Case study

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Background

During a dissection practical in the Anatomy Department of the University of Pretoria, students found an unknown tablet in the rectum of a male cadaver (Fig 1). The deceased was approximately 68 years of age and the cause of death was not known. However, it was noted that the deceased had an enlarged heart with ventricular hypertrophy.

On examination of the tablet, it was found to be brownish of colour, round and approximately 9mm across. It also had a small pin-sized orifice in the centre on the one side. The tablet also had a soft capsule-like texture. When pressure was applied to the tablet, liquid oozed out from the orifice – this was a critical observation.

These features are congruent with that of Adalat XL tablets (Fig 2). Although Adalat XL is rusty-pink in appearance, it was thought that the specimen tablet had discoloured somewhat with its passage through the gastro-intestinal tract and eventual time spent in the rectum.

Fig 1

Adalat XL® 30mg contains the active ingredient, nifedipine.

Fig 2

Clinical pharmacology of nifedipine

Nifedipine is a calcium ion influx inhibitor (slow-channel blocker or calcium ion antagonist) and inhibits the trans-membrane influx of calcium ions into cardiac muscle and smooth muscle. The contractile processes of cardiac muscle and vascular smooth muscle are dependent upon the movement of extracellular calcium ions into these cells through specific ion channels. Nifedipine selectively inhibits calcium ion influx across the cell membrane of cardiac muscle and vascular smooth muscle without altering serum calcium concentrations. It is indicated for use in and treatment of angina and hypertension.

Angina

The precise mechanism by which inhibition of calcium influx relieves angina has not been fully determined, but includes at least the following two mechanisms:

Relaxation and prevention of coronary artery spasm

Nifedipine dilates the main coronary arteries and coronary arterioles, both in normal and ischaemic regions, and is a potent inhibitor of coronary artery spasm, whether spontaneous or ergonovine-induced. This property increases myocardial oxygen delivery in patients with coronary artery spasm, and is responsible for the effectiveness of nifedipine in vasospastic (Prinzmetal's or variant) angina. Whether this effect plays any role in classical angina is not clear, but studies of exercise tolerance have not shown an increase in the maximum exercise rate-pressure product, a widely accepted measure of oxygen utilization. This suggests that, in general, relief of spasm or dilation of coronary arteries is not an important factor in classical angina.

Reduction of oxygen utilization

Nifedipine regularly reduces arterial pressure at rest and at a given level of exercise by dilating peripheral arterioles and reducing the total peripheral vascular resistance (afterload) against which the heart works. This unloading of the heart reduces myocardial

energy consumption and oxygen requirements, and probably accounts for the effectiveness of nifedipine in chronic stable angina.

Hypertension

The mechanism by which nifedipine reduces arterial blood pressure involves peripheral arterial vasodilatation and the resulting reduction in peripheral vascular resistance. The increased peripheral vascular resistance that is an underlying cause of hypertension results from an increase in active tension in the vascular smooth muscle. Studies have demonstrated that the increase in active tension reflects an increase in cytosolic free calcium.

Nifedipine is a peripheral arterial vasodilator which acts directly on vascular smooth muscle. The binding of nifedipine to voltage-dependent and possibly receptor-operated channels in vascular smooth muscle results in an inhibition of calcium influx through these channels. Stores of intracellular calcium in vascular smooth muscle are limited and thus dependent upon the influx of extracellular calcium for contraction to occur. The reduction in calcium influx by nifedipine causes arterial vasodilation and decreased peripheral vascular resistance which results in reduced arterial blood pressure.

Adalat XL formulations release nifedipine at an approximately constant rate over 24 hours.

In fact, this is a novel and unique oral drug delivery system known as Osmotic controlled Release Oral delivery System (OROS) that releases the drug at a "zero order" rate. It is a complex system, which consists of a tablet core containing a water soluble drug and osmotic agents such as NaCl, mannitol, sugars, PEGs, Carbopol, Polyox, etc. The tablet core is coated with a semipermeable polymer such as cellulose acetate. This semi-permeable coating is permeable to water but not to the drug. A laser-drilled hole, 100-250 µm in size, is created as a drug delivery orifice (Fig 3).

The osmotic pressure of the body fluid is 7.5 atm, whereas the osmotic pressure in an OROS tablet is around 130-140 atm. As a result, aqueous fluid present in the gastrointestinal (GI) tract enters into the OROS tablet through the semipermeable membrane and pushes the drug out through a delivery orifice (Fig 4).

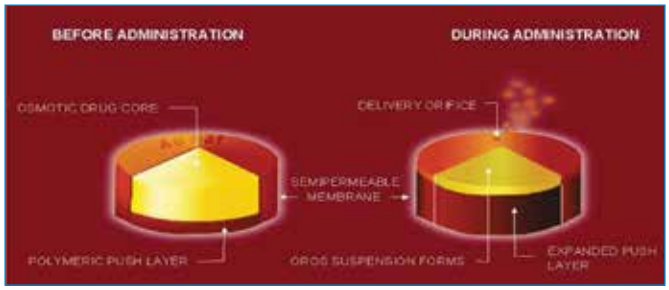

Fig 3

Fig 4

The osmotic pressure of the GI fluid remains constant throughout the GI tract, and as a result, the OROS tablet provides controlled drug release at a constant zero order rate for up to 24 hours. The biologically inert components of the tablets remain intact during gastrointestinal transit and are eliminated in the faeces as an insoluble shell as was found during the dissection practical (Fig 1).