Review

Co-proxamol and suicide: preventing the continuing toll of overdose deaths

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Summary

Restricting means for suicide is a key element in suicide prevention strategies of all countries where these have been introduced. Preventing deaths from analgesic overdoses is highlighted in the National Suicide Prevention Strategy for England. The problem of self-poisoning with the prescription-only drug co-proxamol (dextropropoxyphene plus paracetamol) has received attention in several countries. We have conducted a review of the international literature related to possible strategies to tackle this problem. In England and Wales in 1997–1999, 18% of drug-related suicides involved co-proxamol; these constituted 5% of all suicides. Death usually results from the toxic effects of dextropropoxyphene on respiration or cardiac function. 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. While there is limited evidence that educational strategies have been effective in reducing deaths from co-proxamol poisoning, initiatives in Scandinavia, Australia and the UK to restrict availability of co-proxamol have produced promising results. Given the paucity of evidence for superior therapeutic efficacy of co-proxamol over other less toxic analgesics, there are good reasons to question whether it should continue to be prescribed.

Introduction

Co-proxamol is a prescription-only analgesic that combines dextropropoxyphene hydrochloride 32.5 mg and paracetamol 325 mg. Deaths from dextropropoxyphene overdose have caused concern in several countries, including the UK,¹⁻¹⁰ USA,¹¹⁻¹⁷ Canada,¹⁸ Australia,¹⁹ Sweden,²⁰⁻²⁶ Norway,²⁷ Finland,²⁸ and Denmark.²⁹⁻³¹ Such deaths are usually suicides. The importance of finding strategies to prevent these deaths in the UK was raised more than two decades ago³ and has been re-emphasized by recent research.⁹,¹⁰ Prevention of deaths due to analgesic overdoses has also been highlighted in the National Suicide Prevention Strategy for England.¹² We have conducted a review of the international literature in relation to possible strategies to prevent deaths.
due to co-proxamol poisoning. In addition, we have analysed mortality and prescription statistics for co-proxamol in the UK.

Methods

Literature search

Electronic searches of PsycINFO (1872–2003), MEDLINE (1966–2003), EMBASE (1980–2003) and CINAHL (1982–2003) were done, using search terms for co-proxamol, coproxamol, dextropropoxyphene and distalgesic combined with terms for overdose, self poisoning, suicide and attempted suicide. Four hundred and two papers were identified. From these we selected 42 English language papers where the contents of the abstract were relevant to the aims of this review. Twenty additional relevant papers were identified from reference lists.

Mortality and prescription data

Data on drug-related poisoning deaths with a verdict of suicide or undetermined cause (most of which are probable suicides)33 in England and Wales between 1993 and 2002, where co-proxamol was mentioned on the death certificate, were obtained from the Office for National Statistics. This included cases where both paracetamol and dextropropoxyphene were mentioned separately on the death certificate, and deaths where dextropropoxyphene was mentioned alone, as this is rarely prescribed in England and Wales except in combination with paracetamol.34 Information on co-proxamol prescriptions was provided by the Prescriptions Statistics department at the Department of Health and the Prescribing Services Unit of Health Solutions Wales.

Results

Historical review

Dextropropoxyphene (propoxyphene) was first synthesized in 1953, and was introduced into clinical practice in 1957. An opiate-based analgesic similar in structure to methadone, it is rapidly absorbed, reaching a peak plasma concentration within 1 h of ingestion, and largely converted into its metabolite norpropoxyphene, which also has an analgesic effect. Norpropoxyphene is eliminated more slowly from plasma than dextropropoxyphene; the long half-lives of both dextropropoxyphene (about 16 h) and norpropoxyphene (about 29 h) enable accumulation with regular dosage, so that after 4 days, plasma concentrations are 5–7 times higher than after an initial dose.35

The drug is marketed in various forms, either as dextropropoxyphene hydrochloride or dextropropoxyphene napsylate alone, or in combination with other analgesics and sedatives. Following its introduction, it rapidly became extremely popular. By 1969, American pharmacies dispensed more prescriptions for dextropropoxyphene hydrochloride than for any other drug.36 Dextropropoxyphene was also widely prescribed in Australia,37 New Zealand,38 and Europe.20,27,39 The dextropropoxyphene-paracetamol compound first became available in the UK in 1964 as Distalgesic, and by 1983 was the most commonly prescribed analgesic and the second most prescribed drug in general practice.35 Co-proxamol is still widely prescribed in the UK. In a survey of 30 UK teaching hospitals between April 1994 and March 1995, co-proxamol accounted for 35% of all issues of paracetamol-containing analgesics.40 In 2003, 7 882 000 prescriptions for co-proxamol were dispensed in the community in England, totalling 906 886 100 tablets.41 Over 85% of these prescriptions were dispensed in quantities of a hundred or more tablets (data supplied by Prescription Statistics, Department of Health).

Toxicity

The first death associated with dextropropoxyphene was reported in 1964,42 and concerns about its increasing use for self poisoning were raised in the 1970s, both in the UK1,2,43 and the USA.11–13 The causes of death from co-proxamol overdose include respiratory depression and cardiac effects, including prolonging atrio-ventricular conduction and slowing of the heart rate.35,44 Death often occurs quickly—in some cases, within 1 h of ingestion.2,13,45 An overdose of as few as 15–20 tablets can be fatal,4,10,12,18 especially if taken in conjunction with alcohol or another CNS depressant.1,3,10,14,46–48

If a person who has taken a co-proxamol overdose survives long enough to receive medical attention, the CNS and respiratory depressant effects may be reversed by administration of the narcotic antagonist naloxone (which may need to be given in repeated doses).36 Standard means of management are required for dealing with cardiotoxicity.39

The paracetamol component of co-proxamol rarely contributes directly to death.49 Each tablet contains less paracetamol (325 mg) than the standard paracetamol preparation (500 mg). In most fatalities, death occurs rapidly from cardiorespiratory
effects of dextropropoxyphene overdose, before paracetamol-induced liver damage can take effect.

Co-proxamol (dextropropoxyphene) deaths outside the UK

Mortality from dextropropoxyphene overdose has been reported in studies from the USA, Europe and Australia. Deaths with verdicts other than suicide are often included, and some studies do not differentiate between dextropropoxyphene alone or in compound form.

USA and Canada

In the USA, increases in dextropropoxyphene deaths through the early 1970s were noted in Texas,11 North Carolina12,13 and Florida.14 By 1977, propoxyphene was the second most common drug involved in deaths from prescribed drugs in the USA, and was estimated to cause between 1000 and 2000 deaths per year.50,51 Propoxyphene products were included in Schedule IV of the Controlled Substances Act in 1977, and in early 1978 the Food and Drugs Administration (FDA) warned physicians of its potential fatality in overdose. Following petitions from a consumer advocacy group in 1978 and highly publicized congressional hearings on propoxyphene abuse in early 1979, the FDA carried out an informational campaign between 1978 and 1980 in an attempt to reduce inappropriate prescribing. Finkle16 examined records from 27 medical examiner or coroner offices in the USA and Canada and identified 4412 propoxyphene-associated deaths between 1969 and mid-1983 (although in 48% of these propoxyphene poisoning was not considered to be the main cause of death). About 45% were recorded as suicides, but Finkle suggested that these were under-reported. Numbers of deaths increased annually from 1972–1977, but then decreased so that by 1982 there were less than half as many deaths as in 1977. The fall in fatalities corresponded with a decline in propoxyphene prescriptions (which had begun in 1975 and may be partly explained by a rapid increase in the use of non-steroidal anti-inflammatory analgesics50). A study from Los Angeles County reported a similar decline in propoxyphene-related deaths between 1977 and 1980.17 Soumerai and colleagues50 analysed US data from 1974–1983, which indicated that the risk of propoxyphene-related death per prescription remained constant between 1979 and 1983, at about 52 deaths per million prescriptions (1100 deaths per year). Propoxyphene-associated deaths in Ontario between 1972–1977 were investigated by Cimbura (1979),19 who found a steady increase from 1974 onwards. Propoxyphene was the third most frequent drug (after barbiturates and ethanol) reported in fatalities.

Australia

In an Australian study of deaths between 1989 and 1992, analgesics containing dextropropoxyphene (90% of which were a compound containing paracetamol) had the fourth highest risk of self-poisoning mortality when adjusted for prescription numbers (20.8; 95%CI 8.8–48.9).15 Dextropropoxyphene was the most common single drug cause of death in this study, although the author noted that the number of dextropropoxyphene deaths had decreased since two previous studies in the same area from 1976–1982.52,53

Scandinavia

Dextropropoxyphene-related fatalities have been the subject of several Scandinavian studies. In Sweden, dextropropoxyphene is one of the most frequently prescribed analgesics.21 Carlsten et al. (1996)20 reported an increase in the Swedish suicide rate of dextropropoxyphene overdose between 1969 and 1992, which corresponded with an increase in prescription sales. Jonasson and colleagues have published widely on dextropropoxyphene deaths in Sweden.21–26 In a study of all autopsies in Sweden between 1992 and 1996, 956 were classified as fatal dextropropoxyphene overdose on the death certificate, continuing a pattern of about 112–160 deaths a year seen since the early 1970s.21 Fifty-seven per cent of these deaths were recorded as suicides, 38% undetermined and 5% accidental. Jonasson et al. calculated the defined daily dose (DDD) per 1000 inhabitants during a 12-month period for Sweden, Denmark and Norway.22 In 1996, this was 14.4 in Sweden, compared with only 2.0 in Denmark and 1.6 in Norway, both of which countries had seen a declining death rate from dextropropoxyphene after introducing restrictions on its use. Jonasson and colleagues also drew attention to the use of dextropropoxyphene as a drug of abuse, and suggested that adolescents might be using it to potentiate the effects of alcohol. In a further paper on the contribution of various dextropropoxyphene preparations to fatal poisonings, the authors noted that the ratio of fatal poisonings to DDD was 27 for dextropropoxyphene alone, compared with 6.3 for the paracetamol/dextropropoxyphene combination Distalgesic.23 Distalgesic’s share of the dextropropoxyphene market had fallen from 58% in 1992 to 49% in 1997. The investigators speculated that prescribing of dextropropoxyphene alone might
have increased because clinicians mistakenly believed that it was safer than the compound including paracetamol (which had been predominant in reports of fatalities).

Following the publication of these reports and involvement of politicians, the Swedish Medical Products Agency (MPA) held a seminar in spring 1999 focusing on the pharmacological and toxicological aspects of dextropropoxyphene, which attracted widespread media publicity. In August 2000, the MPA advised manufacturers to improve summaries of product characteristics, labelling and patient information leaflets to include more specific warnings about overdose and concomitant use of alcohol. Doctors were encouraged to prescribe smaller amounts, and not to prescribe to vulnerable patients. Stricter prescribing regulations were introduced in June 2001, involving the use of a special prescription form and stringent monitoring of treatment efficacy. The effectiveness of these measures was assessed by Jonasson and Jonasson,26 who reported that sales of dextropropoxyphene products decreased by 66% between 1999 and early 2003, and the number of fatal dextropropoxyphene poisonings decreased by 62% between 2000 and early 2003.

In Denmark, propoxyphene was one of the most commonly prescribed analgesics in the 1980s39,54 (the paracetamol/dextropropoxyphene combination has never been available there). In 1984, 124 fatal and 297 non-fatal dextropropoxyphene overdoses were reported to the National Board of Health.29 Dextropropoxyphene overdose was the second most frequent cause of death from drug poisoning.29 In Jutland during the early 1980s, dextropropoxyphene was the drug most commonly found in poisoning fatalities examined at the Institute of Forensic Medicine in Aarhus.54 Forty per cent of a series of 85 dextropropoxyphene deaths examined between 1985 and 1987 were recorded as suicides. In a further study of fatal poisonings in Jutland between 1980 and 1989, Kaa and Gregerson (1992)55 reported that dextropropoxyphene caused more deaths than any other drug during the study period (30% of drug-related deaths). Most of these occurred during the early and mid-1980s. In the municipality of Copenhagen there were 234 deaths from dextropropoxyphene between 1982 and 1989.31 These comprised about one-third of all dextropropoxyphene deaths in Denmark. Sixty-three per cent were classified as suicide, 26% as of undetermined cause, and 11% as accidents. The annual number of deaths increased until 1985 and then declined, reflecting a similar decrease in the DDD. As a response to increasing concern about the number of dextropropoxyphene fatalities, the Danish National Board of Health in 1982 wrote to all physicians warning them not to prescribe the drug to known alcohol or drug abusers. Failure to comply would result in disciplinary action.31 This measure did not appear to have an immediate impact, but there was a fall in the number of deaths after 1985, following a national publicity campaign launched by the Danish Board of Health in the mid-1980s, the publication of several papers in the Danish Medical Journal warning of the dangers of dextropropoxyphene, and further guidelines to general practitioners indicating that the drug should only be prescribed to mentally stable patients.31 The number of dextropropoxyphene deaths halved between 1986 and 1987.30,56 From 1988 onwards, all dextropropoxyphene prescriptions were registered centrally, to facilitate tracing of physicians who did not comply with the guidelines. Sales of dextropropoxyphene and the number of dextropropoxyphene-related deaths declined between 1988 and 1989.31

In Norway, the paracetamol compound is the most common form of dextropropoxyphene. Teige and colleagues, in a study of fatal poisonings examined at the Institute of Forensic Medicine in Oslo 1981–1985, reported a steady decrease in dextropropoxyphene fatalities after stricter prescription rules were introduced in 1982.27 Sales of dextropropoxyphene in Norway decreased by over 70% from 1979 to 1983. Ohberg et al. (1996)28 examined records for all suicides in Finland between 1987 and 1988, and estimated the relative suicide risk, compared with sales data, for a range of drugs. The risk for dextropropoxyphene was higher than for antidepressants as a group, and second only to that for barbiturates. Fatal poisoning in drug addicts in the Nordic countries in 1997 was investigated by Steentoft et al. (2001).57 Propoxyphene was the cause of 20% of such deaths in Sweden, and 13% in Finland. Denmark and Norway each had only one propoxyphene death among drug addicts, confirming previous reports of the success of restrictive measures that were introduced in these countries.

Summary
In summary, the international research findings indicate that deaths from dextropropoxyphene overdose appear to reflect its availability, and public health educational initiatives have limited
Co-proxamol (dextropropoxyphene) deaths in the UK

Concern about the growing number of deaths from dextropropoxyphene poisoning in the UK was first raised in the 1970s. Carson and Carson (1977) reported a series of 30 fatalities between 1973 and 1976 in Northern Ireland. Whittington, the coroner for Birmingham, published several studies based on cases dealt with by his court and toxicology analyses conducted by the West Midlands Forensic Science Laboratory. Between 1976 and 1979, there were 35 inquests on Distalgesic overdose deaths, and 97 analyses for dextropropoxyphene poisoning. Whittington suggested that deaths caused by dextropropoxyphene might be under-represented in official statistics, as some might be recorded as paracetamol overdoses. Other researchers indicated that financial restrictions might inhibit some coroners from arranging for comprehensive drug screening, and thus result in dextropropoxyphene fatalities being missed. In a study of coroners’ files in England, Scotland and Ireland between 1976 and 1980, Dwyer and Jones calculated that national mortality data underestimated deaths from the dextropropoxyphene/paracetamol combination by 39%. On the basis of their estimates, the mean numbers of deaths per year due to co-proxamol poisoning during this period were 291 in England, 59 in Scotland and 10 in Northern Ireland. Meredith and Vale (1984) reported a yearly average of 276 deaths from co-proxamol poisoning in 1980 and 1981 in England and Wales (data from the Office of Population Censuses and Surveys). More recently, Hawton et al. (2003) estimated that there were an average of 255 deaths a year involving co-proxamol alone (suicides and open verdicts) in England and Wales between 1997 and 1999.

Four studies from the acute medical unit in West Fife drew attention to the problem of co-proxamol overdoses. Young and Lawson noted a rise in the proportion of overdoses involving Distalgesic from 2% in 1971 to 7% in 1978. This trend paralleled prescribing patterns. Sangster et al., reporting on acute admissions for self-poisoning between 1970 and 1979, found that Distalgesic had replaced barbiturates as the most common cause of death in hospital overdose patients. A study of admissions to the Edinburgh Regional Poisoning Treatment Centre between 1967 and 1982 found that the incidence of Distalgesic poisoning reached a peak in 1978, but declined dramatically in 1980 and remained stable until the end of the study period. This pattern was also noted in West Fife, and reflected prescription levels for Distalgesic in Scotland, which reached a peak of 1 000 000 in 1978 and then fell to half this level by 1983. An overall mortality rate of 10.6% for Distalgesic overdoses, compared with 2.3% for analgesics as a whole, was calculated by Lawson and Northridge when they considered deaths both in the hospital and in the community following overdoses between 1976 and 1986. Hawton et al., comparing data on self-poisoning in Oxford with national mortality figures, showed that the odds of dying after co-proxamol overdose was 2.3 times that for tricyclic antidepressants and 28.1 times that for paracetamol. In the three-year period 1997 to 1999, co-proxamol overdoses accounted for 18% of all drug-related deaths which received a verdict of suicide or undetermined cause. This constituted 5% of all suicides.

Trends in co-proxamol overdoses in the UK appear to reflect prescribing patterns. Between 1980 and 1990, there were an estimated 4.2 deaths per 100 000 prescriptions of dextropropoxyphene compounds. This fatality rate remained stable over the period. Suicides in which co-proxamol was involved and co-proxamol prescriptions in England between 1993 and 2002, based on data supplied by the Office for National Statistics and the Department of Health Prescription Statistics department, are shown in Figure 1. Trends in suicide during this period mirrored trends in prescriptions, peaking in 1996/1997 and declining thereafter. Between 1999 and 2002, there were 2.9 suicide deaths per 100 000 prescriptions of co-proxamol in England and Wales (95%CI 2.7–3.1). Comparable figures for antidepressants (1993–1997) were 5.3 deaths/100 000 prescriptions for tricyclic antidepressants and 0.4 for SSRIs.

Epidemiology

Sex and age

The sex distribution of co-proxamol suicides has differed between studies. Whittington (1981) found no gender difference. Dwyer and Jones, Vale et al. and Hopkins et al. reported a higher proportion of females to males, with male:female ratios of 1:1.25, 1:1.08, and 1:1.22 respectively. This ratio was reversed in studies by Hawton et al. (M:F 1:0.83) and Obafunwa et al. (M:F 1:0.85). Figures from the Office for National Statistics for drug-related poisoning deaths from suicide or undetermined cause in England and Wales between
1993 and 2002, where co-proxamol was mentioned on the death certificate, indicate a male:female ratio of 1:0.9.

The Office for National Statistics provided us with data on co-proxamol suicides by age for 1993–2002 (Figures 2 and 3). The highest rate of female suicides is in those aged 55 years and over; the lowest in the 15–34 year age group (Figure 2). In males, rates do not differ greatly across the age groups, although they have shown a recent decline in 15–34 year-olds and an increase in those aged 55 years and over (Figure 3). The highest rate of male co-proxamol suicides is now in the 35–54 year age group.

Medical and psychiatric problems
Dwyer and Jones\textsuperscript{5} found that 65% of people who died from co-proxamol overdoses for whom their medical history was known had a chronic physical illness, nearly half of which involved skeletal or muscular disorders. Eleven per cent had an acute physical illness. As with suicide in general, psychiatric disorders are common in people who die from co-proxamol overdose. In the series studied by Dwyer and Jones\textsuperscript{5} 55% had a history of depression and a further 21% had an undefined mental illness. Chronic alcohol abuse was identified in one third of the males and 20% of the females. Forty-two per cent of females and 32% of males had a history of previous overdose. In a study based on a sample of coroners’ inquest records for co-proxamol suicides between 2000 and 2001, nearly half of those who died had a history of self harm, and a third were in contact with psychiatric services at the time of death.\textsuperscript{10} The main psychiatric diagnoses were affective disorder (63%) and alcohol dependence (13%). None of the UK studies has indicated that co-proxamol is used much as a drug of abuse.

Circumstances of the act
High levels of alcohol in toxicology reports were recorded in several studies. Sixty per cent of Carson and Carson’s\textsuperscript{1} sample had consumed alcohol, with blood alcohol levels ranging from 29 to 281 mg/dl (mean 139.22 mg/dl). Whittington\textsuperscript{4,46} found the presence of alcohol in 54% of his co-proxamol inquest sample, compared with 14% in other drug overdoses. In his toxicology sample, cases with alcohol had significantly lower mean blood levels of dextropropoxyphene than those without alcohol. Seventy-five per cent of the dextropropoxyphene overdoses in the 20–29 year age group were associated with alcohol. Vale \textit{et al.}\textsuperscript{47} reported significant quantities of alcohol in 56% of cases. The mean alcohol concentration was 1588 mg/l. Dwyer and Jones\textsuperscript{5} estimated that alcohol contributed to death in 757 (52%) of dextropropoxyphene suicides in England. Alcohol consumption was involved in

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59% of the overdoses in Hawton and colleagues’ study (2004),\textsuperscript{10} and was more common in the younger age groups.

Limited information on the number of tablets consumed was available in a few studies: Whittington\textsuperscript{2} reported deaths resulting from as few as 10 tablets; Carson and Carson\textsuperscript{1} reported a range from 20 to 50 tablets. A third of the cases in Hawton et al.’s study\textsuperscript{10} involved an estimated consumption of less than 40 tablets. The lowest number of tablets was 10.
Death after ingestion of a dextropropoxyphene overdose is usually rapid. Whittington et al. found that death frequently took place in <5 h post ingestion, and reported one case where death occurred within 1 h. Ninety-one per cent of his cases died before they could receive hospital treatment. Carson and Carson found a mean of 5.16 h between ingestion and death, with 7 (23%) fatalities occurring within 2 h. Only 11% of the fatal dextropropoxyphene overdoses in England identified by Dwyer and Jones received hospital treatment. Carson and Carson found a mean of 5.16 h between ingestion and death, with 7 (23%) fatalities occurring within 2 h. Only 11% of the fatal dextropropoxyphene overdoses in England identified by Dwyer and Jones received hospital treatment. Carson and Carson identified a ‘gesture or parasuicide’ group (13.9%) who had taken the overdose in front of witnesses or told someone about the act, but had subsequently died. Obafunwa reported details of the source of dextropropoxyphene in 39 suicides: in 22 (56%) the drug was prescribed for the deceased for muscular pains or recent injuries, 8 (21%) were prescribed for others close to the deceased (spouse, parent, friend), and one was an illegal ‘street’ acquisition. Hawton et al. found that co-proxamol had been prescribed for the deceased in 82% of cases, although in only 55% of 10–34 year-olds. In all but two of the cases where it was not prescribed for the deceased, the co-proxamol had been prescribed for a relative or partner. In all cases where prescribing information was available, the tablets had been prescribed by a general practitioner.

Whittington suggested that many Distalgesic overdoses were impulsive responses by young people to relationship problems, involving relatively few tablets and often under the influence of alcohol, more closely resembling an attempted suicide population. Some support for this theory is provided by Hawton and colleagues’ study, in which younger people were more likely to have consumed alcohol with the co-proxamol overdose, and to have lower suicidal intent (apparent intention to die) at the time of the act. Dwyer and Jones identified a ‘gesture or parasuicide’ group (13.9%) who had taken the overdose in front of witnesses or told someone about the act, but had subsequently died.

Efficacy

The comparative efficacy of co-proxamol has been the subject of several studies. Two recent systematic reviews have summarized their results. Li Wan Po and Zhang (1997) conducted a meta-analysis of 26 trials and concluded that there was little objective evidence on the basis of short-term use to support the use of co-proxamol in preference to paracetamol alone, in cases of moderate, short-term pain. Collins et al. carried out a Cochrane Collaboration quantitative systematic review (1998, updated 2004) on the efficacy of single-dose dextropropoxyphene for post-operative pain. Of 130 papers identified, only 11 trials met the study inclusion criteria. Their results showed that treatment with 65 mg dextropropoxyphene and 650 mg paracetamol (two co-proxamol tablets) was no more effective than 100 mg tramadol for controlling post-operative pain, but had fewer adverse effects. Tramadol is also an opioid analgesic, but is less likely to cause respiratory depression. A similar dose of paracetamol combined with 60 mg codeine appeared to be more effective, but this finding was not robust. However, plasma concentrations of dextropropoxyphene accumulate after regular 6-hourly doses, and the longer elimination half-life of its metabolite norpropoxyphene indicates that repeated doses may be more effective than single doses, and thus appropriate for treatment of chronic pain. Well-conducted clinical trials are needed to provide evidence for the efficacy of co-proxamol in long-term pain relief.

Prevention Initiatives

Restricting the means for suicide, including use of analgesics, is one of the strategies proposed in the National Suicide Prevention Strategy for England. Various initiatives in relation to reducing co-proxamol fatalities are possible.

Education of doctors

There is some evidence that this strategy might be effective. A decline in the number of Distalgesic prescriptions in the late 1970s in Scotland and 1980s in England followed reports of fatalities in the medical press, and was accompanied by a reduction in self-poisoning admissions and mortality. A study of prescribing trends in doctors showed that prescribing to patients on discharge from hospital fell after the dangers of Distalgesic were publicized (Alexander et al. 1981, quoted in Drugs and Therapeutics Bulletin 1983). Inappropriate prescribing of co-proxamol on post-operative and orthopaedic trauma wards at a Nottingham hospital ceased after education of nurses and doctors. An initiative by Doncaster Health Authority in 1998 advising general practitioners to be cautious in prescribing co-proxamol (accompanied by removal of the drug from the formulary of Doncaster Royal Infirmary) was followed by a substantial decrease in the number of tablets prescribed: by 2002, this had fallen...
by 60% compared with the period before 1998,\textsuperscript{68} and prescription levels were lower than the national average. There was a suggestion that suicides also declined, but the numbers were too small to draw firm conclusions. In Denmark, a National Health Board educational campaign in medical journals and general newspapers has been linked to a halving of dextropropoxyphene-related deaths between 1986 and 1987.\textsuperscript{56} Steentoft (2001)\textsuperscript{57} reported a decline in fatal propoxyphene poisonings in Finland after a warning to doctors in 1985.

The decline in propoxyphene-related deaths in the late 1970s in America\textsuperscript{16} has been related to an educational campaign by the Food and Drug Administration (FDA).\textsuperscript{17,45} Propoxyphene-containing compounds were placed in Schedule IV of the Controlled Substance Act in 1977, and in 1979 the FDA conducted extensive public hearings in response to the consumer advocacy group Public Citizen’s demand for a federal ban. It was decided not to withdraw the drug, but to change labelling on all dextropropoxyphene products, and conduct a campaign to educate physicians and patients about the dangers of overdose and promote caution in prescribing and use. Quotas were placed on manufacturing in 1980.\textsuperscript{17} Soumerai and colleagues (1987)\textsuperscript{50} analysed trends in propoxyphene overdose deaths and prescribing between 1974–1983 to evaluate the effects of the 1978–1980 informational campaign. They found no significant changes in the areas targeted, including repeat prescriptions and amounts prescribed, and showed that the downward trend in propoxyphene use had begun in 1975 and in fact flattened out after the warnings. Risk of death per prescription had remained constant from 1979. Although sales of the propoxyphene-only product declined, the combination product which included paracetamol (Darvocet-N), and was still under patent, improved its market position in the study period. The authors suggested that the apparent failure of the campaign might be related to the fact that the ‘educational’ face-to-face visits to physicians were conducted by representatives of the main manufacturer of propoxyphene. They recommended that future educational initiatives should be more sophisticated and objective.

Educational strategies should also alert doctors to the dangers of prescribing co-proxamol to vulnerable patients, such as heavy drinkers, people with depression or a history of suicide attempts, and those taking other CNS depressant medication.

Education of patients
There is no direct evidence that attempts to warn patients through labelling has any effect—trends in overdose rates appear to reflect prescription rates.\textsuperscript{50,61} However, there is a growing number of internet sites warning patients of the potential dangers of medication (e.g. [www.doitnow.org/pages/157.html] ‘Darvon, Darvocet and Other Prescription Painkillers’; [www.americaniobmedica.com/products/prophoxyphene_faq.html] ‘Propoxyphene (Darvon®) Frequently Asked Questions’; [www.netdoctor.co.uk/medicines/show preparation.asp?id=599] ‘Information about drugs for patients: co-proxamol’), which may avert some accidental fatalities and encourage patients to keep dextropropoxyphene supplies secure from misuse by others, or even to request alternative medication. Patients should also be encouraged to return left-over tablets following a course of treatment.

Restricting the numbers of tablets prescribed
Co-proxamol is often prescribed in large quantities, commonly in packs of 100 or more tablets, and therefore substantial supplies may be available in the household. This may increase the danger of death from impulsive overdoses of any tablets easily at hand.\textsuperscript{69} However, fatal poisoning may result from relatively few tablets, especially if accompanied by alcohol or other CNS depressants, and for patients with chronic pain small prescription sizes may be inconvenient.

Awareness of the risk to others beyond the patient
The risk of co-proxamol overdose extends beyond the patient for whom it is prescribed. In a study of suicide in young people\textsuperscript{70} in which co-proxamol was the most frequent drug used for self poisoning, in over 70% of cases it had been prescribed for someone other than the deceased. This should be borne in mind when prevention strategies are developed.

Restrictions on prescribing
Several initiatives designed to reduce prescribing of dextropropoxyphene appear to have been successful. There was a fall in admission rates for self-poisoning with dextropropoxyphene/paracetamol compounds after the New South Wales Department of Health published guidelines in 1980 aimed at restricting the use of the drug in public hospitals.\textsuperscript{53} Restrictions on prescribing introduced in Sweden in 2001, in combination with other measures,
are reported to have contributed to a major decline in fatal dextropropoxyphene poisoning. Stricter prescription rules were enforced in Norway in 1982; by 1983, sales of dextropropoxyphene had decreased by over 70% from 1979 levels. In Denmark, although restrictions on prescribing to vulnerable groups introduced by the Danish National Board of Health in the early 1980s appeared to have little initial impact on dextropropoxyphene fatalities, both death rates and DDD started to decline after 1985. More stringent prescribing regulations were enforced in 1988. Dextropropoxyphene death rates in Denmark decreased by 45% between 1986 and 1992. In the UK, the promising initiative by Doncaster Health Authority noted earlier provides another example where reduced prescribing of co-proxamol may have resulted in fewer poisoning deaths involving this drug. However, policy makers should take care that restricting availability of a drug does not result in its replacement by an equally dangerous substance. Reduced prescribing of dextropropoxyphene compounds following an initiative in an Australian teaching hospital to restrict prescribing to consultants only was accompanied by an increase in prescriptions for other compound analgesics, especially those with high doses of codeine.

**Improved management of co-proxamol overdose**

There may be potential for improving the management of patients who present to hospital following co-proxamol overdose, for example by prompt administration of antidotes such as naloxone. However, as noted earlier, only a minority of people who die from co-proxamol overdose reach hospital alive.

**Complete withdrawal**

There is little justification for continuing the use of co-proxamol for short-term pain relief, but there is as yet no evidence from clinical trials to support this. If other equally effective and less dangerous alternatives are available, complete withdrawal should be considered. The extent to which this will have an impact on suicide rates will depend on the degree of substitution of methods for suicidal behaviour. It is worth noting that the reduction in suicides involving domestic gas which accompanied the changeover from toxic coal gas to North Sea gas in domestic supplies appeared to result in very little substitution of method.

**Conclusions**

Self-poisoning with co-proxamol is a relatively common method of suicide. Specific factors which increase the danger of this method of overdose include the highly toxic effects of dextropropoxyphene on respiration and cardiac function, and the facts that death often occurs very rapidly, the lethal dose can be relatively low, and the effects are potentiated by alcohol (and other CNS depressants). Also, co-proxamol tends to be prescribed in very large amounts and poses a risk not only to those for whom it is prescribed but also others in the household.

There are a variety of approaches to suicide prevention, including wider social initiatives to reduce socio-economic deprivation and substance abuse, and improve health care. An approach for which there is reasonable evidence of success is reducing the availability or toxicity of means for suicide. Initiatives to restrict co-proxamol prescribing have in some cases been beneficial. This is likely to be the most effective means of prevention. Whether this should go as far as total withdrawal of the drug depends on a careful cost-benefit analysis, including of the availability of less toxic alternatives and of the relative efficacy of co-proxamol compared with other analgesics. Tackling the problem of co-proxamol overdoses effectively could have a significant beneficial effect on national suicide rates.

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