PLANTS IN CARDIOLOGY

Verapamil and morphine

When the unripe seed capsule of the opium poppy *Papaver somniferum* (Papaveraceae) is incised a milky fluid exudes. The dried juice, opium (from the Greek, opos, juice), has been used medicinally for over 5000 years. The 25 or so alkaloids of opium belong to two distinct chemical classes with quite different actions. Morphine and codeine belong to the phenanthrene class. Papaverine, which accounts for only 1% of the alkaloids, is in the benzylisoquinoline class and was isolated in 1848. But its lack of analgesic activity inhibited pharmacological investigation until 1917 when David Macht initiated this at Johns Hopkins Medical School. Because it relaxes smooth muscle it is a good vasodilator; in cardiac muscle it depresses conduction and prevents chloroform induced ventricular fibrillation. But Paul D White found it to be of little use in angina or hypertension and it was tried without success in cardiac arrhythmias. Nevertheless, papaverine and its synthetic analogues were popular as anti-spasmodic drugs for gastrointestinal and genitourinary ailments and in 1937 the German pharmaceutical firm Knoll asked their chemist, Ferdinand Dangel, to synthesise it. He worked on the compound for over 20 years and in May 1959 he produced an analogue, D365 (D for Dangel), which was soon shown to be pharmacologically much more active than other analogues or similar other drugs. Unlike other vasodilators it had negative inotropic and chronotropic effects. It wasiproveratril, later to be called verapamil, and was marketed as Isoptin. Because it was thought to be a β blocker clinical trials in angina began in 1961. Fleckenstein’s study of verapamil started in 1963 and led to his seminal discovery of calcium antagonism as its mode of action. In 1972 Schamroth, Krieker, and Garrett (*British Medical Journal* 1972;4:660–2) were the first to link the clinical action of verapamil in terminating arrhythmias with Fleckenstein’s concept of calcium channel blockade.

Morphine, still pre-eminent for pain relief, was formerly valuable in acute left ventricular failure, and in 1942 Crichton Bramwell and J T King said, “morphine acts on a specific and what is more it is the only drug which is effective.” *Papaver somniferum* originated in the western Mediterranean and is cultivated chiefly in Asia and Tasmania. Its seed is free of opium and is used on bread. The poppy family, Papaveraceae, has 23 genera and 210 species, mostly in the northern hemisphere. None of its other species has alkaloids that are either better or different from those in the opium poppy.

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