

# Quick, simple test developed to identify patients who will not respond to the painkiller tramadol

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French researchers have found a way to identify quickly the 5-10% of patients in whom the commonly used painkiller, tramadol, does not work effectively. A simple blood test can produce a result within a few hours, enabling doctors to switch a non-responding patient on to another painkiller, such as morphine, which will be able to work in these patients.

Dr Laurent Varin, an anaesthesiologist at the Caen [Teaching Hospital](#) (Caen, France), presented the findings to the European Anaesthesiology Congress in Paris today (Sunday).

Tramadol is a synthetic opioid that is metabolised in the liver via an enzyme called cytochrome P450 2D6 (CYP2D6) to produce a small molecule (or "[metabolite](#)") called O-demethyltramadol (ODT). ODT is between two and four times better at inducing [analgesia](#) than tramadol that is not metabolised successfully. This is because ODT has a 200-fold higher affinity to the opioid receptors in humans than un-metabolised tramadol, meaning that it binds to the receptors more successfully, blocking out the signals for pain.

Dr Varin said: "In our hospital we frequently use tramadol after surgery - about 50-60% of [patients](#) are treated with it, while the rest are treated with nefopam, which is a non-opioid painkiller. However, in about 5-10% of Caucasian patients the CYP2D6 enzyme is inefficient and

does not produce enough ODT to bind effectively to the [opioid receptors](#) ; these patients are known as 'poor metabolisers' and will have poorly controlled pain unless the problem is identified quickly and they are switched to [morphine](#) or nefopam."

In order to identify the "poor metabolisers", Dr Varin and his colleagues decided to investigate the ratio between tramadol and ODT in patients' blood to see if this would give an indication of how efficiently CYP2D6 was working. They recruited 294 Caucasian patients who were receiving tramadol after surgery for a number of digestive conditions such as stomach, bowel and [liver](#) cancer, or for surgery on the spleen, gall bladder or pancreas. They collected blood samples after 24 and 48 hours post-surgery, and tested them for concentrations of tramadol and ODT using "high performance liquid chromatography tandem mass spectrometry", which separates out the different components in the blood.

The researchers also used genotyping to analyse and identify the DNA make-up of the patients to discover which of them had inefficient CYP2D6. This revealed that eight per cent (23) of the patients were "poor metabolisers". Then the researchers assessed the ratio of tramadol to ODT in the blood samples of the "poor metabolisers" and the other patients.

"We found that, after 24 hours, an ODT/tramadol ratio of less than 0.1 indicated a deficient CYP2D6 activity with an accuracy of 87% sensitivity - the test's ability to correctly identify positive results - and 85% specificity - the test's ability to correctly identify negative results," said Dr Varin [1]. "This means that this ratio is highly accurate at detecting 'poor metabolisers' who need to be switched to another painkiller."

Dr Varin and his colleagues believe that the ODT/tramadol ratio gives

doctors a new tool to identify 'poor metabolisers' in the clinic. "This test is simple and cheap, costing only about 30 Euros. It can be performed quickly in just a few hours, instead of many days when the genotyping method is used, and will enable clinicians to make the best treatment choices for their patients. If a patient is suffering unrelieved postoperative pain and the [blood test](#) reveals an ODT/tramadol ratio of less than 0.1, then the clinicians can switch quickly to morphine, rather than trying to increase the dose of tramadol and risk adverse drug effects by overdosing.

"Furthermore, once a patient has been identified as a 'poor metaboliser', this means that other drugs that are also metabolised via CYP2D6 will be less effective, such as codeine and, to a lesser extent, oxycodone, and so this knowledge will help clinicians to decide on alternative treatment strategies for their patients," concluded Dr Varin.

The researchers are continuing to investigate the ODT/tramadol ratio in more patients. The study was carried out in a number of hospitals and so Dr Varin and his colleagues believe their results are independent of the way different hospitals and doctors might prescribe tramadol. They also believe that use of the ODT/tramadol ratio tool could be extended to patients prescribed tramadol in circumstances other than for post-operative pain relief.

**More information:** Abstract no: ESAPC1-5

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