OVER STORY

Cure-all no more

The world's favourite over-the-counter pain remedy, paracetamol, has a dark side, finds Tiffany O'Callaghan

OU'VE got a terrible headache. Niggling knee pain. An aching back. What do you reach for? Chances are that you'll open your medicine cabinet and grab some paracetamol. Half an hour or so later, you'll feel a lot better. Or will you?

Paracetamol, also known as acetaminophen, is the cure-all of our age, used to treat everything from sprained ankles to toothaches and even labour pain. It is on the first rung of the World Health Organization's "analgesic ladder", which doctors use to treat cancer pain. We spoon it to our children to fight fever; as adults we pop it to relieve headaches or period cramps, and as we get older we're prescribed it to soothe arthritis or backache. In the US, 27 billion doses of the drug are sold each year, and it is found in more than 600 products.

Given its ubiquity, you might assume that paracetamol is safe and effective – at least at the recommended dose. That's why we lean on it more than aspirin or ibuprofen, which can irritate the stomach lining and cause bleeding. But as it turns out, this stalwart of the medicine cabinet is not quite as reliably gentle as you might think.

Paracetamol was discovered in the late 19th century, but it was rejected almost immediately because of a bizarre side effect: it seemed to turn some people blue (see timeline, page 36). That was probably because of contamination with a different drug, but as a result paracetamol was sidelined until the 1940s, when further tests showed it was good at reducing fever. Later studies concluded that it was a pretty effective painkiller too. But it really took off in the 1960s, in response to emerging concerns about the long-term side effects of aspirin and other non-steroidal antiinflammatory drugs (NSAIDs). Today in the US, there are about 16,500 NSAID-related deaths a year in people with arthritis alone.

Paracetamol, on the other hand, we think of as relatively safe. Sure, if you take lots of tablets it could seriously damage your liver, but at the recommended dose, it's fine, right?

This assumption is now being challenged by research suggesting that, when taken for prolonged periods, it may damage the stomach as much as NSAIDs. That might be an acceptable risk in exchange for pain relief, but in many of those who take it, paracetamol barely works better than a placebo.

Mysterious drug

How could this be? The fact is, despite its ubiquity, we still don't really understand how paracetamol works. A leading theory is that, in part, it works like aspirin and ibuprofen, by blocking enzymes known as cyclooxygenases. These enzymes are responsible for making hormone-like compounds called prostaglandins, which trigger pain and swelling in the body as well as stimulating production of the mucous that shields our stomachs against digestive acids. NSAIDs halt the swelling process, but leave the stomach vulnerable. The suspicion was that paracetamol inhibited cyclooxygenases, but to a much lesser extent; it doesn't reduce inflammation as these other drugs do.

Although studies in the past decade have hinted that long-term use of paracetamol might trigger internal bleeding, these findings were widely dismissed by critics who cited shortcomings of the study designs. In 2011, however, Michael Doherty of Nottingham City Hospital, UK, published a study that was harder to ignore. He followed the progress of 892 men and women with the niggling knee pain that often sets in at middle-age – usually an early symptom of osteoarthritis. Some were given paracetamol, others ibuprofen, while a third and fourth group took either a high or low-dose combination of the two.

Paracetamol is the first drug most doctors turn to for patients with such symptoms, but when Doherty looked at the blood results of those taking it, he was shocked: levels of haemoglobin, the protein that carries oxygen in the blood, were dropping fast. What's more, their red blood cells were growing smaller and paler. The most logical explanation was that they were losing blood internally, and significant quantities of it. After three months, a fifth of them seemed to have lost the equivalent of an entire unit of blood (about 400 millilitres). That was the same amount as those taking ibuprofen – only the ibuprofen group reported feeling less pain (Annals of the Rheumatic Diseases, vol 70, p 1534).

In those combining high doses of both paracetamol and ibuprofen, the haemoglobin loss after three months was even more startling: 7 per cent of the people in that group lost the amount of haemoglobin you would find in two units of blood. The upshot: when taken for long periods, paracetamol may be just as damaging to the stomach lining as NSAID drugs are.

"The horrifying aspect of this is that people look at me and say 'it's over the counter, it must be safe'," says Kay Brune, a professor of pharmacology and toxicology at the University of Erlangen-Nuremberg in Germany. Brune has been campaigning to have paracetamol removed from over-thecounter sale in Germany, but has so far been unsuccessful. "Before, physicians simply said 'OK, if it doesn't work, it may not do any harm'. But now we know it can do harm," he says.



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