How sumatriptan transformed the lives of millions of migraine sufferers

When Glaxo subsidiary Allen & Hanburys initiated a programme of migraine research in 1972, it would not have expected instant results. But it was nearly 20 years before it was able to launch sumatriptan (Imigran) — the first of a new generation of selective serotonin receptor agonists that was to transform the lives of millions of migraine sufferers worldwide.

Like many other doctors who were involved in the early trials of the drug, Anne MacGregor, clinical research director at the City of London Migraine Clinic, vividly recalls its impact: “We realised it was something really different when our patients told us that, instead of having to stay at home and go to bed when they had a migraine, they were able to get up and go to work,” she says.

Before the arrival of the triptans, standard treatment for migraine was based around aspirin and metoclopramide, and ergotamine. But, since the latter has a narrow therapeutic window, most patients relied on painkillers such as paracetamol, ibuprofen and acetylsalicylic acid (aspirin) and went to work, says Dr MacGregor.

Searching for the right receptor

The idea that serotonin might play a major role in migraine went back to the 1960s, when researchers from three different continents showed that intravenous 5-hydroxytryptamine (5-HT) could abort a migraine attack. Armed with this knowledge, Patrick Humphrey and colleagues in the A & H laboratories set about finding a 5-HT agonist that would mimic serotonin’s beneficial effects while avoiding its side effects. Working on the basis that serotonin alleviated migraine by constricting cranial blood vessels that were inflamed and distended during an attack, Humphrey and his colleagues identified a new serotonin receptor, now called 5-HT1B, which was found mainly in cranial rather than peripheral blood vessels. Hundreds of 5-HT analogues were synthesised and screened for activity against the new receptor, and preclinical studies eventually confirmed the vasoconstrictor effects of GR43175 (sumatriptan) within the carotid circulation. This selective activity at 5-HT1B and, as it turned out, 5-HT1D receptors gave sumatriptan the antimigraine efficacy that was needed, seemingly without the potential for the more generalized effects of less selective compounds.

Clinical trials with subcutaneous sumatriptan showed that 70–80 per cent of patients had reduced head pain by one hour after treatment, and the drug was launched in the subcutaneous formulation in 1991. In subsequent studies of oral sumatriptan 100mg–300mg, around 70 per cent of patients responded to treatment within two hours of administration and this led to the launch of 100mg sumatriptan tablets. A nasal spray also followed.

Safety alert

During the sumatriptan clinical trial programme, 3–5 per cent of patients reported symptoms of pressure and warmth in the chest, but investigations suggested that these were not normally associated with cardiac dysfunction. However, within a short time of sumatriptan’s launch, reports started to accumulate of angina-like chest pain, sometimes with ST elevation on electro-cardiogram. 5-HT1 receptors were not totally restricted to cerebral vessels after all, they were in coronary vessels, too.

“There were huge concerns at the time within the medical profession, especially as migraine is not a life-threatening condition. It became clear that heart disease patients had more 5-HT1 receptors in their coronary arteries than healthy individuals, so there was concern that people who were already at increased risk were being put at even greater risk by taking sumatriptan,” Dr MacGregor explains.

In 1992, the Committee on Safety of Medicines warned against the use of sumatriptan in patients with ischaemic heart disease or Prinzmetal’s angina but, with the future of sumatriptan (and other triptans in development) under threat, a number of studies tried to get to the root of the problem.

Research started to suggest that the chest pain was oesophageal rather than coronary in origin, and that sumatriptan was associated with increased oesophageal contractions and sphincter pressure. In addition, clinical experience was showing that the 100mg dose at which oral sumatriptan was launched was too high, and that a 50mg dose was just as effective at controlling migraine.

“We started to use lower doses of sumatriptan and had fewer patients reporting chest pain. As heart disease is more common in older patients and migraine is more common in younger patients, there wasn’t a lot of crossover between patients who needed sumatriptan for their migraine and those who couldn’t have it because they had heart disease,” says Dr MacGregor.

The controversy rumbled on through much of the 1990s, and doctors tended to reserve sumatriptan for their most severe migraine patients. But eventually the sheer numbers of patients using sumatriptan without mishap and the arrival of rival triptans on the market, ensured the drugs’ continued place in migraine treatment.

Triptans: the next generation

The second generation of triptans got off to an unusual start. By the mid 90s, Glaxo had a second 5HT1 analogue, naratriptan, waiting in the wings. This was a slower onset but more powerful vasoconstrictor than sumatriptan with an apparently placebo-like side-effect profile.

But in 1995 Glaxo merged with Wellcome, which had developed its own 5HT1 analogue called zolmitriptan. The US Federal Trade Commission ruled that having all three drugs in its portfolio would give GlaxoWellcome an unfair monopoly on the migraine market, and required that the company divest itself of zolmitriptan to a company that was capable of marketing it to its full potential. It was arch rival, Zeneca, which...
took zolmitriptan to market in 1997, first in an oral formulation and later as a nasal spray, and provided stiff competition for GlaxoWellcome’s naratriptan. Before long there were four more triptans: rizatriptan, eletriptan, almotriptan and frovatriptan, each boasting unique properties.

Dr MacGregor explains that formulation and cost have proved the key to triptan use in the UK. “Patients who have rapid onset migraine need a really fast acting formulation that can bypass gastric stasis, so the subcutaneous, needle-free and melt-in-the-mouth formulations are very useful for these people. Nasal sprays have been less popular because of their taste. But, overall, most patients use generic sumatriptan because it’s very cheap,” she says.

However, as Dr MacGregor points out, most migraine patients still do not go to their doctor and manage their symptoms with over-the-counter products. Since 2006, GlaxoSmithKline has marketed sumatriptan as a pharmacy-only product, Imigran Recovery, which reaches a significant number of patients whom the triptan era had bypassed as a pharmacy-only product, Imigran Recovery, which reaches a significant number of patients whom the triptan era had bypassed. As such it continues to be popular, and continued to rely on standard treatments for some types of patient,” she says.

Research also continues to investigate the underlying cause of migraine, and vascular and neurological theories have competed for prominence during the nearly 20 years that triptans have dominated the migraine market. Calcitonin gene-related peptide (CGRP) antagonists are being developed for migraine by a number of pharmaceutical companies. Instead of constricting dilated blood vessels like the triptans, CGRP antagonists block vasodilatation of intracranial vessels.

“Sumatriptan started a revolution in migraine treatment, and the triptans are a hard act to follow,” concludes Dr MacGregor. “There are a lot of potentially effective drugs in development but, if they are no better than the triptans, they won’t go anywhere. Sumatriptan’s legacy is that it’s now much harder to get a new migraine treatment on the market, and it’s been a privilege to see the impact of sumatriptan from the start right through to becoming available for patients to buy at the pharmacy. It’s not something that clinicians see very often.”

References