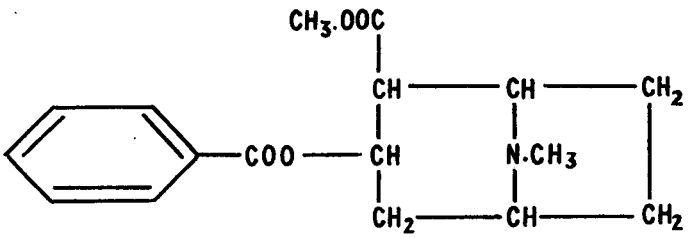
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Cocaine: A review

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COCAINE is an alkaloid which occurs naturally in a concentration of about 1 per cent in the leaves of Erythroxylon coca, a tree indigenous to Peru and Bolivia. Like most local anaesthetics, cocaine has a tertiary amine structure derived from the amino-alcohol base ecgonine which is methylated and esterified with benzoic acid to form cocaine, the full chemical title of which is benzoylmethylecgonine.



Structural formula of cocaine.

Coca leaves have been chewed for centuries by the North Andean Indians for their effect in reducing hunger and increasing work tolerance and resistance to cold. The use of coca leaves is still reported to be widespread in South America. Cocaine was first isolated from the leaves in Germany in 1857 and its local anaesthetic effect was first exploited by Köller in 1884 who used it in ophthalmology. Following Köller's discovery, the use of cocaine topically and by infiltration rapidly became widespread, and despite reports of occasional fatalities, its addictive potential and the introduction of safer synthetic local anaesthetics, it remains the most popular topical anaesthetic in otolaryngology (Johns and Henderson, 1977), particularly for nasal surgery. Its property of causing vasoconstriction as well as local anaesthesia is largely responsible for this but after almost a century of use in medicine and as a drug of abuse, there remain many gaps in our knowledge of its pharmacology and metabolism.

Pharmacology of cocaine

Local anaesthetic actions: Cocaine blocks conduction of nerve impulses when brought into contact with nerve tissue, and concentrations as low as 0·02 per cent will block terminal sensory fibres (Ritchie and Cohen, 1975). Higher concentrations are necessary to block nerve trunks

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and for topical application to mucous membranes. As the concentration of local anaesthetic applied to mucous membranes increases, the latency of the anaesthetic effect decreases and duration of action increases until a concentration is reached beyond which no further changes will occur; for cocaine applied to the tongue this is 20 per cent which gives a latency of 0·3 minutes and a duration of action of 54·5 minutes, a 4 per cent concentration having a four minute latency and a duration of action of about 10 minutes (Adriani and Zepernick, 1964).

C.N.S. actions: The central nervous system is first stimulated then depressed from above downwards. Within a few minutes of administration, cerebral cortical stimulation causes euphoria, garrulousness and excitement; motor activity increases and is well co-ordinated at first until lower motor centres are affected causing tremors and convulsive movements. The respiratory rate increases as the medulla is affected and respiration is rapid and shallow. There may be vasoconstriction and vomiting as the appropriate medullary centres are affected. Spinal cord reflexes increase and tonic and clonic convulsions may occur. When central nervous depression sets in, unconsciousness is followed by death from respiratory depression. In some cases, the depressive phase is reached rapidly and death from respiratory depression may occur without the excitatory phase being clinically evident.

Actions on the sympathetic nervous system: A property of cocaine unique among the local anaesthetics is its ability to enhance the effects of sympthatic stimulation and of catechol amines on sympathetically innervated organs. The actions of adrenaline and noradrenaline whether endogenous or administered clinically are mainly terminated by uptake into sympathetic nerve endings and cocaine blocks this uptake (Muscholl, 1961). Consequently features of sympathetic overactivity are prominent in cocaine overdosage, notably tachycardia, dilated pupils and intense vasoconstriction.

Actions on the cardiovascular system: Very small systemic doses of cocaine cause heart slowing apparently by a central vagal stimulating effect (Ritchie and Cohen, 1975). Larger doses cause an increase in heart rate both by a central effect and by sympathetic stimulation. The rise in heart rate, together with vasoconstriction causes a marked rise in blood pressure. Patients receiving 150 mg. doses of cocaine topically for laryngoscopy have been shown to have a high incidence of cardiac dysrhythmias in addition to rises in pulse and blood pressure (Orr and Jones, 1968). These dysrhythmias can be reversed by propranolol. Sudden collapse due to cardiac depression may also occur (British National Formulary, 1976–8).

Other actions: Cocaine causes a marked increase in body temperature by increasing muscular activity, which increases heat production, and by vasoconstriction which diminishes heat loss. There is no evidence for the commonly held belief that cocaine increases muscular strength, though

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physical endurance is improved because its central stimulating action decreases the sense of fatigue.

Absorption from mucosal surfaces

Topical application is considerably safer than subcutaneous or intravenous administration, but systemic absorption does occur when cocaine is applied to mucosal surfaces and there is evidence that absorption occurs more readily from some sites than from others. Intratracheal administration to rabbits for instance is considerably more toxic than intranasal administration (Aström and Persson, 1961) and a survey of U.S. otolaryngologists conducted by Johns and Henderson (1977) showed that more toxic reactions had occurred when cocaine was applied to the tracheobronchial tree than to any other mucous membrane. The local vasoconstriction caused by cocaine is said to limit its absorption (Ritchie and Cohen, 1975); this means, however, that absorption is likely to continue over a prolonged period since it is not possible to remove all the drug from a mucosal surface even if it is applied on gauze packing. Van Dyke *et al.* (1976) have demonstrated the persistence of cocaine in the nose up to three hours after topical application; they also demonstrated that peak blood levels of the drug were reached 15–60 minutes after nasal administration and that cocaine persisted in the plasma for 4–6 hours. Similar results have been reported by Johns *et al.* (1977) and Miller *et al.* (1977). These findings are surprising in view of the fact that those who abuse cocaine experience their 'High' within 3–5 minutes and dose themselves repeatedly to maintain the effect.

The addition of adrenaline to cocaine solutions is commonly held to lessen the systemic absorption of the latter (Thomson and Negus, 1948; Keogh, 1965) and to improve haemostasis. While this is certainly the case with infiltrational local anaesthetics, there is no evidence that it is true topically. The only experimental evidence is that of Campbell and Adriani (1958) who demonstrated no difference in the blood cocaine levels attained after application of cocaine, and cocaine and adrenaline mixtures, to the pyriform fossae of dogs although the methods of estimation available at the time were not capable of detecting the very low levels obtained in human plasma after clinical application.

It has been said that cocaine is largely hydrolysed when given orally (Ritchie and Cohen, 1975) but this is not the case. Packaged, illicit cocaine swallowed to avoid detection has caused fatalities and a trial comparing blood levels and subjective 'High' ratings after oral and intranasal cocaine has been conducted by Van Dyke *et al.* (1978); this shows no significant difference between the two routes although peak plasma levels occur later after oral administration, possibly because the drug is not absorbed until it reaches the alkaline conditions of the small intestine.

pH has a significant effect on local anaesthetic activity, and the addition

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of sodium bicarbonate to topical cocaine has been shown to increase its efficacy (Sollmann, 1918). This is to be expected because in aqueous solution local anaesthetics dissociate and an equilibrium is established between the uncharged anaesthetic base and its cationic form thus:

$$\text{Base} + H_3O^+ \rightleftharpoons BH^+ + H_2O$$

The direction of the equilibrium depends on the pH of the solution and the pK of the compound, more free base being present at higher pH. It is the uncharged form which is lipid-soluble and diffuses through membranes although there is some evidence that the cationic form actually produces the nerve block (de Jong, 1970). Apart from Moffett's solution which is freshly prepared at the time of use, clinically used cocaine solutions are not usually made up with sodium bicarbonate because the drug is readily oxidized in alkaline solutions. One of the reasons topical anaesthetics need to be at higher concentrations than when they are given by infiltration is that mucous membrane surfaces are less efficient at buffering than tissue fluids and it is necessary to provide more molecules to give sufficient base for diffusion.

It is sometimes said that the higher the concentration of cocaine used, the more potent will be the vasoconstriction produced and the less will be the systemic absorption (Thomson and Negus, 1948). There is little experimental evidence on this point, but a small double-blind study by Miller *et al.* (1977) in patients undergoing rhinoplasty showed peak plasma levels approximately twice as high in those receiving 10 per cent as in those receiving 5 per cent solutions. No differences in the quality of the operative field were noted.

Metabolism and excretion

The full details of cocaine metabolism are not known; a proportion of the drug passes unchanged into the urine (Fish and Wilson, 1969), but most is metabolized with urinary excretion of the metabolic products. Ecgonine methyl ester, the product of cocaine hydrolysis by plasma cholinesterase, is one of the major metabolites, others include benzoyl ecgonine and ecgonine which are produced in plasma by simple hydrolysis (Stewart *et al.*, 1977). Some breakdown of cocaine also takes place in the liver (Inaba *et al.*, 1978).

Dosage

Topically, the maximum safe dose of cocaine is variously quoted as being 100 mg. (British National Formulary, 1976–8) and 200–300 mgm. (Adriani and Zepernick, 1964). These statements are largely empirical, but doses in this range and above are commonly administered by otolaryngologists with few side-effects (Johns and Henderson, 1977). There is no doubt, however, that systemic changes occur with such dosages; in a trial of the systemic effects of intranasal cocaine in regular users, Resnick *et al.*, (1977) showed that 10 mg. produced changes no different from placebo,

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25 mg. gave minimal changes in systolic blood pressure and 100 mg. caused significant rises in heart rate and systolic and diastolic blood pressure as well as changes in various subjective parameters.

Adverse reactions

Feehan and Mancusi-Ungaro (1976) have commented on the 'heavy veil of folklore' which seems to exist regarding the detrimental qualities of cocaine, the mechanism of toxic reactions to which is still not understood. The fact that adverse effects have been reported with doses as low as 10 mg. (Johns and Henderson, 1977) indicates that simple overdose is not the only factor at work although this may well be the case in many instances, particularly with preparations such as cocaine crystals or paste which are difficult to measure accurately.

Incidence: The incidence of toxic reactions is not high. Feehan and Mancusi-Ungaro (1976) in a survey of American plastic surgeons using cocaine for submucous resections and rhinoplasties reported 291 mild reactions, 34 severe reactions and 5 fatalities out of a total of over 108,000 cases.

Features of acute cocaine poisoning: C.N.S. stimulation is particularly prominent and its features include excitement, restlessness, garrulousness, anxiety, headache, increased reflexes and irregular respiration. Nausea and vomiting may occur (Ritchie and Cohen, 1975). The cardiovascular signs are tachycardia, pallor and a rise in blood pressure. Other features are fever, chill and dilated pupils. Later, Cheyne Stokes respiration, convulsions and unconsciousness occur with death resulting from respiratory arrest. Death may occur very rapidly in these cases and prompt treatment is necessary.

Treatment of cocaine poisoning: If it is possible to remove the source of the drug or to limit its absorption in some way this should be done. C.N.S. stimulation is controlled by intravenous administration of diazepam or a short-acting barbiturate such as thiopentone. It may be necessary to institute artificial respiration for respiratory depression. The effects of sympathetic stimulation, particularly if cardiac dysrhythmias occur, may be controlled by a beta-adrenergic blocking agent such as propranolol given intravenously (Orr and Jones, 1968). The outlook should be good if treatment is started in time because the drug will be metabolized fairly quickly.

Prevention of toxic effects: The problem of cocaine reactions has been recognised for many years. In 1924, the American Medical Association set up a committee to investigate deaths resulting from local anaesthetics (Mayer, 1924). Twenty-six of these were attributable to cocaine, six occurred after nasal application and twenty after infiltration for tonsillectomy. The committee recommended the discontinuation of cocaine by infiltration and stressed the need for accurate measurement of topical doses. They also

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noted that toxicity was often greater when 1 mg. or more of adrenaline had been added to cocaine solutions and advised against the use of cocaine 'mud' (cocaine crystals made into a paste with adrenaline solution). Despite this and other warnings, cocaine mud is still widely used in the U.S.A. (Johns and Henderson, 1977).

Premedication with propranolol has been found to be effective in preventing dysrhythmias when cocaine is used to provide surface anaesthesia for laryngoscopy (Orr and Jones, 1968). The risk of dysrhythmias makes ischaemic heart disease a contraindication to the use of cocaine.

Some authors recommend a cocaine sensitivity test. This involves a subcutaneous injection of 10 mg. of cocaine (0·2 mls. of a 5 per cent solution) and taking the pulse every 5 minutes for half an hour. A rise of heart rate of more than 20 per cent is considered indicative of undue sensitivity (Martindale, 1977).

Abuse of cocaine

The drug is sniffed in powder form ('snorting', 'blowing snow') or taken by intravenous injection for the euphoria which it produces. Its effects are apparently of quite short duration and repeated doses are often taken at intervals of ten minutes or so. With continued use, restlessness, tension and paranoia may develop. Heavy users may suffer from weight loss, insomnia, anxiety reactions, formication, hallucinations (particularly of the miniaturized visual variety) and violence (Cohen, 1975). Unlike the opiates, there are no withdrawal symptoms on stopping cocaine although depression may occur after a bout of drug taking ('crashing', 'post coke blues'). Illicit cocaine is expensive and it is unusual for addicts to use cocaine alone, it being much commoner to combine its abuse with a narcotic such as heroin. The fact that cocaine increases sexual awareness and delays ejaculation has led to its use as an aphrodisiac by some.

Other complications of cocaine use

Nose: Nasal septal ulceration and perforation is a well known complication of chronic cocaine abuse and results from mucosal necrosis due to vasoconstriction.

Eye: Clouding and ulceration of the cornea has resulted from repeated use of cocaine eye drops in ophthalmology. Acute glaucoma has been caused by topical application to the eye although cocaine more commonly reduces intraocular pressure.

Ear: Vertigo, nausea and vomiting have been caused by application of cocaine to the middle ear and it should not be used for the removal of foreign bodies in the ear canal (Senturia, 1968).

Larynx: The potential danger of aspiration occurring when cocaine is applied to the superior laryngeal nerve or when the drug is applied to the

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nose and runs down to anaesthetize the larynx and pharynx has been commented on by Keogh (1965).

Cholinesterase deficiency: Impaired hydrolysis of cocaine in the plasma of individuals with cholinesterase deficiency has been demonstrated by Jatlow *et al.* (1976). This suggests that untoward reactions could be more likely in such patients although there is no direct evidence for this.

Drug interactions

Cocaine may potentiate the action of concurrently administered adrenaline by its blocking action on catechol amine uptake at adrenergic nerve terminals. The use of the two drugs together has been frowned upon by pharmacologists for this reason (Ritchie and Cohen, 1975). Furthermore, inhalational general anaesthetics such as halothane are known to sensitize the myocardium to dysrhythmias induced by adrenaline (Hall and Norris, 1958) and cocaine has been shown by Koehntop *et al.* (1977) to enhance the ability of adrenaline to induce dysrhythmias during halothane/nitrous oxide anaesthesia.

In a review of the pharmacology of cocaine and noradrenaline metabolism, Smith (1973) discusses several categories of drugs which, like cocaine, act on the adrenergic neurone and could, theoretically at least, interact with cocaine, or cocaine and adrenaline mixtures. These include a number of antihypertensives, tricyclic antidepressants and, in particular, monoamine oxidase inhibitors.

Preparations and application

Cocaine is usually used clinically as the hydrochloride in which form the drug is more readily soluble in water. Solutions of 2–10 per cent are commonly used in E.N.T. practice but solutions up to 20 per cent have been used, particularly for laryngoscopy. Even higher concentrations are obtained with cocaine mud and the popular 25 per cent paste which contains powdered adrenal gland in addition to cocaine and soft paraffin. Apart from adrenaline 1:1000 solution which is added to many cocaine preparations, various substances have been alleged to potentiate the effect of topical cocaine including 0·25 per cent phenol, demulcents, detergents and cations such as Ca^{++}, K^{+}, Na^{+} and Mg^{++}. Adriani and Zepernick (1964) were unable to demonstrate any advantage of these solutions over cocaine alone. Preservatives such as chlorbutol and colouring agents like amaranth are also usually added to clinical preparations.

In the nose, preliminary spraying of cocaine solution facilitates examination and the placement of cotton-wool tipped probes which carry the local anaesthetic preparation. These may be placed either in direct contact with the part to be operated on or if paste is used a wide area of nasal mucosa may be smeared (Thomson and Negus, 1948). Alternatively, the nose may be packed with ribbon gauze or cotton wool moistened and

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wrung out in cocaine solution. The method of postural instillation described by Moffett (1941) involves instilling cocaine solution into the nose with the head in three different positions to bathe the whole mucous membrane. Nerve trunk anaesthesia is also of value in nasal surgery. Two probes are used, one is passed backwards under the middle turbinate and is lodged between the posterior end of the middle turbinate and the septum where it lies over branches of the pterygopalatine ganglion. The second is placed as high up and as far forward as possible to anaesthetize the anterior ethmoidal nerve. Whichever method is used, adequate time should be allowed for the anaesthetic effect to reach its maximum; this is 15–20 minutes.

The pharynx may also be sprayed with cocaine solution to suppress gagging and permit indirect laryngoscopy. The patient holds the solution in the throat for as long as possible, then spits it out. Procedures which require instrumentation of the larynx and pharynx are nearly always performed under general anaesthesia nowadays but satisfactory local anaesthesia of the pharynx and larynx can be obtained by spraying followed by application of a cotton wool swab wrung out in cocaine to each pyriform fossa in turn. This blocks the internal laryngeal nerves as they run under the pyriform fossa mucosa.

Uses of cocaine

Cocaine is no longer given by infiltration because of its high toxicity. Its principal clinical use is as a topical local anaesthetic particularly for nasal surgery. Not only does it provide very effective surface anaesthesia but the vasoconstriction it causes lessens operative bleeding and, by shrinking the mucosa, makes visualization and access easier. The latter property is often utilized when there is no need for anaesthesia as in clinical examination of the nose (Thomson and Negus, 1948) and in nasal surgery performed under general anaesthesia (Ballantyne, 1973).

It is now used much less frequently than formerly on other mucous membranes for such procedures as laryngoscopy. Cocaine is commonly given orally in combination with diamorphine for the relief of terminal pain but its euphoric effect has not been found to be of any value in the treatment of endogenous depression (Post *et al.*, 1974). More esoteric uses of cocaine include nasal application for the treatment of migrainous neuralgia (North, 1971), and essential parosmia (Zilstorff, 1966). Its application by laryngeal spray has been advocated for acute oedema of the larynx, adductor spasm and for the relief of pain in advanced laryngeal tuberculosis (Thomson and Negus, 1948). Thomson and Negus also recommend cocaine spray for the diagnosis of nasal lupus vulgaris, it demonstrates the characteristic 'apple jelly' nodules by blanching the surrounding tissue in the same way as pressure of a glass slide does this on the face.

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Summary

Current knowledge of the pharmacology of cocaine is summarized and discussed.

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