pressant poisoning in people prescribed antidepressants is much higher.[5] Assuming that an average prescription is for one month's treatment, the fatal toxicity index of venlafaxine suggests that it will cause a death from poisoning about every 6000 patient years of use. Clinicians need to consider whether factors in their patients reduce or compensate for this risk before prescribing venlafaxine.

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Drug points

Leflunomide can potentiate the anticoagulant effect of warfarin

V Lim, I Pande

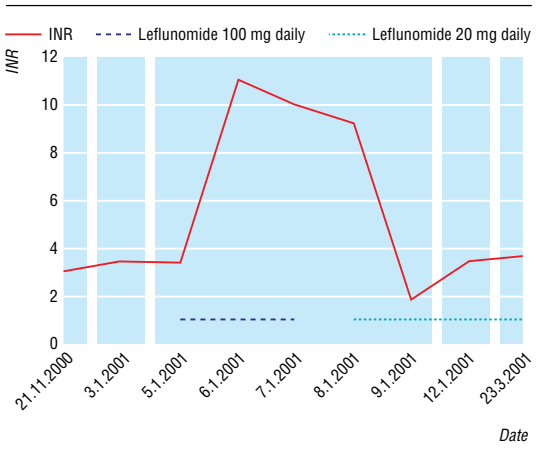
Leflunomide (Arava; Aventis Pharma) is used widely to treat inflammatory arthritis. We report a case of a probable interaction between leflunomide and warfarin.

A 49 year old man with resistant rheumatoid arthritis started taking leflunomide at the recommended loading dose of 100 mg daily for three days. His international normalised ratio had been stable for a year while he was taking warfarin, and two days before starting treatment with leflunomide it was 3.4. After he took the second dose of leflunomide, he developed gross haematuria, for which he required hospital admission. His international normalised ratio had risen to 11, and warfarin was discontinued. His haemoglobin concentration was satisfactory and the haematuria spontaneously resolved several hours after admission. His ratio remained raised for the next two days, even though he had stopped taking warfarin, and he was given 1 mg of vitamin K intravenously on the third day. Twelve hours later, the ratio decreased to 1.9 (figure), which coincided with the change to the leflunomide maintenance dose of 20 mg daily. Subsequently he began taking warfarin again but at a lower dose of 1 mg daily, which was sufficient to maintain his international normalised ratio within the recommended range.

Leflunomide was considered to have caused the increase in the patient's international normalised ratio. Such a role for leflunomide is supported by the temporal relation to the abnormal ratio and the subsequent lower warfarin doses required to maintain the ratio within the normal range. A rechallenge was not possible or ethical.

Leflunomide is rapidly converted to the active metabolite A771726 by first pass metabolism in the gut wall and liver. A771726 inhibits cytochrome *P*-4502C9 and can increase the bioavailability of drugs metabolised by cytochrome *P*-4502C9, such as warfarin and phenytoin. This is important as many patients with inflammatory arthritis also take warfarin. The interaction between leflunomide and warfarin was not detected in clinical trials[1 2] nor is it mentioned in the *British National Formulary*.[3] We found no published reports of an interaction between leflunomide and warfarin.

The first information booklet for healthcare professionals on leflunomide[4] implied that it was metabolised by cytochrome *P*-4502C9 and its effects may be increased, rather than decreased, by warfarin. This was contrary to the pharmacokinetics, according to the summary of product characteristics for Arava.[5] We informed our hospital drug information department, the Committee on Safety of Medicines, and Aventis Pharma. The Committee on Safety of Medicines had received over 300 reports of raised international normalised ratio in patients taking leflunomide concurrently with warfarin. Aventis Pharma has released CD Roms (*Information for professionals* and *Information for patients*), which contain the correct drug information.



International normalised ratio (INR) in relation to leflunomide treatment

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