



Plants and the Heart

Coca, barley, and the giant reed: the discovery of local anesthetics and their use in cardiology

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About 30 important modern medicines, completely assessed by proper clinical trials, owe their origin in one way or another to plants. Sometimes, as with quinidine, the drug is actually contained within the plant, and on other occasions, as with amiodarone, it was investigation of a plant compound that led to the synthesis of a related, but better drug. So we may ask ourselves the question "How were the plants that yield good medicines discovered in the first place?" Quite often the answer is in folk medicine, long continued trial and error in the community having identified a plant such as the opium poppy as having useful healing properties. But folk medicine is not the only source. Valuable discoveries have been made from veterinary medicine, from large-scale screening programs of plant extracts, from observations by patients themselves, from physicians, and from research in organic chemistry. It is these last avenues of discovery that concern us here, because the local anesthetic action of cocaine was found during a psychiatric study, while lidocaine



Figure 1. Botanical illustration of the coca plant, *Erythroxylon coca* L. Source not identified. All rights reserved.

(lignocaine) was found from a chemical investigation of chlorophyll-defective mutants of barley.

COCAINE

The coca plant, *Erythroxolon coca* L., was sacred to the Incas of Peru, and an account of its properties was published in Seville by Nicholas Mondares in 1565 (Figure 1). Pure cocaine was isolated much later by Albert Niemann

of Gottingen in 1860. It was then used as a mild stimulant, rather like caffeine, and a report that it had helped Bavarian soldiers to counter fatigue led Sigmund Freud to investigate its properties. During one of his experiments, a subject tasted the compound and found that cocaine numbed his tongue, and he mentioned this to one of Freud's assistants, Karl Koller, an ophthalmologist. Koller had been searching for a topical anesthetic for eye surgery, and in 1884 he reported the great value of using cocaine for eye operations. The search then began for a cocaine analog that would be a safe nonirritant injectable local anesthetic, and after many attempts by himself and others, Albert Einhorn of Munich produced procaine in 1910. However, procaine was rapidly metabolized and, finally, in the 1950s, this problem was solved by the introduction of procainamide.¹

The coca plant is a member of the small tropical family *Erythoxylaceae*, which has no other species with medical uses. Coca leaves dried and powdered and mixed with lime are used orally by people in South America to combat fatigue, and allegedly the leaf helps to maintain a good level of blood glucose in spite of a poor diet. Coca-Cola®, introduced in 1886, contained cocaine in the form of coca leaf until 1902. Nowadays cocaine has led

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Dialogues Cardiovasc Med. 2005;10:109-112

to a pernicious form of drug addiction with 13 million addicts consuming over 800 metric tons per annum worldwide.

LIDOCAINE

It is probably safe to say that without the purely academic research of a chemist, lidocaine would never have been discovered, especially since it has nothing to do with the development of cocaine analogs. The story starts in 1933 when Professor Hans von Euler of the University of Organic Chemistry in Stockholm (Nobel prize 1929) pioneered a new concept when he sought to identify chemical differences between genetically different types of plant. For his first study, he chose four chlorophyll-deficient mutants of barley, *Hordeum vulgare* L, which he obtained from the famous Swedish plant geneticist H. Nilsson-Ehle (Figure 2). Extracts of two of them showed UV absorption bands typical for indole derivatives, and he isolated the compound responsible for these bands, which he called "gramine" after the name of the plant family *Gramineae*. On elemental analysis it was C11 H14 N2 with a spectrum similar to that of 2-methylindole.² His assistant Holger Erdtman was given the task of synthesizing the compound and having done so he was disappointed that his compound, 2-dimethyl-aminoethylindole, was not gramine. It was in fact an isomer of gramine and was named isogramine. Chemists would often taste a new compound and when he did so Erdtman found that isogramine numbed his tongue, which gramine did not. Using the starting material of his isogramine synthesis, Erdtman and a young chemistry student, Nils



Figure 2. Botanical illustration of barley, *Hordeum vulgare* L. This is not the chlorophyll-deficient mutant.

Reproduced from: Prof Dr Otto Wilhelm Thomé. Flora von Deutschland, Österreich und der Schweiz. 1885, Gera, Germany. With kind permission from Kurt Stüber, Max-Planck Institut für Züchtungsforschung. © 1999.

Löfgren, prepared a number of analogs, which were tested by Ulf von Euler (Nobel prize 1970) with the support of the Astra company.³ But the compounds were too irritant to use as a local anesthetic and it was not until some years later that Löfgren took up the work again. This time, in 1943, he succeeded in producing an excellent compound that differed from one of the original Erdtman and Löfgren

compounds only by the addition of an extra methyl group in the 6 position of the benzene ring (Figure 3). This was Xylocaine, and clinical trials in Stockholm at the Karolinska Sjukhuset led to it being available in 1948 for general use and marketed by Astra. It was entered under that name in the British Pharmacopeia in 1955, but its generic names became lignocaine in the UK and lidocaine in the USA. Gramine had been isolated by Russian chemists in 1935, and called by them donaxine, from the giant or Asiatic reed *Arundo donax* L, which they investigated because it had been noted that grazing camels refused to eat it! (Figure 4) This plant is the "reed" of the Bible and it is used to make clarinet and organ reeds. The plant family *Gramineae* is now called *Poaceae* (all family names for plants now have to end in *aceae*). It is a huge family with 9000 species and of great importance to man, containing rice, maize, wheat, barley, oats, and sugar cane, among others, but none contain therapeutic compounds—indeed, as we have noted, the actual barley compound gramine is inactive medically. Plants in the family range from humble lawn grasses to giant bamboos.

EARLY USE OF PROCAINE IN CARDIOLOGY

While everyone knows about lidocaine in arrhythmias, it is not well known that the use of local anesthetic agents in cardiology goes back a long way. In the early 1930s, Dr Claude S. Beck was undertaking pioneer cardiac surgery at the Lakeside Hospital in Cleveland, Ohio. He was doing pericardial resection for constrict-

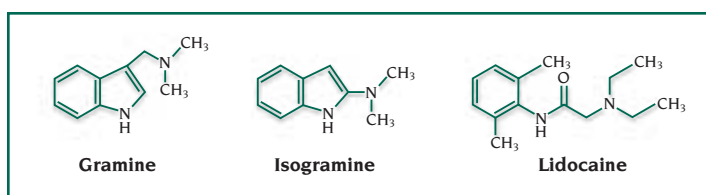


Figure 3. Chemical formulae of gramine, isogramine, and lidocaine (lignocaine, xylocaine).



tive pericarditis, an operation first performed in 1913 by Ferdinand Sauerbruch and reintroduced in 1928, and also attempting to revascularize the heart by suturing a pedicle graft of pectoralis muscle onto the left ventricle. However, arrhythmias during and after surgery, including ventricular fibrillation, presented an important problem, which was investigated experimentally by Dr Frederick R. Mautz. He chose drugs in the cocaine group because they were readily absorbed from mucous membranes and were already known to have some effect on the myocardium. Mautz showed that cocaine produced a monophasic action current in the epicardial electrogram and that it prevented extrasystoles when the heart was stimulated electrically. Beck put procaine hydrochloride into the pericardial sac, with some benefit.⁴

However, the short life of intravenous procaine due to metabolism by esterase enzymes in the blood, plus a high incidence of central side effects, made it a nonstarter for the treatment of arrhythmias. Fortunately, the formulation and introduction in 1951 of procainamide, which was enzyme-resistant and active by mouth, overcame these problems, and the drug became widely used both acutely and chronically for atrial and ventricular arrhythmias. Nevertheless, after it was found that about 80% of patients developed antinuclear factor (ANF) antibodies and 30% got the systemic lupus erythematosus (SLE) syndrome, procainamide had to be withdrawn for the long-term prevention of arrhythmias. Currently, it is hardly used, though it does have one interesting application in that it can unmask the typical electrocardiogram of the Brugada syndrome when this is initially absent.

THE RISE AND FALL OF LIDOCAINE

When Xylocaine, as it was then known, came onto the market in 1948, its main use was as a very effective local anesthetic, especially for dental surgery, but it was not long before its value in cardiology was appreciated with a paper in 1950 by J. L. Southworth et al.



Figure 4. Botanical illustration of the giant, or Asiatic, reed, *Arundo donax* L.

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They reported an adult with congenital heart disease in whom ventricular fibrillation (VF) developed during right heart catheterization. Although six electrical countershocks over a period of 40 minutes proved ineffective,

intracardiac lidocaine enabled a seventh shock to restore sinus rhythm.⁵ Lidocaine was soon found to be very effective for ventricular, but not for atrial arrhythmias. The development of coronary care units (CCUs) from 1962 onwards gave a great impetus to the study and management of arrhythmias with acute myocardial infarction (MI), and it was shown by D. G. Julian et al in 1964 that ventricular ectopic beats, especially if they were of the R on T variety often presaged the onset of VF, but that in some cases, especially if the VF developed early, there was no warning.⁶ From an analysis of 600 patients, D. M. Lawrie et al showed that although the risk of VF was greatest in the first few hours after the start of symptoms, when VF developed early in the course of infarction it was seldom preceded by warning arrhythmias.⁷ In 1967, B. Lown et al published a very influential paper based on 130 patients in a CCU, of whom 78% had ventricular arrhythmias. If they were of a certain type, lidocaine was given to suppress them, and no patient developed primary VF. There was no statement as to how soon after the onset of symptoms the treatment was given, nor about the number of patients treated. Lown wrote, "For the first time, it has become materially possible to reduce death resulting from arrhythmias in hospitalized patients with acute myocardial infarction."⁸ This practice was enthusiastically adopted in many hospitals, overlooking the fact that most of the deaths from primary VF occur early without warning arrhythmias. It was true that lidocaine would abolish about 90% of frequent ventricular extrasystoles with acute MI,⁹ and an overview in 1988 from 14 randomized trials showed that prophylactic lidocaine reduced the odds of VF by about one

third.¹⁰ However, it was also the case that this treatment increased the odds of early death by one third: patients given lidocaine were dying from asystole.¹⁰ Carruth and Silverman questioned the use of prophylactic lidocaine. They analyzed 2200 admissions to their CCU (1200 were later documented as having acute MI) and if lidocaine had been given routinely to all, irrespective of arrhythmias, it would have been of no use in the 97% who did not develop VF.¹¹

Prophylactic lidocaine is now no longer used for the prophylaxis of VF in acute MI and the main indication for lidocaine is for its very effective termination of episodes of ventricular tachycardia. It is not recommended for out-of-hospital prophylaxis of ventricular arrhythmias in suspected acute MI.

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