

Why is co-proxamol not recommended for prescribing?

Co-proxamol is an analgesic, containing paracetamol 325mg and dextropropoxyphene 32.5mg. It was used very widely for the treatment of mild-to-moderate pain, but its use has now declined due to concerns about the efficacy and toxicity of the product.

Recommendations

- No new patients should be started on co-proxamol.
- Co-proxamol should not be used for any acute pain indication.
- Co-proxamol should not be used in patients under 18 years of age.
- Co-proxamol is contra-indicated in particular groups of people and so should not be prescribed for:
 - Patients who are alcohol-dependent or who are likely to consume alcohol whilst taking co-proxamol.
 - Patients who are suicidal or have history of addiction.
- Carry out a review of patients still being prescribed co-proxamol with a view to switch them to an alternative pain management regime.
- Document clinical reason(s) for continuing to prescribe co-proxamol and efforts made to switch to suitable alternatives.
- Highlight co-proxamol's potential for serious cardiac side-effects, even at therapeutic doses, and make patient aware of the symptoms and what to do if they experience any of them.

Background

The license for co-proxamol was withdrawn on the advice of the Committee on Safety of Medicines amid serious safety concerns in January 2005¹. The withdrawal was phased over two years to allow prescribers and patients time to discuss alternative pain management regimes. The interim prescribing advice for co-proxamol pending its full withdrawal was that it could be used for mild to moderate pain in adults where first line analgesics have proved ineffective or are inappropriate.

Clinical Evidence

Co-proxamol is used to treat mild to moderate pain and is a combination of two

active ingredients dextropropoxyphene (a weak opioid) and paracetamol. The paracetamol content in each tablet is lower dose (325mg) than in standard OTC preparations (500mg).

There is no robust evidence that co-proxamol is more effective than full strength paracetamol used alone in either acute or chronic use. No patient group was identified in which the risk:benefit of co-proxamol was positive².

Compound analgesic preparations that contain a simple analgesic (such as paracetamol) with an opioid component reduce the scope for effective titration of the individual components in the management of pain of varying intensity.

The advantages of using compound analgesic preparations have not been substantiated. The addition of a low dose of an opioid can result in opioid side-effects (e.g. constipation) and can complicate treatment of overdose without any additional pain relief. The elderly are particularly susceptible to the side effects of opioids.

Clinical data shows that dextropropoxyphene, even at normal therapeutic doses, has serious effects on the electrical activity of the heart resulting in prolongation of the P-R and Q-T intervals and widening QRS complexes³.

The licence was withdrawn due to concerns about the high incidence of suicide with the drug. In England and Wales in 1997–1999, 18% of drug-related suicides involved co-proxamol; these constituted 5% of all suicides. The toxic effects of dextropropoxyphene on respiration or cardiac function are usually the cause of death. Death from co-proxamol overdose may occur rapidly, the lethal dose can be relatively low, and the effects are potentiated by alcohol and other CNS depressants. The majority of co-proxamol overdose deaths occur before hospital treatment can be received. The risk can extend to others in the household of the person for whom the drug is prescribed. The risk of dying after co-proxamol overdose was 2.3 times greater than for tricyclic antidepressants and 28.1 times greater than for paracetamol.

Treatment of dextropropoxyphene overdose is not straightforward. Dextropropoxyphene has a very long duration of action so, like methadone, patients need to be monitored for a long periods following overdoses. This can also mean that additional doses of naloxone, which reverses its opioid effects, may be needed.

Since the withdrawal of the licence, the number of deaths associated with co-proxamol has fallen dramatically from 388 in

1999 to 18 deaths in 2011 in England and Wales.

A six-year follow-up study to the withdrawal of co-proxamol reported in 2012 that there has been a significant reduction in poisoning deaths involving co-proxamol without a significant increase in deaths involving other analgesics, even though prescribing of other analgesics rose⁴. However, the results of this study were limited as it only considered deaths mentioning one substance. If deaths mentioning more than one substance are also considered, the number of deaths involving some analgesics has increased. Tramadol death rates are of particular note as they have risen steadily as prescriptions for the drug rose by 42% between 2008 and 2012. There is also evidence that tramadol recreational use has also increased. Therefore prescribers should take care when considering alternative analgesics to co-proxamol.

Co-proxamol is now unlicensed and is only available on a 'named patient' basis. As an unlicensed drug, responsibility for the use of the drug rests solely on the prescriber.

Rationale for switching from co-proxamol to an alternative pain medicine

No patient group has been identified in which the risk:benefit ratio of using co-proxamol is positive.

There is a risk of addiction and abuse associated with co-proxamol.

Clinical data from the USA has shown that dextropropoxyphene can have serious effects on the electrical activity of the heart even at normal therapeutic doses. The lethal dose of co-proxamol is relatively low and can be potentiated by alcohol and other CNS depressants.

Death from co-proxamol overdose can occur

rapidly, even before hospital treatment can be received. The risk of dying after co-proxamol overdose is 2.3 times that for tricyclic antidepressants and 28.1 times that for paracetamol.

The risk of overdose can extend to others in the household of the person for whom the drug is prescribed.

Co-proxamol price comparisons

There is a significant difference in cost of co-proxamol compared to paracetamol and other compound analgesics (Drug Tariff, August 2013)

Product	Cost per 100 tablets
Co-proxamol 32.5mg/325mg	£21.38
Codeine phosphate 30mg	£5.46
Co-codamol 30mg/500mg	£4.93
Co-codamol 8mg/500mg	£3.70
Paracetamol 500mg tablets	£2.94

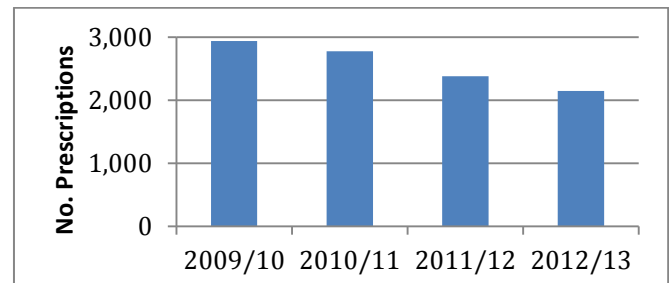
Switching options

Consider a switch from co-proxamol to paracetamol 500mg tablets or capsules at a dose of 1g four times a day. If paracetamol on its own is ineffective, the addition of codeine phosphate might be beneficial. The BNF recommends a dose of 30-60 mg every 4 hours when necessary, to a maximum of 240 mg daily for mild to moderate pain. This dose will need to be reduced in patients with hepatic or renal impairment. It also warns that codeine is too constipating for long-term use.

Alternatively, and if safe and appropriate, consider a switch from co-proxamol to co-codamol 8mg/500mg tablets. Bear in mind that the elderly are more susceptible to the side-effects of opioids.

Use of co-proxamol in Cumbria

The use of co-proxamol in Cumbria has decreased, but there is still about 170 prescriptions supplied each month.



Summary

Co-proxamol still poses a risk to patients. Prescribers should actively review all patients being prescribed this unlicensed medicine and renew efforts to identify and prescribe an effective alternative analgesic.

¹ MHRA Safety warnings, alerts and recalls for medicines: Co-proxamol. Accessed 05/02/13. <http://www.mhra.gov.uk/Safetyinformation/Safetywarningsalertsandrecalls/Safetywarningsandmessagesformedicines/CON1004254>

² The withdrawal of co-proxamol: alternative analgesics for mild to moderate pain. MeRec Bulletin; 2006; 16 (4) 5.

³ (Dextro)propoxyphene: new studies confirm cardiac risks. Drug Safety Update 2011; 4 (6): H1 Accessed 20/02/13. <http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON105759>

⁴ Hawton K, Bergen H, Simkin S, et al. Six-year follow-up of impact of co-proxamol withdrawal in England and Wales on prescribing and deaths: Time-series study. PLoS Med 2012; 9(5): e1001213. Accessed 05/02/13 <http://www.plosmedicine.org/article/info%3Adoi%2F10.1371%2Fjournal.pmed.1001213>