Annex 3

ADVICE ON ANALGESIC OPTIONS IN TREATMENT OF MILD TO MODERATE PAIN

Introduction

The CSM Pain Management Working Group reviewed alternative pain management strategies excluding co-proxamol (paracetamol and dextropropoxyphene) for acute and chronic mild to moderate pain.

The group considered supporting evidence in currently available guidelines on pain management noting in particular the very limited role for co-proxamol.

General Principles

The group reinforced the need for prescribers to adopt general principles of pain management advised by current guidelines. These principles include:

1. Diagnosis Adequate assessment and accurate diagnosis of the cause of acute or chronic pain is essential for specific treatment options to be pursued.

2. Acute on chronic pain Acute pain may arise on a background of chronic pain, for example due to superimposition of osteoporotic vertebral collapse or nerve entrapment upon other pre-existing conditions. Pain management strategy as for an acute episode is advised.

3. Progressive conditions In a proportion of patients the underlying disease will be expected to deteriorate, in both malignant and non-malignant conditions, and the pain management strategy will require continual adjustment.

4. Psychosocial factors may contribute to pain severity, and should be treated and/or referred if necessary.

5. Non-drug interventions should be considered. Topical rubifacients or other therapies, for example, Trans-Epidermal Nerve Stimulation (TENS) may be beneficial to some patients.

6. Pharmacological interventions should be increased to full therapeutic doses before switching to a different agent.

7. Patient requirements All treatment strategies need to be individualised to specific patient needs and tolerance. Particular formulations may meet individual patient needs such as modified release or skin patch presentations.

8. Combination analgesics Individual patient treatment strategies should be worked out on the basis of single constituent analgesics where each component can be titrated independently. Fixed combination analgesics have a limited role in pain management, but may be convenient for patients so as to reduce the overall quantity of tablets. If

Step V: Full therapeutic dose of low potency opioid e.g. codeine or dihydrocodeine in addition to full dose of NSAID or paracetamol.

Most patients will respond to this regimen, but for the small minority who do not:

Step VI: Therapeutic trial of a tricyclic antidepressant (e.g. amytriptyline) or an anti-convulsant (e.g. carbamazepine or gabapentin) for pain which is more complex or difficult to control. Note that the prescriber should check the licensed indications for individual products in these classes.

Class IIb – Chronic long-term pain of a progressive nature

This group includes cancer patients and some patients with neuropathic pain e.g. diabetic patients.

Treatment should follow the guidance for Class IIa chronic pain in relatively stable conditions (see above). If there is a possibility of neuropathic pain an early trial of a tricyclic antidepressant (e.g. amytriptyline) or anti-convulsants (e.g. carbamazepine or gabapentin) should be considered at the outset. In addition, the patient should be reviewed regularly and more potent opioids, eg morphine, oxycodone or fentanyl, should be considered as soon as pain fails to respond to lower potency opioids. This is particularly likely to happen in the case of cancer pain or some severe complex pain syndromes, where there may be a neuropathic component.

[Treatment of severe progressive cancer pain is not within the scope of this advice.]

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October 2004

combination preparations are used, prescribers are encouraged to give therapeutic doses e.g. codeine 30mg and paracetamol 500mg per tablet.

9. Guidelines Additional sources of data on analgesics and published pain management guidelines should be consulted for detailed information. These include the Summary of Product Characteristics and patient information leaflets for specific products, the British National Formulary (BNF), the National Prescribing Centre (NPC), Scottish Intercollegiate Guidelines Network (SIGN), Prodigy NHS, the Pain Society and the World Health Organisation (WHO)[1]. This is not a comprehensive list.

Pain Management Strategies for Acute and Chronic Mild to Moderate Pain

Treatment strategies are considered in the following clinical settings where pharmacological agents can be introduced in a step-wise manner.

1. Acute pain either as a self-limiting episode or upon a background of chronic pain

2. Chronic pain due either to stable or progressive conditions.

Class I – Acute pain either as acute self-limiting episode or on a background of chronic pain: e.g. soft tissue injuries, post-operative pain, osteoarthritis, low back pain, dysmenorrhoea.

Step I: Paracetamol

Step II: Substitute ibuprofen

Step III: Add Paracetamol to Ibuprofen

Step IV: Continue paracetamol and replace ibuprofen with an alternative NSAID

An alternative approach where NSAIDs are contraindicated or not recommended (see product information) is to substitute a low potency opioid e.g. codeine or dihydrocodeine for the NSAID in place of, or in addition to full dose of paracetamol at steps II and III.

Where pain is not controlled on Step IV, a low potency opioid e.g. codeine or dihydrocodeine may be added.

Class IIa – Chronic stable pain requiring long-term regular analgesic use e.g. in osteoarthritis

Steps I to IV above may be effective for many patients.

Where chronic pain is not controlled after Step IV, the addition of a low potency opioid at therapeutic doses should be considered early in the management of chronic pain:

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[1] http://www.bnf.org/
http://www.npc.co.uk/
http://www.sign.ac.uk/
http://www.prodigy.nhs.uk/
http://www.painsociety.org/

Annex 4

MHRA

Medicines and Healthcare products Regulatory Agency

Safeguarding public health

To: Interested organisations and individuals

Date: 30 June 2004

Dear Sir/Madam

REVIEW OF THE UTILITY OF THE PAIN RELIEVER CO-PROXAMOL (DISTALGESIC; COSALGESIC; DOLGESIC) AND REQUEST FOR EVIDENCE ON RISKS AND BENEFITS

INTRODUCTION

1 The Medicines and Healthcare products Regulatory Agency (MHRA) is currently conducting a review of the risks and benefits of co-proxamol, in the light of longstanding concerns about safety and efficacy and more recent data concerning safety in overdose. We are writing to seek your assistance. The evidence currently available to the MHRA indicates that there are possible concerns about whether the benefits of co-proxamol outweigh the risks. We are therefore seeking to obtain any further available information relevant to our review. This includes not only evidence on the general safety and efficacy of co-proxamol, but also evidence as to the balance of risks and benefits in particular patient groups.

2 In the light of further evidence gained in response to this request, the Committee on Safety of Medicines (CSM) will be asked to advise further on the risk: benefit of co-proxamol and on possible regulatory options, set out below. The Licensing Authority will make a final decision after reviewing the evidence and considering the CSM advice.

BACKGROUND

3 Co-proxamol is indicated for *'mild to moderate pain'* with a maximum daily dose of 8 tablets. It contains dextropropoxyphene (32.5mg), a weak opioid analgesic that is known to be toxic in overdose and a dose of paracetamol (325mg) that would on its own be considered sub-therapeutic. Concomitant ingestion of alcohol or other central nervous system depressants significantly increases risk of toxicity.

4. Each year there are 300-400 fatalities following deliberate or accidental drug overdose involving co-proxamol in England and Wales. Approximately one-fifth of these deaths are considered to be accidental. There is growing concern prompted by recently published UK research showing that co-proxamol alone is involved in almost

one-fifth of drug-related suicides and is second only to tricyclic antidepressants as an agent of fatal drug overdose.

5. The National Institute of Mental Health in England (NIMHE) is an organisation set up by the Department of Health aimed at improving the quality of life for people of all ages who experience mental distress. A key goal of NIMHE's National Suicide Prevention Strategy is to reduce the number of suicides as a result of self-poisoning. Reduction of access to means of suicide, such as by limiting the availability of medicines commonly used in self-poisoning, has been identified by NIMHE as an effective method of achieving this goal.

6. Dextropropoxyphene was developed in the 1950's and co-proxamol has been marketed since 1965, long before the current system of medicines regulation existed. As a long established medicine, co-proxamol has not been subjected to modern standards of clinical research; clinical trials were often either poorly designed or of very short duration and many did not produce definitive results. Although co-proxamol is mostly used as a long-term treatment for chronic muscular/skeletal pain in the elderly, most of the studies were in relatively young patients treated for acute injuries, obstetric or post-operative pain. For chronic pain (>48 hours), the analgesic efficacy of co-proxamol has not been demonstrated.

7 The Committee on Safety of Medicines first drew prescribers' attention to the toxicity of co-proxamol in 1985 and advised a series of precautionary measures to reduce the risk of self-poisoning. Key sources of reference information such as the British National Formulary and the National Prescribing Centre (MeReC Bulletin Vol 11, No1, 2000) discourage the use of co-proxamol because it is no/little more effective than paracetamol alone and is significantly less safe than paracetamol.

8 Co-proxamol is licensed in other European countries and actions to reduce usage have taken place over a number of years. In some Scandinavian countries, strict prescribing rules and education of prescribers have reduced the number of deaths due to medicines containing dextropropoxyphene. In the UK products containing dextropropoxyphene only are no longer available and in Northern Ireland dextroproxyphene/co-proxamol has been removed from prescribing formularies.

INFORMATION SOUGHT

9 We would be grateful for:

(i) Any information from clinical trials, observational data or other scientific studies not mentioned in the attached summary, which cast light on the risks and benefits of co-proxamol.

(ii) Any additional evidence to support the use of co-proxamol in specific patient groups, for whom risk: benefit is favourable – identifying the specific indication, dosage and duration of use.

(iii) Any evidence of the impact of local restriction or withdrawal of co-proxamol from use, particularly in relation to other analgesics.

NEXT STEPS

10 Depending on the outcome of the review, a range of regulatory options would be available. These could include:

(i) Restricting the indications – for example to a defined use; duration of use (acute or long term); second line therapy where paracetamol alone has failed; and/or specialist initiation of therapy.

(ii) Further strengthening of warnings in the product information and improvements in label and packaging design with regard to patient safety.

(iii) Widening the range of available pack sizes – currently most manufacturers provide 100 tablet packs (equivalent to 14 days' treatment) but smaller pack sizes may encourage reduced prescribing and prevent retention by the patient of any unused product.

(iv) A co-ordinated programme of education and communication for healthcare professionals to alter prescribing behaviours.

(v) Product withdrawal possibly over a specified timescale.

CIRCULATION OF REQUEST FOR INFORMATION

11 This letter is being sent in hard copy to those organisations listed. Copies are also available from our website - www.mhra.gov.uk – and replies are welcome from all interested parties. A form is attached for your reply. Responses should be addressed to Ms Amanda Lawrence, MHRA, Room 14-152, Market Towers, 1, Nine Elms Lane, London SW8 5NQ (or e-mail amanda.lawrence@mhra.gsi.gov.uk) to arrive no later than **22 September 2004.** Replies received after that date will not be taken into account.

MAKING COPIES OF REPLIES AVAILABLE TO THE PUBLIC

12 To help informed debate on the issues raised by the Agency's review, and within the terms of the Code of Practice on Access to Government Information, the Agency intends to make publicly available copies of replies and supporting information that it receives. Copies will be made available as soon as possible after any regulatory decision has been made. It will be assumed that your reply can be made publicly available in this way, unless you indicate that you wish all or part of it to be treated as confidential and excluded from this arrangement.

13 The Agency's Information Centre will supply copies on request. An administrative charge, to cover the cost of photocopying and postage, may be applied. Alternatively, personal callers can inspect replies at the Information Centre by prior appointment (telephone 020-7084 2351).

Yours faithfully

[redacted]

ANNEX A

SUMMARY OF EVIDENCE ON SAFETY AND EFFICACY OF CO-PROXAMOL

1 Clinical pharmacology

Paracetamol is a non-opioid antipyretic analgesic. When taken orally, it is rapidly absorbed and peak plasma concentrations occur within 30-60 minutes. Unlike dextropropoxyphene, it has a short plasma half-life (2 hours) and does not accumulate. Dextropropoxyphene (DXP) is a synthetic opioid analgesic, structurally similar to methadone. When taken orally, it is rapidly absorbed and peak plasma concentrations occur within 1-2.5 hours of ingestion. Both DXP and its active metabolite norpropoxyphene (NXP) have long half-lives (15-24 hrs for DXP and 23-34 hrs for NXP[1] or longer) so they tend to accumulate with repeated 6 or 8-hourly dosing, especially in the elderly or patients with renal impairment.

2 Toxicity

Paracetamol overdose may result in potentially fatal liver damage, which is preventable if appropriate treatment is given within 24 hours of ingestion. Like other opioids, DXP and NXP depress respiration, but unlike other opioids, they also prolong atrio-ventricular conduction and slow the heart rate, predisposing to cardiac arrhythmias such as torsade de points[1]. This effect on QRS interval appears to be dose dependent[2] and may explain why overdose with co-proxamol is more likely to be fatal than other opioids. Furthermore, as DXP is rapidly absorbed from the gastrointestinal tract, cardiac and respiratory effects appear early, with hours.

3 Interaction with alcohol

Alcohol with co-proxamol is a particularly hazardous combination. In healthy volunteers the concomitant intake of alcohol increased the bioavailability of an oral dose of DXP (130mg) by a mean of 25%[3], by reducing first pass metabolism. A study in Sweden[4] found that of all groups, middle-aged men who are habitual or social drinkers receiving medication for pain were most at risk of non-suicidal death due to co-ingestion of DXP-containing products with alcohol.

4 Mortality data (Office of National Statistics, England and Wales)

The 1974-1983 mortality data published by the CSM in 1985[5] showed that during this period there were approximately 150-200 co-proxamol-related fatalities per year. The Office of National Statistics, UK (ONS) mortality data for 1993-2001 show that there were between 300 and 400 deaths in England and Wales each year where DXP-containing products were judged to cause or to contribute to the death. The majority of these were suicides or open verdicts, with approximately one fifth being due to accidental poisoning.

5 Epidemiological data

A study examining the role of co-proxamol in deliberate self-poisoning[6] showed that co-proxamol alone accounted for 18% of drug-related suicides in England and Wales during 1997-1999 in individuals aged 10 years and over, compared with 22% with tricyclic anti-depressants alone and 9% with paracetamol alone. The authors found that a higher proportion of suicides in the 10-24 age group (expressed as a percentage of all drug-related suicides in age group) were due to co-proxamol than in the other age groups. The authors compared the annual rate of drug related suicides and open

verdicts in England and Wales with the figures for non-fatal self poisoning in Oxford over the same period in order to calculate relative lethality and found that co-proxamol was about twice as likely as tricyclic antidepressants and 28 times as likely as paracetamol alone to have a fatal outcome. The same group also found that young adults aged under 25 years tended to use co-proxamol belonging to a third party[7].

6 Efficacy-Acute studies

There have been very few controlled clinical comparisons of co-proxamol versus low dose paracetamol alone or DXP alone, and most have been single-dose studies. Data from randomised controlled clinical studies have been reviewed in two systematic reviews, described below.

Acute moderate pain

In 1997, Li Wan Po and Zhang[8] reviewed data from 24 randomised, double-blind single oral dose clinical trials, evaluating whether DXP (65mg or 100mg) in combination with 650mg paracetamol (DXP+P) was more effective than paracetamol 650mg alone for moderate pain. The review covered over 2000 patients receiving medication for post-partum or musculoskeletal or arthritic pain or for pain following various types of surgery. Most of the trials were placebo controlled, so two independent sub-meta-analyses were used to produce indirect comparisons between treatments. The indirect comparisons showed that both paracetamol alone and DXP+P had significantly greater efficacy than placebo, but there was no difference between the two active treatments. The three trials where direct comparisons were used (N=301 patients) also showed that the effects of the combination of DXP+P were not significantly different from those of paracetamol alone for pain intensity or rate response ratio.

Moderate-severe post-operative pain

In 1998 Collins et al[9] published a similar systemic review of single-dose trials comparing DXP (DXP HCl 65mg) versus paracetamol 650mg plus DXP (65mg HCl or 100mg napsylate (equivalent)) for moderate-to-severe post-operative pain. Of 130 articles identified, only 6 reports could be used for DXP (440 patients, 214 receiving DXP) and only 5 reports could be used for DXP+P (963 patients, 478 receiving DXP+P). Indirect comparisons were made as the trials were placebo controlled. Both DXP and DXP+P showed significantly greater efficacy than placebo (number needed to treat for one patient to achieve at least 50% pain relief versus placebo were 7.7 for DXP and 4.4 for DXP+P; confidence intervals overlapped). No direct comparison was made with paracetamol.

7 Efficacy-Chronic studies

The efficacy of co-proxamol in chronic use has rarely been studied and cannot be extrapolated from results of short-term or single dose studies. There is potential for accumulation of DXP and its active metabolite over a number of days, with gradual build up to plasma levels 5-7 times greater than that achieved with a single dose. Li Wan Po and Zhang[8] identified two repeat dose studies (Buck, 1978 and Messick, 1979) during their review which failed to demonstrate a beneficial effect of DXP+P over paracetamol but the studies only lasted for 48 hours, which might not fully represent chronic dosing. A double-blind cross-over study[10] in 31 rheumatology patients, who had already been taking co-proxamol for an average of 2 years, compared 1g paracetamol against 650mg paracetamol plus 65mg DXP for one week each at their usual dosage frequency. Significantly more patients preferred the combination, but the study was methodologically flawed.

8 Clinical experience

The view has been expressed that in the experience of some specialists in pain management, pain not controlled by regular dosing with paracetamol alone was relieved by repeat doses of co-proxamol[11]. Patients who attended pain clinics had often tried several compound analgesics and, for some of these, co-proxamol was the most effective therapy, which may have reflected a neuropathic component to their pain that is different to post-operative pain[12].

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4	Jonasson, U, Jonasson, B & Saldeen, T. Preventative Medicine 31 (2000) 103-106. Middle-aged men – a risk category regarding fatal poisoning due to dextropropoxyphene and alcohol in combination.
5	CSM Current Problems 14 Feb 1985. Death with dextropropoxyphene.
6	Hawton, K, Simkin, S & Deeks, J. BMJ Volume 326 (2003) 1006-1008. Co-proxamol and Suicide: a study of national mortality statistics and local non-fatal self-poisonings.
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9	Collins, S L, Edwards, J E , Moore, R A & McQuay, H J. European Journal of Clinical Pharmacology 54 1998 107-112. Single dose dextropropoxyphene in post-operative pain: a quantitative systemic review.
10	Owen M, Hills LJ. Med J Aust 1980;1: 617. How safe is dextropropoxyphene?
11	Marples, I L. BMJ 327 (2003) p 287. Co-proxamol should be restricted not banned.
12	Hanks & Forbes. BMJ 316 (1998) p1980. Co-proxamol is effective in chronic pain.

From : _____
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REQUEST FOR INFORMATION ON CO-PROXAMOL

My reply and supporting information may be made freely available.
My reply and supporting information is confidential.
My reply and supporting information is partially confidential (indicate clearly in the text any confidential elements)

Signed : _____

Delete as appropriate

HARD COPY CIRCULATION LIST

NB: this list is not intended to be exhaustive. Copies of the letter are also available from our website - www.mhra.gov.uk – and replies are welcome from all interested parties.

Acne Support Group
ACEVO
Advanced Life Support Group
Age Concern London
All Party Pharmacy Group
All Party Pro-Choice Group
All Party Pro-life Group
Allergan Ltd
Ambulance Services Association
Antroposphical Medical Association
Aqueous II (NHS Information Authority)
Arthritis Care
Arthritis Research Campaign
Association of Anaesthetists of Great Britain and Northern Ireland
Association of British Cardiac Nurses
Association of British Dispensing Opticians
Association of British Health Care Industries
Association of British Neurologists
Association of British Pharmaceutical Industry (ABPI)
Association of Chief Police Officers
Association of Chief Police Officers Scotland
Association of Clinical Research in the Pharmaceutical Industry
Association of Clinical Research Contractors
Association of Head Teachers
Association of Community Health Councils of England & Wales
Association of Medical Microbiologists
Association of Medical Research Charities
Association for Nurse Prescribing
Association for Residential Care
Association for Sick Children
Association of Hospice Management
Association of Palliative Medicine
Association of Respiratory Nurse Specialist
Association of Scottish Trusts CP (ASTCP)
Association of Surgeons of Great Britain and Ireland
Asthma & Allergy Research
AstraZeneca
ATC
Aventis Pharma Ltd
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BHMA
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Bioindustry Association
Breakthrough Breast Cancer
Breast Cancer Care
British Association for A&E Medicine
British Association of Dermatologists
British Association of Nutritional Therapies
British Association of Optometrists
British Association of Pharmaceutical Physicians
British Association of Pharmaceutical Wholesalers
British Association of Research Quality Assurance
British Acupuncture Council
British Cardiac Patients Association
British Chiropody and Podiatry Association
British College of Optometrists
British Complementary Medicines Association
British Contact Dermatitis Group
British Dental Association
British Dental Association (Northern Ireland)
British Dental Association (Wales)
British Dental Association (Scotland)
British Dental Trade Association
British Diabetic Association
British Dietetic Association
British Epilepsy Association
British Generic Manufacturers Association
British Geriatrics Society
British Heart Foundation
British Institute of Regulatory Affairs
British Medical Association
British Medical Association (Northern Ireland)
British Medical Association (Scottish Branch)
British Medical Association (Welsh Office)
British Medical Journal
British Menopause Society
British Nuclear Medicine Society
Bristol-Myers Squibb
British International Doctors Association
British Oncological Association
British Pharmacological Society (Scotland)
British Pharmacological Society (Wales)
British Pharmacological Society
British Society for Allergy, Environmental and Nutritional Medicine (BSAENM)
British Society for Allergy and Clinical Immunology
British Society for Rheumatology
British Society of Gastroenterology
British Toxicology Society
Brittle Bone Society
Brook Advisory Centres
Burford Research Consultants

Camedica
Cancer BACUP
Cancerline UK
Cancer Research Campaign
Cancer Research UK
Care
Carers National Association
Central Medical Advisory Committee
CCCPH
Central Office for Research Ethics Committees
Cephalon UK Ltd
CMAS
Co-operative Pharmacy Technical Panel
Co-operative Union Ltd Parliamentary
College of Optometrists
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College of Pharmacy Practice
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Commission for Healthcare Audit and Inspection (CHAI)
Commission for Racial Equality
Committee for Practitioners & Health Visitors Association (NI)
Common Services Agency
Community Pharmacy Wales
Community Practitioners & Health Visitors Association
Community Services Pharmacists Group
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Consumers for Health Choice
Council for Professions Supplementary to Medicine
CTPA Ltd
CWS Ltd (Trade Liaison Department)
Dental Defence Union
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Department of Health (UK)
Department of Health Commissions Directory
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