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Tramadol : new legal classification

Summary

- **Tramadol became a Schedule 3 controlled drug on 10th June 2014. It is classed as a weak opioid with additional effects on serotonin and noradrenaline in the CNS which probably contribute to its analgesic effect.**
- **Prescriptions now need to comply with CD requirements, with the dose being stated, total quantity to be supplied given in both words and figures, also limits to validity of prescriptions and length of supply that can be provided. However tramadol is not subject to storage in a CD cupboard.**
- **The change in legal status presents an opportunity to review current prescribing of tramadol, particularly in primary care. If tramadol is withdrawn after use for more than a few weeks, this should be done slowly to avoid withdrawal symptoms.**
- **There is no alternative analgesic to tramadol that is not a Controlled Drug. However an alternative analgesic strategy for mild-moderate pain is outlined here based on currently available agents.**

Background and Introduction

The UK Home Office announced in March 2014 that tramadol would become a Schedule 3 Controlled Drug, following the finding of an increased number of deaths associated with use of the drug which rose from 83 in 2008 to 175 in 2012 (source: Office for National Statistics(1)). Most of the deaths followed use where tramadol was obtained through non-prescribed means.

Prescriptions for this drug will need to comply with requirements for a Controlled Drug, with the form, strength and total quantity being written in words and figures and the prescription signed by the prescriber, also dated and bearing the address of the prescriber. The new legal classification means that prescriptions are valid for 28 days and no more than 30 days' supply should be dispensed at one time. Prescriptions issued before 10th June which do not comply with these requirements will not be valid after this date.
The NHS England Health and Justice Clinical Reference Group has produced a guide that includes details of changes to the legal status of tramadol; many of the issues considered in the guide apply to all sectors that handle the drug (2).

Clinical issues

Tramadol is a weak opioid agonist with an active metabolite. It has additional actions on central serotonin and noradrenaline neurotransmitters that are thought to add to its analgesic activity.(3) Its popularity as an analgesic for general use has grown over recent years, particularly as problems have been highlighted with other agents such as NSAIDs and use of these agents have become less appropriate for many patients. Tramadol is also perceived to have fewer opioid-related side effects including respiratory depression and constipation than other drugs in this group. At the same time, concern has also grown over the continued rise in use of the drug.(4.5) Reports of dependence and withdrawal symptoms occurred soon after launch of the drug and the MHRA advised in 1996 that prescriptions should be intermittent with a maximum of 3 months continuous use. Tramadol has also been reported cause hallucinations and seizures in susceptible patients (6), and can precipitate serotonin syndrome when prescribed at the same time as other drugs that raise serotonin activity e.g. SSRIs.(3)

The reclassification of tramadol as a Controlled Drug means that its current place in therapy may need to be reviewed and in some cases, clinical use will be restricted due to the need to write individual prescriptions. This may necessitate consideration of alternative analgesics, however there is no straightforward alternative.

If it is considered appropriate to withdraw tramadol in an individual patient, the dose should be reduced slowly to avoid precipitation of withdrawal symptoms. These may include anxiety, nausea, diarrhoea, insomnia, sweating, rigors, pain and tremor but also seizures and hallucinations. A suggested approach would be to reduce the dose e.g. by 50 mg at a time, whilst keeping the dosing frequency the same. There are no studies to inform this and patients would need to be monitored closely.

Analgesic potency

Measurement of relative analgesic efficacy is problematic as effectiveness may vary according to site, cause and severity of pain and there is considerable variation between patients in their tolerance of pain.(7) However the Oxford league table of analgesics website has the best available data from systematic reviews of analgesic

efficacy in acute pain, presented as a league table of Numbers Needed to Treat (or NNT).(8)

In this table, the most effective analgesics have an NNT close to 2, which means that 1 in 2 patients would achieve at least 50% pain relief with that dose of analgesic. For weaker analgesics, NNT is higher – for example, for paracetamol at a dose of 1000mg, NNT is 3.8; for tramadol 100mg it is 4.8. Amongst NSAIDs, NNT for ibuprofen 200mg is 2.7 ibuprofen 400mg is 2.5 and for naproxen 500mg the NNT is 2.7. For paracetamol 1g plus codeine 60mg, the figure is 2.2, but there is no information about co-codamol 8/500 or co-dydramol (insufficient trial data is available for these analgesics).(8)

Less information is available about comparative efficacy of analgesics where these are taken as regular doses several times a day or in chronic pain. Some drugs may become more effective because of accumulation with repeated dosing but equally side effects may become more prominent.

The National Prescribing Centre proposed a pain management strategy following withdrawal of co-proxamol in 2006 and this seems appropriate today, for initial treatment of mild-moderate pain.(9) The steps are summarised below:

Step1: Paracetamol 1g up to four times a day. Regular use is thought to be more effective than single 'prn' doses, but good trial evidence to support this is lacking.

Step 2: Substitute low dose ibuprofen e.g. 400mg three times a day, increased if necessary to a maximum of 2.4g/day. Doses may need to be more frequent if analgesic effect wears off between doses. Note: avoid this step if patient has renal impairment or past history of GI bleed).

Step 3: Add paracetamol 1g four times daily to low dose ibuprofen as described in Step 2.

Step 4: (omit this step if NSAIDs are contraindicated because of past GI bleed or significant renal impairment): Regular paracetamol 1g four times a day, with the addition of naproxen 500mg twice daily instead of ibuprofen. Add proton pump inhibitor cover if patient aged over 65 or otherwise high risk.

Step 5: Add therapeutic dose of weak opioid (e.g. 30-60 mg codeine or dihydrocodeine 30mg) to regular paracetamol and ibuprofen/NSAID. See note below about metabolism of codeine.

Step 6: For the small minority of patients with chronic stable pain who do not respond to the above, consider a trial of tricyclic antidepressant (e.g. amitriptyline) for neuropathic pain or pain that disturbs sleep or antiepileptic (carbamazepine, gabapentin) for neuropathic pain.

Use of strong opioids and/or referral to specialist services should be considered where the strategies outlined above do not resolve the problem (e.g. see SIGN guidance on management of chronic pain, (10)).

The guidance also noted that the use of combination analgesics (e.g. co-codamol) is probably not appropriate until the optimum dose of codeine has been identified in an individual using single constituent analgesics following titration to the optimum dose of codeine. Introduction of fixed combination analgesics may be more convenient for patients in order to reduce the overall quantity of tablets needed, once a suitable therapeutic regimen has been established.

Codeine: The effective dose of codeine may vary considerably between individuals. It has become apparent that there is a diversity of CYP2D6 hepatic enzyme phenotypes in the population which means that some individuals metabolise codeine particularly rapidly to morphine and these individuals may be more susceptible to side effects of codeine, including sleepiness, confusion or respiratory changes. Conversely other patients may be slow metabolisers and codeine may be less effective.(11)
Dihydrocodeine may be an alternative to codeine; there is no data comparing the two. Similar considerations apply in terms of optimising the dose (i.e. it is best prescribed separately until the optimum dose is established). There is little information on use in renal impairment, though its effect appears to be prolonged and respiratory depression is more likely in severe renal impairment.(12) Constipation is inevitable with codeine/dihydrocodeine and advice on this and/or laxatives should always be included when prescribing these weak opioids.

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