Editors' view

Dysrhythmias associated with cocaine overdose

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In the Journal this month we publish a short themed section on cocaine-associated cardiac dysrhythmias [1–3]. Cocaine is a weak base extracted from the South American plant *Erythroxylon coca*. Leaves of this plant have been chewed by Amerindian peoples for thousands of years, making it one of the most venerable of 'lifestyle drugs' [4], and its numbing effect on the tongue and buccal mucosa was known before Christopher Columbus's voyage of 1492. The alkaloid was first isolated and proposed as a local anaesthetic in 1860. Sigmund Freud tried (unsuccessfully) to harness its 'psychic energizing' properties for therapeutic use, but also gave a sample to a Viennese ophthalmologist friend, Karl Köller, who reported on the use of cocaine eye drops as a local anaesthetic in 1884. This was rapidly adopted and the use of cocaine was soon extended to dental and general surgery. Procaine was synthesized in 1905, followed by other synthetic substitutes that also lack psychic and vasoconstrictor effects, but cocaine continues to be used to this day in ear nose and throat surgery, since it readily penetrates mucous membranes following topical administration by spray and its intense vasoconstrictor sympathomimetic action is an advantage to the surgeon in this setting.

The physical harm and social mayhem caused by cocaine as a drug of abuse in the 20th and 21st centuries followed, ironically, from increased purity of illicit supplies of the drug. This resulted from an extraction process based on manipulating its ionization, by altering the pH of an aqueous 'mulch' and extracting uncharged base into an organic solvent, which is then evaporated (petroleum is said to be favored by small producers who sell to criminal organizations). Subsequently, a new set of medical problems has arisen from deliberate adulteration and 'cutting' of the pure drug.

Much of the human morbidity/ mortality that cocaine causes is related to its addictive properties. These result from activation of the mesolimbic dopaminergic reward pathway via increased extra-neuronal dopamine in the

nucleus accumbens [5]. The same pathway is activated by virtually all drugs of dependence, including nicotine, ethanol, amphetamines, and opioids, as well as cocaine. Other forms of risk-taking (distinct from drug abuse) also activate this reward system – conceivably a selective advantage for a hunter-ancestor faced with a carnivorous quarry at bay, and doubtless a contributor to the 'buzz' of high-risk occupations and leisure activities today. In addition to its local anaesthetic and central nervous system effects, cocaine enhances peripheral sympathetic neurotransmission by blocking uptake 1 (the high affinity transporter that terminates the action of noradrenaline by reuptake into sympathetic nerve endings). Thus, it increases heart rate and systemic blood pressure and is a powerful vasoconstrictor.

Its addictive properties have resulted in large illicit sales world-wide. Wood and Dargan summarise the epidemiology of cocaine use, highlighting the paucity of data on the true prevalence of acute cocaine toxicity in general and of cocaine-induced dysrhythmias in particular [1]. The main countries cursed with illicit production of cocaine are Columbia, Bolivia, and Peru, which between them exported (illegally) an estimated 845 tonnes around the world in 2008. It is thus unsurprising that acute cocaine-related toxicity is a common cause of presentation to accident and emergency departments. In addition to tachycardia and dysrhythmias (the focus of our themed section), other clinical features of acute toxicity include hypertension, agitation and aggressive behaviour, hallucinations, dilated pupils, hypertonia, hyper-reflexia, fits, fever, acid-base disturbance, stroke (both cerebral haemorrhage and infarction), arterial (notably aortic) dissection, acute coronary syndrome, and myocardial infarction. Extreme agitation is associated with increased sympathetic outflow from the central nervous system; coupled with blockade of peripheral noradrenaline transport by uptake 1, this would be expected to result in increased circulating noradrenaline concentrations, as has indeed been observed. Not

surprisingly, acute hypertension and tachycardia can precipitate a catastrophic vascular event in patients with pre-existing vascular disease. However, autopsies of young patients who died following cocaine use have shown that in many such cases death occurs in apparently healthy individuals with no evidence of myocardial damage or coronary artery disease, implicating a fatal dysrhythmia as the likely cause of death.

O'Leary and Hancox [2] describe how the direct effects of cocaine on cardiac ion channels (voltage-gated sodium, potassium, and calcium channels) work in tandem with indirect sympathomimetic effects on the heart and on the coronary vasculature to disrupt the co-ordinated electrical activity of the heart and produce potentially life-threatening dysrhythmias. How is this basic information to be translated into the emergency treatment of cocaine-intoxicated patients? The British National Formulary (www.bnf.org) recommends initial treatment with intravenous diazepam to control agitation and cooling measures for hyperthermia, adding that 'hypertension and cardiac effects require specific treatment and expert advice should be sought'. 'Expert opinion' has a lowly place in the hierarchies of evidence-based medicine gurus – but in our (non-expert) opinion in this case (as in many others) this is extraordinarily good advice: a true expert in human toxicology can avoid tragedy in such cases, if only by protecting the patient from inappropriate interventions. A little learning is a dangerous thing¹, and it is tempting to argue from what seem to be reasonable principles. Faced with a patient who has taken an overdose of cocaine and presents with acute hypertension and a tachyarrhythmia, who would not be tempted to use a β -adrenoceptor antagonist? And yet in this evidence-poor zone, one thing we do know is that both animal experiments and experience with intoxicated human patients point to catastrophic risks that 'serve as the basis for the absolute contra-indication to the use of β -adrenergic receptor antagonists in the setting of cocaine toxicity' [3]. The explanation for the increased risk is uncertain, but enhanced vasoconstriction due to loss of

¹ 'A little learning is a dang'rous thing; drink deep, or taste not the Pierian spring: there shallow draughts intoxicate the brain, and drinking largely sobers us again' (Alexander Pope: 'An essay on criticism') – a complex dose-response relationship, reminiscent of some in immunopharmacology...

β_2 -mediated vasodilatation, as in patients with pheochromocytoma, is one plausible mechanism.

Robert Hoffman [3] gives an insight into true expert thinking in this difficult context. He considers dysrhythmias in the setting of slow-on slow-off (Vaughan Williams class Ic) sodium channel blockade (with prolonged depolarization, characterized by prolongation of the QRS complex as the precursor to ventricular tachycardia, and on occasion a Brugada-like pattern on the electrocardiogram), potassium-channel blockade (QT prolongation, torsade de pointes) primarily of the inward potassium rectifier current, and catecholamine excess. He explains rationales (based on theory, animal experiment and in some cases anecdotal evidence in humans) for what appear as unconventional approaches in some of these settings, including intravenous administration of hypertonic sodium bicarbonate, magnesium chloride, lidocaine (rapid kinetics, class Ib), rapidly eliminated α -adrenoceptor antagonists (e.g. phentolamine), and/ or calcium channel blockers (e.g. nicardipine); and explains the need to avoid class Ia and Ic drugs as well as β -adrenoceptor antagonists. True bench to bedside work; fascinating and logical stuff; just don't try it on your own!

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