Usage of paracetamol-containing combination analgesics remains high in primary care

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Aims

Paracetamol-containing combination analgesics are widely prescribed but the use of paracetamol/dextropropoxyphene (co-proxamol) is particularly controversial. We aim to examine the prescribing patterns of the paracetamol-containing analgesics in Ireland.

Methods

A national primary care prescribing database was used to investigate patterns of usage. Twenty-six thousand three hundred and eighteen patients who were new to therapy with paracetamol and paracetamol-containing analgesics between January and June 2002 were identified as follows: no previous analgesic medication in the 6 months prior to enrolment into the study, and followed up for at least 12 months from the time of enrolment. Duration of therapy and the number of prescriptions received post enrolment were analyzed according to age. Odds ratios for receiving long-term (>1 month) compared with short-term (1 month) prescriptions for co-proxamol, paracetamol only or a paracetamol combination-type analgesic were calculated for women vs. men, and in those aged over 65 vs. those aged under 65 years.

Results

Co-proxamol was the most commonly prescribed analgesic, accounting for 42% of all prescriptions dispensed during 2003. Long-term use of paracetamol-containing analgesic preparations was uncommon, with 56.7% receiving only 1 month's prescription during the study period. However, women (OR = 1.18, 95% CI 1.07, 1.28, $P < 0.0001$) and those over 65 years (OR = 1.71, 95% CI 1.57, 1.86, $P < 0.0001$) were more likely to receive a follow-up prescription for co-proxamol, but also for paracetamol (women, OR = 1.28, 95% CI 1.16, 1.39; over 65 year olds, OR = 2.67, 95% CI 2.44, 2.93) and the paracetamol combinations (women, OR = 1.33, 95% CI 1.20, 1.47; over 65 year olds, OR = 1.69, 95% CI 1.53, 1.87).

Conclusions

Co-proxamol was the most commonly prescribed paracetamol-containing analgesic preparation in Ireland. The results may indicate inappropriate use in primary care.

Introduction

Paracetamol-containing combination analgesics are widely prescribed; A UK survey reported that they accounted for 73% of all prescriptions for paracetamol

containing medicine [1]. The most commonly prescribed combination in that study was reported to be paracetamol/dextropropoxyphene (co-proxamol). Its use as an analgesic for the management of acute pain is

controversial as it has been suggested that the combination is no more effective than use of paracetamol alone [2, 3]. Although some workers [4] have suggested that it may be superior to paracetamol alone for chronic pain, repeated use may result in tolerance, requiring increased dosage and cases of abuse have been reported in the literature [5]. Moreover, its use in the elderly is regarded as potentially inappropriate [6].

In 2004, the Medicines and Healthcare products Regulatory Agency (MHRA) in the UK instituted a review of this combination, in light of ongoing concerns about the risks and benefits associated with its use, and its safety in overdose [7]. As a result of this review and based on the advice of the Committee on Safety of Medicines (CSM) the MHRA has recently announced that co-proxamol should be withdrawn from the market over a period of time [8]. The aims of this study were to evaluate and compare the prescribing patterns of the paracetamol-containing analgesics currently dispensed in Ireland.

Methods

The General Medical Services (GMS) scheme in Ireland is a means-tested scheme providing free medical care for all those eligible and covers approximately 31% of the total population (approximately 1.2 million). The prescription database records all prescriptions dispensed by any pharmacist in the country for claims purposes. It has been used previously for research purposes. Information on the age of patients and gender is available. However, there is no information on diagnosis. All prescription items are coded according to the WHO Anatomical Therapeutic Chemical (ATC) classification system (co-proxamol N02AC54; Paracetamol N0BE01; Paracetamol combinations N02BE51).

The total number of prescriptions dispensed for the paracetamol-containing analgesic preparations for Ireland from January – December 2003 was calculated. In order to evaluate more closely patterns of usage, we examined the prescription database of all patients, who were from the largest health region in Ireland, the Eastern region (including counties of Dublin, Kildare and Wicklow). Patients who were new to any therapy (i.e. co-proxamol, paracetamol or paracetamol combinations) between January and June 2002 were identified as follows: they had not received any medications in the 6 months prior to initiation of any therapy, to be included in the cohort for study ($n = 26\,318$ patients). Follow-up data were available for 12 months from the month of initiation of therapy. This enabled the prescribing trends after starting new therapies to be examined further. Duration of therapy was examined by

calculating the number of months that prescriptions were received post enrolment. Odds ratios for receiving long-term (>1 month) compared with short-term (1 month) prescriptions for co-proxamol, paracetamol only or a paracetamol combination-type analgesics were calculated for women compared with men, and in those aged over 65 compared with those aged under 65 years.

Patients who received a prescription for co-proxamol and paracetamol and/or paracetamol combinations, or switched between analgesics, during the 12 month follow-up period were excluded in order to examine only those patients who stayed on the same therapy as their initial prescription, and to limit the analysis to those patients with less severe forms of pain.

All statistical analysis was carried out using SAS Version 8 (SAS Institute Inc.).

Results

National pattern of analgesic prescribing

Analysis of national prescribing data shows that co-proxamol is the market leader accounting for 42% of the prescriptions dispensed for the paracetamol-containing analgesic preparations in Ireland in 2003 (Table 1).

New users of paracetamol-containing analgesic preparations

Twenty-six thousand three hundred and eighteen patients were identified as being new to the paracetamol-containing analgesic preparations from January–June 2002, with a prescribing rate of 71.4 male patients and 94.7 female patients per 1000 GMS population. The total number of patients receiving any prescription in the same period was 278 866. Thus, patients receiving paracetamol-containing analgesic preparations comprised 9.4% of the 'at-risk' population. The incidence for receiving the first analgesic prescription increased with age and peaked in those over 65 years. The percentage receiving their first analgesic prescription in those aged 0–15 years, 16–44 years, 45–64 years and over 65 years was 4.8%, 30.5%, 22.3% and 42.3%, respectively.

Prescribing trends for co-proxamol, paracetamol and paracetamol combinations

Female patients were more likely to receive a prescription for all paracetamol-containing analgesic preparations in the year following their initial prescription than male patients and patients aged over 65 years were more likely to receive a follow-up prescription for all paracetamol-containing analgesic preparations than patients aged under 65 years (Table 2).

Drug	Total number of prescriptions	% of total number of prescriptions
Co-proxamol*	366 212	42%
Paracetamol 500 mg	271 636	31% (29% tablets, 2% suppositories)
Paracetamol 500 mg Codeine 8 mg	122 004	14%
Caffeine 30 mg Paracetamol 500 mg	61 544	7%
Codeine 30 mg Paracetamol 500 mg	50 889	6%
Dihydrocodeine 10 mg Paracetamol 500 mg	8 404	1%
Metoclopramide hydrochloride. 5 mg		

*Dextropropoxyphene hydrochloride 32.5 mg, paracetamol 325 mg.

Table 1

Total number of prescriptions on the GMS in 2003 for the paracetamol-containing analgesic preparations

	OR (95% CI) Female vs. male#	OR (95% CI) Over 65 vs. under 65 years old#
Co-proxamol	1.18 (1.07, 1.28)***	1.71 (1.57, 1.86)***
Paracetamol only	1.28 (1.16, 1.39)***	2.67 (2.44, 2.93)***
Paracetamol combinations	1.33 (1.20, 1.47)***	1.69 (1.53, 1.87)***

Table 2

Odds ratios and 95% confidence intervals for the long-term receipt (vs. short-term) of follow-up prescriptions for the paracetamol-containing analgesic preparations in 12 months post initiation of therapy

Reference category. * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$.

Duration of therapy

Long-term use of the three analgesics was uncommon with 56.7% receiving only 1 month's prescription for co-proxamol, 48.7% receiving only 1 month's prescription for paracetamol combinations and 49.8% receiving only 1 month's prescription for paracetamol only.

Discussion

This study has shown that the combination analgesic paracetamol/dextropropoxyphene (co-proxamol) was the most commonly prescribed, representing a significant percentage (42%) of prescriptions for this group of analgesic agents. It is acknowledged that there may be many reasons for choosing co-proxamol as a first line prescription analgesic and the GMS database does not provide diagnostic data. However, by excluding patients who had received a prescription for more than one type of analgesic or who had switched analgesic types, we aimed to limit our study group to those with less severe

forms of pain. Patients on the GMS scheme are entitled to free medical consultations and free prescription medicines, therefore they are more likely to seek a prescription for an analgesic rather than pay for OTC medication, even for mild to moderate symptoms. Individual responses to a given therapy, including analgesics are highly variable, therefore it is possible that our results reflect the fact that some prescribers or patients favour the use of co-proxamol compared with paracetamol alone. It has also been noted previously that in the hospital setting, this drug combination continued to be prescribed out of habit [1]. The use of personal formularies has been noted with other medicines [9] and some workers have reported the efficacy of co-proxamol in clinical practice [10]. However our results may also suggest that prescribers are not aware of the ongoing controversy with its use [2, 3, 5, 11–13] and may point to the need for better communication of the risks and benefits of use of co-proxamol to prescribers in primary care.

The study showed that long-term use of paracetamol alone, co-proxamol or other paracetamol-containing combinations was relatively uncommon in the study population, supporting the view that treatment was for the management of mild to moderate pain. The relatively longer prescribing term noted for female patients over 65 years may reflect the fact that arthropathies tend to occur more frequently in this patient population [14]. It could also reflect a tendency to prescribe differently for these older patients [15]. It does however, appear that prescribers may exercise more care in the elderly where proportionally more prescriptions are for paracetamol alone than for compound preparations. Many workers have advised that use of dextropropoxyphene-containing combinations is inappropriate in elderly populations [6, 16]. It has been reported that the half-life of dextropropoxyphene may be longer in elderly patients, even in the absence of apparent hepatic or renal disease [17, 18]. The American Geriatrics Society expert Panel on persistent Pain in Older Persons, has recommended that analgesic strategies, which do not involve the use of dextropropoxyphene, should be used for the management of mild to moderate pain in elderly patients [19], because of the risk of drug accumulation, neuro-excitatory effects and ataxia with use. Moreover, some workers have suggested that females are at increased risk of adverse effects with the use of dextropropoxyphene [20]. These results highlight the need for better communication of clinical recommendations to prescribers.

There are several compound analgesic preparations containing paracetamol and an opioid (such as codeine or dextropropoxyphene) currently available either via prescription only (as is the case for co-proxamol) or for self-medication via over-the-counter availability. It has been reported that dextropropoxyphene offers no substantial advantage over codeine in terms of efficacy [21] and may result in greater respiratory depression, especially when consumed with alcohol [22, 23]. In addition, one of the metabolites of dextropropoxyphene (nordextropropoxyphene) has a very long half-life, which may cause seizures and cardiac toxicity [24], not seen with codeine, thereby suggesting that the risk/benefit profile of dextropropoxyphene is less favourable than that of codeine. The high prescribing rate of co-proxamol noted in our study suggests that an educational intervention may be needed to highlight risks and benefits of use of this paracetamol/dextropropoxyphene combination to prescribers. Such interventions have been previously reported to successfully reduce the rate of prescribing of paracetamol/dextropropoxyphene combinations both at hospital and primary care level [1, 25].

Calls to have the use of co-proxamol restricted or even removed from the marketplace were recorded when it was first licensed [2, 11] and were renewed more recently [10, 26, 27], because of concerns over its safety. However, the usage remained relatively high in the UK [1, 26] until recently and this study shows usage of this combination is also significant in Ireland. Following an assessment of the risk/benefit analysis of co-proxamol, undertaken in the UK by the MHRA, in association with all interested expert bodies, the regulatory agency has decided that co-proxamol will be withdrawn from the UK market over a period of time as 'the benefits are not considered to outweigh the risks' of its use [8]. The Irish regulatory authority the Irish Medicines Board has not yet taken any such action but has announced that it will participate in a European-wide evaluation of the use of this combination [28].

In conclusion, co-proxamol comprised a large percentage of all paracetamol-containing analgesics prescribed in Ireland with relatively longer-term usage noted in females and in elderly patients. The results may indicate inappropriate use in general practice and suggest the need for an educational programme highlighting the relative benefits and risks of use of such combination analgesics.

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