Drug interactions

Drug interactions that can occur with St John's wort

Good quality information regarding drug interactions with herbal medicines is generally lacking, although the number of studies available is growing. The pharmacokinetic interactions of one herb, St John's wort, are well characterised, but drugs and herbs may also interact by pharmacodynamic mechanisms, and this type of interaction seems to be less well recognised. The following case will be used to highlight some of the interactions of St John's wort.

Case study

A patient taking gabapentin for nerve pain and using the contraceptive pill was admitted to hospital after a car accident. She was given three doses of intravenous pethidine followed by regular paracetamol and tramadol for pain from a broken leg. Within three days she developed tremors, fever, confusion and visual hallucinations. The serotonin syndrome was suspected and so tramadol was withheld and cyproheptadine given. When the patient was quizzed regarding her recent use of medicines, illicit drug use and non-prescription medicines, she mentioned that for several months she had been taking St John's wort. On discussion with the pharmacist she was told that St John's wort can affect the efficacy of hormonal contraceptives, and so she decided to stop taking the herb. A pregnancy test proved negative.

St John's wort is an inducer of the cytochrome P450 isoenzyme CYP3A4, predominantly in the gut, and can therefore increase the metabolism of drugs that are CYP3A4 substrates. Case reports and studies suggest that St John's wort reduces the levels of drugs including ciclosporin, hormonal contraceptives, imatinib, indinavir, oral midazolam and verapamil by this mechanism. Usually dose titration of the affected drug would adequately manage these interactions. However, the interacting constituent of many herbal medicines is unknown and therefore not standardised. Its potency could vary widely between different products and batches of the same product. Therefore managing the interaction safely and consistently becomes difficult. Furthermore, decreasing the levels of drugs that are being given for serious conditions can be extremely hazardous, and it is for these reasons that St John's wort is generally considered to be contraindicated with ciclosporin and indinavir (and other protease inhibitors).

Serotonin syndrome

Serotonin syndrome is thought to arise from over-stimulation of serotonin receptors in the brain. It usually develops when two or more serotonergic drugs are given together. Drugs implicated in this reaction include lithium, metoclopramide, opioids (pethidine, tramadol), sibutramine, selective serotonin reuptake inhibitors, tricyclic antidepressants, triptans and venlafaxine. St John's wort has also been implicated in cases of serotonin syndrome (with venlafaxine and sertraline). Therefore, in the case above, serotonin syndrome may have been caused by a pharmacodynamic interaction between St John's wort and tramadol or pethidine. Caution is generally advised if several drugs with serotonergic effects are given. In practice this probably means being alert for symptoms of the serotonin syndrome, which include altered mental status (agitation, confusion), autonomic dysfunction (diarrhoea, fever, shivering) and neuromuscular abnormalities (hyperreflexia, tremor). The problem usually resolves within about 24 hours if both drugs are withdrawn and supportive measures given. Non-specific serotonin antagonists (such as cyproheptadine) have also been used for treatment. Most patients recover uneventfully, but there have been some fatalities.

Interactions with antiepileptics

The final potential interaction in the case is that of St John's wort and gabapentin. It had been predicted that the metabolism of antiepileptics such as carbamazepine would be increased by St John's wort, but studies suggest any effect is not clinically significant. Nevertheless, the Medicines and Healthcare products Regulatory Agency has received reports of possible interactions with antiepileptics, resulting in reduced antiepileptic effects. These reports have included those antiepileptics that would not be expected to have a pharmacokinetic interaction, such as lamotrigine. The mechanism of this effect is currently unknown. Recent guidance from the MHRA suggests that patients with epilepsy should be advised to avoid St John's wort. At this stage it is unclear whether this advice extends to those taking antiepileptic medicines for conditions other than epilepsy, such as gabapentin for nerve pain. However, some caution would seem prudent. — *Karen Baxter, editor, Alison Marshall, staff editor and Jennifer Sharp, staff editor, Stockley's Drug Interactions*