PrescQIPP Community Interest Company

Reviewing existing co-proxamol patients

This bulletin focuses on co-proxamol and provides the rationale for patients to be switched to alternative analgesics and for new patients not to be started on co-proxamol. Information on co-proxamol's market withdrawal, adverse effects, alternative treatment options in support of the switch and potential switch savings are provided. Further support materials are available on the PrescQIPP website, available at www.prescqipp.info

Recommendations

- Do not start any new patients on co-proxamol.[1]
- Review all patients still being prescribed co-proxamol with a view to assess their pain management and switch them to an alternative pain management regime (either drug or non-drug treatment).
- Co-proxamol should not be used for any acute pain indication.
- Co-proxamol should not be used in patients under 18 years of age.[1]
- Co-proxamol is contraindicated in particular groups of people and so should not be prescribed for:[1]
  - 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.
- If a patient is unable to stop co-proxamol, refer them to a specialist for a review of their pain management and support to switch to suitable alternatives.
- Review safe keeping procedures for repeat prescriptions for co-proxamol as the number of forged prescriptions for this drug is on the increase.

Background

The NHS England 'Items which should not routinely be prescribed in primary care guidance' lists products that are regarded as low priority for funding, poor value for money or for which there are safer alternatives (https://www.england.nhs.uk/wp-content/uploads/2017/11/items-which-should-not-be-routinely-prescribed-in-pc-ccg-guidance.pdf). Co-proxamol features on the list as an item that is poor value for money and has limited clinical value with safer treatment alternatives available.

Withdrawal of dextropropoxyphene containing products

Co-proxamol was withdrawn from the market on the advice of the Committee on Safety of Medicines (CSM) amid serious safety concerns in January 2005.[2] The withdrawal was phased over two years to allow prescribers and patients time to discuss alternative pain management regimes. To help prescribers, the Medicines and Healthcare Regulatory Agency (MHRA) provided a number of alternative pain management strategies for mild to moderate pain. 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. All licences for co-proxamol products were cancelled by the end of 2007.[3]

It is estimated that the withdrawal of co-proxamol from the UK has saved around 300–400 lives each year from self-poisoning, around a fifth of which were accidental.[3] When the guidance to cancel all

co-proxamol licences was issued in 2005, the MHRA did recognise that there would be a small group of patients who were likely to find it very difficult to change or where there was an identified clinical need, when alternatives appear not to be effective or suitable. For these patients, continued provision of co-proxamol through normal prescribing could continue until the cancellation of the licences at the end of 2007. After this time, a provision would remain for the supply of unlicensed co-proxamol, under the responsibility of the prescriber. It has now been 10 years since the licences were cancelled and prescribers should review the appropriateness of patients continuing therapy on an unlicensed basis.

In June 2009, the European Medicines Agency recommended a complete review of the safety and effectiveness of dextropropoxyphene-containing medicines. The Agency's Committee for Medicinal Products for Human Use (CHMP) concluded that the benefits of dextropropoxyphene do not outweigh its risks, and recommended that all marketing authorisations for dextropropoxyphene-containing medicines should be withdrawn throughout the European Union (EU).[4] This was later followed and supported by a statement from the Food and Drug Administration (FDA) that the overall balance of risk and benefit can no longer be considered favourable. The agency recommended that propoxyphene products be removed from the US market.[5]

New clinical data in 2011 from the USA showed that dextropropoxyphene can have serious effects on the electrical activity of the heart (resulting in prolongation of the P-R and Q-T intervals, and widened QRS complexes), even at normal therapeutic doses.[3] As a result, products containing this active ingredient, either alone or in combination with acetaminophen (paracetamol), were withdrawn from the US market, and the FDA advised healthcare professionals to stop prescribing dextropropoxyphene to their patients. So, by 2011, recommendations had been made to withdraw co-proxamol for all major markets (UK, Europe and USA).[3]

The Department of Therapeutic Goods Administration (TGA), part of the Australian Government, made a decision to cancel a number of dextropropoxyphene containing products from the Australian Register of Therapeutic Goods (ARTG) due to safety concerns associated with use of medicines containing dextropropoxyphene, including heart rhythm disorder.[3]

As dextropropoxyphene has been gradually withdrawn from all markets, the demand for co-proxamol has decreased. This in turn has increased the costs of the raw ingredients and has given rise to the high costs it has been associated with recently. It is now considered a "special" product and it no longer represents good value for money. It is therefore not a cost-effective product for the NHS. It is expected as more countries withdraw dextropropoxyphene containing products, there will be a further rise in the cost of raw ingredients.

As co-proxamol is now an unlicensed medicine, it has to be obtained from specific suppliers and this can also incur additional costs such as out-of-pocket expenses, e.g. posting, packaging and courier costs, as well as specials costs.

It has been 10 years since the withdrawal of co-proxamol in the UK. Any patients who have been prescribed co-proxamol for chronic pain for the last 10 years should have their pain reviewed in light of current guidance and pain management strategies.

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 contained in each tablet is at a lower (sub therapeutic) dose (325mg) than in standard paracetamol-only OTC preparations (500mg).
- Clinical data from the USA shows that dextropropoxyphene can have serious effects on the electrical activity of the heart (resulting in prolongation of the P-R and Q-T intervals, and widened QRS complexes), even at normal therapeutic doses.[5]
- In England and Wales in 1997–1999, 18% of drug-related suicides involved co-proxamol; these constituted 5% of all suicides. Death usually resulted from the toxic effects of dextropropoxyphene on respiration or cardiac function.[7]

- Co-proxamol was withdrawn from the UK in 2005 amidst safety concerns in therapeutic use, abuse potential and lack of evidence of efficacy. The UK Office for National Statistics (ONS) noted changes in levels and trends in prescribing and deaths following the 2005 announcement of co-proxamol withdrawal. These changes were associated with a major reduction in suicide deaths due to poisoning that equated to 500 fewer deaths occurring between 2005 and 2010 than would have occurred had co-proxamol not been withdrawn. On average, there were 20 co-proxamol-related deaths (suicides and accidental poisonings) per year during 2008–2010 compared to more than 250 per year in the 1990s.[8]
- These findings show that, during the six years that followed the beginning of the phased withdrawal of co-proxamol in the UK, there has been a major reduction in poisoning deaths involving this drug in England and Wales. The findings provide little evidence for an increase in deaths involving other analgesics.[8] However, because the ONS does not distinguish between deaths due to oral and intravenous morphine or between deaths due to morphine and heroin, the researchers did not assess whether there have been any changes in deaths involving morphine since 2005.[8]
- The ONS review did not assess suicides related to the use of multiple drugs or investigate whether suicides involving methods other than drug-related poisoning have increased since co-proxamol withdrawal. Despite these limitations, these findings suggest that the withdrawal of co-proxamol in the UK and possibly elsewhere should have major beneficial effects on suicide rates, at least in the relatively short term.[8]

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

- There is no robust clinical evidence that co-proxamol is more effective than full strength paracetamol in either acute or chronic use.
- There is a risk of addiction and abuse associated with co-proxamol.
- No patient group has been identified in which the risk: benefit ratio of using co-proxamol is positive.
- 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 is an unlicensed medicine so all prescribing responsibility rests solely with the prescriber. If the GP does decide to take on prescribing he/she should consider the GMC guidance around prescribing unlicensed medicines, http://www.gmc-uk.org/guidance/28349.asp
- Anecdotal evidence suggests that the number of forged co-proxamol prescriptions is on the increase.

Alternative strategies for management of long term pain

- Use medication for pain only as part of a wider management plan aimed at reducing disability and improving quality of life.
- Patients should be informed that analgesia will only offer a 30-50% reduction in pain relief.[9,10]
- There is little evidence that one opioid is more effective and associated with fewer side effects than others and that opioids are helpful long term.

During long term treatment with opioids, review at least monthly in the first six months after stable dosing has been achieved.[9,10]

Further information about managing non-neuropathic pain can be found at: https://www.prescqipp.info/resources/send/349-non-neuropathic-pain/3238-bulletin-149-non-neuropathic-pain-briefing

Costs

There is a significant difference in cost of co-proxamol, as it is an unlicensed medicine. The cost of sourcing the raw materials is greater and the charge to the NHS for the tablets can vary, from £55 to £385 (ePACT).

Table 1 below illustrates the cost differences between the average cost of co-proxamol compared to other analgesics. Although this switch away from co-proxamol is primarily for safety reasons, there is a significant difference in cost between co-proxamol and paracetamol.

Table 1: Co-proxamol price comparison with other analgesics for mild to moderate pain – Drug Tariff December 2017[11]

Product	Cost per 100 tablets
Co-proxamol 32.5mg/325mg tablets (average cost)	£164.55 (ePACT)
Codeine phosphate 30mg tablets	£3.50
Co-codamol 8mg/500mg tablets	£2.80
Co-dydramol 10mg/500mg tablets	£2.77
Paracetamol 500mg tablets	£2.00

In England and Wales, over £5.8 million is spent on co-proxamol annually. Reducing prescribing to the levels of the 10% of prescribers nationally could release savings of over £4.5 million. This equates to £7,739 per 100,000 patients. Savings would be offset (minimally) by alternative treatments prescribed if this was appropriate.

Full data pack available at: https://pdata.uk/#/views/B194_Co-proxamolupdateDROP-List/FrontPage?:iid=1

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 at a 'when required' dose might be beneficial.
- For codeine phosphate, the BNF recommends a dose of 30-60 mg every four hours when necessary, to a maximum of 240mg 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.[5]
- Alternatively, and if safe and appropriate, consider a switch from co-proxamol to co-codamol 8mg/500mg tablets or co-dydramol 10mg/500mg.
- Bear in mind that the frail elderly are more susceptible to the side-effects of opioids. It is important to ensure that a patient has a wider pain management strategy in place that is not solely reliant on medication.
- Analgesia may only offer 30-50% pain relief and the patient should be informed of this as part of their review.

In a paper which assessed the systematic overview of co-proxamol to assess analgesic effects of addition of dextropropoxyphene to paracetamol, in both head to head and indirect comparisons of paracetamol and the combination, the combination was no better than paracetamol on its own.[12]

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Additional PrescQIPP resources

Data pack

Available here: https://pdata.uk/#/views/B194_Co-proxamolupdateDROP-List/FrontPage?:iid=1

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