal release of catecholamines, cocaine's dysrhythmic effects may potentially be reduced.[97,101]

Drug Interactions

Medical examiner reports involving cocaine suggest that drug interactions may be a prominent cause of morbidity and mortality associated with cocaine use.[102] The most important interactions involve adrenergic neurotransmission.[103–105] Cocaine markedly potentiates both direct-acting sympathomimetics and other vasoactive compounds that are substrate for neuronal amine re-uptake.[56,63,65] A single case report of myocardial infarction in a healthy 28-year-old following topical nasal cocaine may have been attributable to an interaction between cocaine and, initially, epinephrine infiltrated with lidocaine, and subsequently, with ketamine used to treat anxiety consequent to the development of angina.[106] Infiltration of the nasal septum with lidocaine 0.5% with 1:200,000 epinephrine (4 ml), used by many surgeons to elevate the mucosa and decrease bleeding with deep dissection, has been shown to rapidly produce a fourfold increase in plasma epinephrine.[107] Cocaine's actions may augment other direct vasoconstrictors. Severe intraoperative hypertension to 280/130 mmHg and myocardial ischemia was noted after a combination of topical cocaine (100 mg) and felypressin (synthetic polypeptide vasoconstrictor).[108]

Unpredictable but clinically significant interactions have been noted with virtually all classes of psychotropic drugs.[109] Tricyclic antidepressants, which also block monoamine re-uptake, have complex interactions with cocaine. Timing is important. In rats, amitriptyline, administered either 10 days or 1 day before an LD_{50} (lethal dose in 50% of subjects) dose of cocaine, protected against death (0% and 15% mortality, respectively). In contrast, 100% died when it was administered just before co-

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caine.[110] In chronic cocaine abusers, desipramine reduces cocaine-craving.[111] Lithium may decrease cocaine euphoria.[109,111,112] Conversely, naloxone has been reported to augment cocaine euphoria.[113]

Cocaine and other local anesthetics have additive proconvulsant effects.[50] The "ester" local anesthetics, tetracaine, procaine, and chloroprocaine, compete with cocaine for metabolism by plasma cholinesterase, as does succinylcholine. The anticholinesterase, echothiophate, and cytotoxics such as nitrogen mustard, cyclophosphamide, and chlorambucil, may inhibit cholinesterase metabolism of cocaine, and thus potentiate its effects.[114]

Examples of the dangerous interactions that may occur with cocaine have come following the popularity, since 1980, of a solution called TAC in emergency departments.[115] TAC solution contains tetracaine, adrenaline (epinephrine), and cocaine; it is used for topical anesthesia of dermal lacerations, sparing children the fear and pain associated with local anesthetic injections.[115] Its absorption is unpredictable, particularly through mucosal surfaces. Using the recommended 2–5-ml dose of TAC (5 ml contains 25 mg tetracaine, 2.5 mg adrenaline, and 590 mg cocaine), children are exposed to cocaine doses higher than accepted adult limits, as well as significant doses of tetracaine and epinephrine. The death of an infant and other nonfatal toxic reactions have been reported.[116–118] Symptoms of mild toxicity may be overlooked, particularly in children, in the Emergency Room. Toxicity may arise from any of the constituents of TAC alone, or in combination.

Toxicity and Complications

Cocaine toxicity may lead to sudden death.[5,119] Severe reactions are characterized by unpredictability and rapidity of onset.[5] They may be manifest as overwhelming stimulation of the central nervous, respiratory and cardiovascular systems, culminating in seizures, and followed by profound depression and cardiorespiratory collapse.[5,25] Alternatively, cardiac dysrhythmias may progress to ventricular fibrillation.[120,121] Cocaine both increases myocardial work load and decreases oxygen supply due to coronary artery occlusion or spasm, and may induce myocardial ischemia or infarction in susceptible patients.[11,69,121] Recently, Lange *et al.*[122] reported a series of cardiac catheterization laboratory patients who received intranasal topical cocaine (2 mg/kg). In contrast to the control group (normal saline), the cocaine-treated subjects sustained significant increases in heart rate and arterial pressure while coronary blood flood decreased. Angiography revealed an 8–12% reduction in the diameter of the left coronary artery.

Most information regarding cocaine toxicity comes from sources not directly applicable to the operative setting.[9,123] Surveys and isolated case reports suggest that fatalities are rare in the clinical setting, although less severe sequelae are more frequent. A survey of 94,000 rhinoplasties revealed an incidence of 0.3% mild reactions, 0.04% severe reactions, and 0.005% fatalities.[13] When 2,434 otolaryngologists were surveyed in 1977, a total of 492 reactions, with 15 fatalities, were recorded in their lifetime clinical practices.[14] In contrast, when Moore and Bridenbaugh[124] investigated complications in 36,000 patients having regional anesthesia (all local anesthetics), 1.2% had minor systemic toxic reactions, and 0.3% had severe reactions characterized by convulsions, respiratory arrest, or cardiovascular collapse. Similarly, the incidence of convulsions following peridural anesthesia has been variably reported as 0.07–0.44%.[125] This suggests that the use of other local anesthetics is associated with a higher incidence of major reactions, but that prompt treatment results in a better outcome.

Assessment of a lethal dose is difficult because of variability in rate and route of administration, absorption, and metabolism, and individual tolerance. Postmortem blood levels of cocaine must be interpreted with caution, because of the timing of sampling and the possibility of other factors contributing to death. The Drug Evaluation Handbook of the American Medical Association suggests a maximum safe dose of 1 mg/kg for topical use. However, Barash,[7] on reviewing the literature, suggests 1–3 mg/kg. Unfortunately, many application techniques make accurate estimation of the dose administered impossible.[126] Of the 492 reactions reported in 1977, equal numbers were seen above and below an estimated dose of 200 mg (dose range, 10–3,000 mg).[14] Six (6/15) fatalities followed application of less than 200 mg. Importantly, seven deaths were associated with airway endoscopy, and more than half the reactions observed were associated with the use of epinephrine (used in 30% of cases).

Cocaine toxicity relating to the use of epinephrine has been previously alluded to. Early animal experiments demonstrated that epinephrine, used with high doses of cocaine, injected intrathecally, intraperitoneally, or subcutaneously, did not confer protection against toxicity, but delayed it. In many cases, toxicity was actually increased.[26,87] It appears that the influence of stimuli increasing endogenous circulating epinephrine and *norepinephrine* are more commonly associated with cocaine reactions than is the topical application of a cocaine–epinephrine preparation.

Other complications may occur. Anaphylaxis to cocaine is extremely rare, there being only one convincing case in the literature.[7] Numerous medical complications have been observed after illicit use, of relevance to clinical practice. There are three reports of acute aortic dissection in men with underlying hypertension.[127,128] One case was ascribed to the combined use of cocaine and the α-adren-

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ergic nasal spray, oxymetazoline. Cerebral vasospasm and ischemia may be consequent to enhanced noradrenergic and serotonergic activity. Acute vascular events have also been reported in renal and intestinal circulations.[9,129,130] Platelet thrombi have been observed in autopsies, after coronary occlusion.[8]

Hyperpyrexia, with seizures or, in one case, with rhabdomyolysis and acute renal failure, may follow cocaine abuse.[131,132] Hyperpyrexia (to 41° C) with muscle rigidity, including the respiratory muscles, was implicated as the cause of death in a series of seven cocaine "overdoses" in which blood levels were relatively low.[131] During general anesthesia, the fever and sympathomimetic effects of a cocaine overdose could mimic malignant hyperthermia.

In the pregnant patient, uterine vasoconstriction with impaired placental function or placental abruption may follow cocaine's use.[133] A single case of exacerbation of acute porphyria variegata has been reported, as has impaired control of diabetes and precipitation of acute glaucoma.[24,49,134]

Management of Toxic Reactions

Cocaine should not be used clinically without the knowledge, ability, medications, and equipment to rapidly treat sudden unpredictable reactions. Primary efforts should be directed toward maintenance of adequate ventilation, restoration of normal cardiac rhythm and hemodynamics, suppression of seizures, and temperature regulation.[7,135] Hypertension, tachycardia, myocardial ischemia, and dysrhythmias require treatment. Although propranolol has been used successfully to treat the β-adrenergic cardiac effects of cocaine, labetalol potentially offers better hypertension control with α- and β-blockade. The short-acting, but selective, β_1 blockade of esmolol has allowed titratable control of blood pressure, with avoidance of alpha-mediated coronary and peripheral vasospasm.[136–139] Parenthetically, propranolol had minimal effect on the lethal dose of cocaine in dogs.[140] Nitrates, calcium channel blockers, and α-adrenergic blockers also have been useful. In cocaine-intoxicated rats, calcium channel blockers restored cardiac rate and rhythm while improving coronary blood flow, whereas flow and cardiac performance deteriorated after propranolol.[141] Although useful for ventricular dysrhythmias, lidocaine will potentiate cocaine-induced seizures.[7]

The benzodiazepines, which affect on the limbic system, appear the most appropriate therapy for cocaine-induced convulsions. Diazepam antagonizes local anesthetic-induced seizures. In addition, it has anxiolytic and mild muscle-relaxing properties, of potential benefit in cocaine-induced toxicity.[135] In cats given convulsant doses of lidocaine, an equiprotective dose of pentobarbital led to longer sleep times, delayed recovery, and more cardiovascular complications than pretreatment with diazepam.[142] Diphenylhydantoin may actually enhance local anesthetic seizures.[142] Hyperthermia may require treatment with cooling blankets and ice-water sponges. Chlorpromazine has been used to treat the hyperthermia and decrease cocaine's cardiovascular toxicity, but it may lower the seizure threshold.[140,143]

Cocaine as an Analgesic

There has been recent interest in the action of cocaine on the modulation of pain, leading to a reappraisal of the use of cocaine as an adjuvant therapy for chronic pain.

Brompton's Cocktail

In 1896, Herbert Snow prescribed cocaine with opium or morphine for patients with advanced malignancy, maintaining that cocaine helped "sustain vitality."[144] In 1930, a morphine–cocaine elixir was reintroduced as an analgesic post-thoracotomy, at the Brompton Hospital in London. This "Brompton's Cocktail" found a firm place in the treatment of the chronic pain, nausea, and depression of terminal illnesses at St. Christopher's Hospice, and was finally recognized in the "British Pharmaceutical Codex" in 1973. Its formulation was standardized as 10 mg diamorphine hydrochloride, 10 mg cocaine hydrochloride, ethyl alcohol 1.25 ml (90%), syrup 2.5 ml, and chloroform water to 10 ml.[145] Cocaine was added for its central stimulant and euphoric effects. In 1976, Twycross and Gilhooley[145] determined that tolerance to its initial beneficial effects developed rapidly. Others demonstrated that cocaine (10 mg) did not affect analgesia, and occasionally caused restlessness and confusion.[144,146,147] Today, cocaine is generally excluded from these "euphoriant elixirs."

Sphenopalatine Ganglion Block

Cocaine administered intranasally in the region of the sphenopalatine ganglion has been used to treat acute and chronic pain since 1909. Success with the technique was initially reported in "sphenopalatine ganglion neurosis," a syndrome characterized by severe pain radiating from the nose to the occiput, or to the neck, shoulder, and hands, associated with painful vascular and muscular spasms.[148] It has since been advocated for relief of pain involving muscle spasm, neuralgia, vasospasm, reflex sympathetic dystrophy, low back pain, sciatica, and angina.[148–151] It has been successfully used in the treatment of cluster headache.[152] One recent study demonstrated relief of experimental tourniquet-induced ischemic pain, with little change in psychologic status.[153]

The sphenopalatine ganglion has parasympathetic, sensory, and sympathetic functions, with major branches

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to the trigeminal nerve, facial nerve, carotid plexus, and indirectly the superior cervical ganglion; it is known to contain the nerve cell bodies of fibers containing vasoactive intestinal polypeptide (VIP), a neuropeptide modulating vascular tone in the major cerebral arteries, and fibers containing substance P, innervating the mucosa of the upper airway.[154] Double-blind studies are required to determine whether the technique is efficacious, as its advocacy has become a social and political storm center.

Pain Modulation

Historically, anecdotal reports have suggested that cocaine has analgesic properties, although the euphoria produced by the drug has made assessment difficult. In 1910, Ritter[155] operated on awake, calm dogs using intravenous cocaine as an analgesic. In 1924, a patient, under the influence of cocaine, claimed to feel no pain while undergoing suture of a deep wound.[24]

Brain serotonergic and noradrenergic projections from brain stem to spinal cord play an important role in pain modulation. Cocaine, *via* its effects on monoamine turnover, may enhance analgesia. Dextroamphetamine, which increases central catecholamine release, significantly augments morphine analgesia in postoperative patients.[156] Misra and colleagues[71] have shown that cocaine potentiates opiate-induced analgesia in rats. Pseudococaine (*d*-cocaine), which has minimal effect on amine re-uptake, does not potentiate opiate-induced analgesia. An intriguing observation in rats, by Misra *et al.*,[157] showed that implanted cocaine pellets block both the development and expression of tolerance to morphine analgesia. In experimental animals, cocaine administration produces an increase in plasma β-endorphin and significant release from the pituitary occurs with chronic treatment.[158] These areas of research warrant further exploration, and may lead to new, or reuse of old, applications of cocaine.

Alternatives to Cocaine

Regulations and recommendations restricting the use of cocaine have led to a search for alternatives. Although alternatives to 5% cocaine may be readily found, few match the effects of 10% and greater concentrations. There is an abundance of anecdotal information, but a dearth of controlled, investigational data evaluating suitable combinations of agents that provide equivalent operating conditions. As yet, no *single* synthetic topical anesthetic, with lower toxicity, provides similar anesthesia, vasoconstriction, tissue shrinkage, and duration of action.[6]

Tetracaine provides excellent topical anesthesia with a duration comparable to cocaine but with longer latency; it does not provide vasoconstriction. It appeared a suitable alternative until many severe reactions were observed.[6] In 1956, Adriani and Campbell[159] reviewed a number of fatalities resulting from its topical use, and stressed its extreme potency, the sudden onset of syncope and circulatory collapse consequent to rapid systemic absorption, the higher incidence of reactions with topical use *versus* nerve blockade or spinal anesthesia, and the inability of epinephrine to retard its absorption. They concluded that cocaine was the topical anesthetic of choice.

Lidocaine is suitable only for brief procedures, and those not requiring vasoconstriction. Dibucaine use is restricted by its toxicity. Various combinations of agents have been successfully substituted before nasotracheal intubation; lidocaine (4%) with phenylephrine 0.5% had the same effect as 5% cocaine on the severity of epistaxis.§ Lidocaine (3%) with phenylephrine (0.25%) resulted in fewer hemodynamic changes than cocaine or phenylephrine alone.[160] Significant mucosal shrinkage occurred after either cocaine or lidocaine with phenylephrine.[161]

For major otolaryngologic procedures, many surgeons prefer to infiltrate with lidocaine or bupivacaine, and epinephrine. Some stress the importance of freshly added epinephrine, avoiding the low *p*H (3–4.5) of prepackaged antioxidant-containing solutions, as such a low *p*H may increase the latency of anesthesia. Whether topical cocaine is necessary in addition to adequate infiltration requires objective assessment. Pseudococaine was considered a better topical anesthetic than cocaine, but had no vasoconstrictor action.[24] No work appears to have been done evaluating its use in conjunction with an added vasoconstrictor. Until more formal studies are done evaluating combinations of topical and infiltrated agents, global recommendations for alternatives are difficult to make.

Conclusion

Soon after cocaine was introduced to clinical medicine, the virtues of its use as well as risks of abuse became apparent. For the anesthesiologist, cocaine is unique, being the only drug capable of causing local anesthesia and vasoconstriction, and being the prototype of a class of drugs interacting with the autonomic nervous system. Unfortunately, the use of cocaine still presents several dilemmas to the anesthesiologist.

Despite a low incidence of toxic reactions, those that have occurred have been rapid, unexpected, and severe. The role of epinephrine in precipitating toxicity is obscure. Delayed absorption of cocaine may be countered by increased end-organ sympathomimetic response to the combination, and occasional rapid mucosal absorption as vasoconstriction wanes. Dubious clinical efficacy of the combination appears not to justify its use and inherent

§ Mitchell RL, Lecky JH, Levy WJ: A comparison of nasal spray with cocaine, lidocaine/phenylephrine, and saline for nasal intubation. Anesthesiology 61:A217, 1984

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risks. The role of endogenous catecholamines seems at least equally important. Toxic reactions frequently occur during times of stress and sympathetic overdrive. The importance of anesthetic technique has received little consideration in the literature. With greater understanding of cocaine's physiologic effects, and the influence of other pharmacologic agents and anesthetic technique, cocaine toxicity may be avoided.

Finally, cocaine presents many ethical dilemmas to the anesthesiologist. Does ready access to a drug of addiction with maximal reinforcing properties present an unreasonable temptation to physicians? Should patients be exposed to a drug they wish to avoid, even though it has no known addictive risk when used appropriately on a one-time basis as a local anesthetic? If cocaine is found to have considerable benefit in augmenting analgesia, is it appropriate to use it on a chronic basis for the relief of intractable or terminal pain?

As with any anesthetic, successful use of cocaine requires preanesthetic evaluation, adherence to an appropriate dosage schedule, and the ability and equipment to manage adverse side effects. A greater understanding of the complexity of cocaine's actions should enable continued and safe use of this valuable agent.

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