Use of distalgesic in intentional drug overdose presentations to hospital before and after its withdrawal from the Irish market
Background

Distalgesic (known as co-proxamol in the UK) is a prescription-only analgesic compound of paracetamol and dextropropoxyphene. Evidence of the dangers of distalgesic in overdose began with a case-series study in Northern Ireland over 30 years ago [1] and culminated with a study that showed that the drug was the second most commonly used drug in overdose suicides in England and Wales, accounting for 5% of all suicides and with a higher risk of fatal outcome in overdose acts than other commonly used medicines [2]. Death from distalgesic overdose may occur rapidly, even with a relatively low dose, and lethality is increased by use of alcohol and other central nervous system depressants. As a consequence, the majority of overdose deaths occur before hospital treatment can be received [3]. After extensive review of the risks and benefit, the drug was withdrawn from the UK market over a three-year period, 2005-2007. Distalgesic was withdrawn totally from the Irish market as of January 2006.

The efficacy of various suicide prevention strategies to reduce the risk of suicide involving distalgesic has been evaluated, including educational strategies for doctors, restricting the number of prescribed tablets, restrictions on prescribing and complete withdrawal [3]. So far, restricting availability of distalgesic has produced promising results in the UK, Scandinavia and Australia [3, 4].

This study aimed to evaluate the impact of the withdrawal of distalgesic from the Irish market in terms of intentional drug overdose (IDO) presentations to hospital emergency departments (EDs) nationally. Specifically, we compared the rate of presentations to hospital of IDO acts involving distalgesic before and after its withdrawal, tested for evidence of substitution whereby there was a change in the rate of overdose presentations involving other paracetamol-containing drugs and examined whether there was a change in the number of tablets taken in overdose presentations involving distalgesic. We also examined changes in sales into pharmacies of paracetamol-containing analgesics.
Methods

Data sources

The National Registry of Deliberate Self Harm collects data from all hospital emergency departments (EDs) in Ireland using standardised procedures and an internationally-recognised definition that includes all intentional drug overdose (IDO) acts [5]. The Registry methods have been described in detail previously [6, 7]. Population data from the 2006 national census and annual population estimates for 2003, 2004, 2005 and 2007 (disaggregated by sex and age group) were obtained from the website of the Central Statistics Office (CSO; http://www.cso.ie/). IMS Health supplied data on sales of paracetamol-containing drugs to pharmacies in Ireland for the study period 2003-2007.

Data analysis

Of the 40 hospital EDs operating in Ireland in 2003-2007, the Registry obtained data from 37 hospitals in 2003, 38 hospitals in 2004-2005 and all 40 hospitals in 2006-2007. Statistical analysis was limited to the data collected from the 37 hospitals that contributed to the Registry for the complete study period (2003-2007). The three other hospitals accounted for 13.9% of all Registry-recorded IDO presentations in 2006-2007. This proportion was used to derive a weighting (1 + 13.9 / (100 - 13.9) = 1.16) that was applied to the data of the 37 hospitals for all study years and these weighted data were used to calculate national presentation rates. Total, male and female rates of IDO presentations to hospital per 100,000 population were age-standardised using the European standard population [8]. Assuming that the number of presentations (x) followed a Poisson distribution, 95% confidence intervals (CIs) for the rates were calculated using the Normal approximation, i.e. confidence interval = (x +/- 2√x) * 100,000 / population.

Data analysis was carried out relating to all IDO presentations, presentations involving any paracetamol-containing drug and presentations involving distalgesic. We also examined
presentations involving the other common, paracetamol compound, prescription-only, moderate-severe painkillers that were available in the country across the study period (Kapake, Paramol, Solpadol, Syndol and Tylex; referred to as ‘other prescription compound analgesics’ in the paper) and presentations involving solpadeine, by far the most common over-the-counter paracetamol compound painkiller available only from pharmacies.

Chi-square tests were used to assess whether the proportion of IDO presentations to hospital involving distalgesic varied by sex, age and year. Poisson regression analysis was used to assess rate changes between the three pre-withdrawal years collectively (2003-2005) and each of the post-withdrawal years (2006 and 2007). The changes were reported as incidence rate ratios (IRRs) with the 95% CIs. The number of distalgesic tablets taken was recorded in 85% of the IDO presentations involving the drug. Because of its skewed distribution, the number of tablets was summarised by the median and interquartile range, and the non-parametric Mann-Whitney and median tests were used to test whether the median number of tablets taken varied between two and more than two groups, respectively.

The statistical analysis was carried out using SPSS version 16.0 (SPSS Inc., Illinois, USA) except for the Poisson regression analyses, which were carried out using Stata version 6.0 (StataCorp, Texas, USA).

Results
In 2003-2007, there were 35,805 recorded intentional drug overdose (IDO) presentations to the 37 hospital EDs that contributed fully to the Registry during these five years (annual mean (min-max): 7,161 (6,836-7,714)). Women accounted for 61.5% of all IDO presentations, a proportion that did not vary by year (Chi-square = 2.96, df = 4, p = 0.565). The total, male and female annual rates of IDO presentations to hospital EDs were 191.3 (95% CI = 189.3-193.3), 144.9 (95% CI = 142.4-147.3) and 238.7 (95% CI = 235.6-241.8) per 100,000 population, respectively. The female rate was therefore 65% higher than the
male rate. At least one paracetamol-containing drug was involved in 10,970 (30.6%) of the IDO presentations. The total, male and female annual rates of IDO presentations to hospital involving paracetamol were 58.0 (95% CI = 56.9-59.1), 36.1 (95% CI = 34.9-37.3) and 80.4 (95% CI = 78.6-82.2) per 100,000 population, respectively. Thus, the female rate was more than twice (+122%) the male rate. The national rate of IDO presentations to hospital deceased over the period 2003-2007 (Figure 1). This trend was evident for men and women and for IDO presentations involving a paracetamol-containing drug.

Sales to pharmacies of distalgesic, other prescription compound analgesics, solpadeine and other paracetamol-containing drugs increased 4-6% per year over the eight years (1998 to 2005) before distalgesic was withdrawn from the Irish market. In 2005, approximately 40 million tablets of distalgesic were sold to pharmacies. This fell to 500,000 in 2006 and to approximately 2,000 in 2007. Between 2005 and 2006, there was a 48% jump in sales of the other prescription compound analgesics, an 11% increase in sales of solpadeine and a 22% increase in sales of other paracetamol-containing medicines.

Of the 35,805 recorded IDO presentations, distalgesic was one of the drugs taken in 1,289 (3.6%) acts. The involvement of distalgesic in IDO acts varied by sex (Chi-square = 10.91, df = 1, p < 0.001), age (Chi-square = 35.00, df = 6, p < 0.001) and year (Chi-square = 355.33, df = 4, p < 0.001). Distalgesic was more common in female IDO acts (3.9% vs. 3.2%). It was most common in acts by 15-19 year-olds (4.4%) and became less common with increasing age (2.0% in acts by over 65 year-olds). In the three years pre-withdrawal, it was involved in almost 400 presentations annually, approximately 5% of all IDO presentations (386 (5.0%) in 2003, 356 (4.9%) in 2004, 371 (5.3%) in 2005). This reduced to 112 (1.6%) and 64 (0.9%)
presentations in 2006 and 2007, respectively. A similar pattern was observed over the study period when the data were stratified by sex and by age group.

The age-standardised rate of IDO presentations to hospital involving distalgesic was approximately 10 per 100,000 in 2003-2005 (Figure 3). In 2006 and 2007, the first and second years after its withdrawal, the rate fell to 2.8 (95% CI = 2.3-3.3) and 1.6 (95% CI = 1.2-2.0) per 100,000, respectively. In contrast, the rate of IDO presentations involving the other prescription compound analgesics was 4.1-4.3 per 100,000 in 2003-2005, rising to 5.2 (95% CI = 4.5-6.0) and 6.5 (95% CI = 5.7-7.3) per 100,000 in 2006 and 2007, respectively. Presentations involving solpadeine were relatively stable at around 6 per 100,000 each year.

The rate of IDO presentations to hospital involving distalgesic in 2006 and 2007 was just 28% and 16% of what it had been in the three years before it was withdrawn (Table 1). Respectively, 2006 and 2007 saw 26% and 55% increases in the rate of IDO presentations involving the other prescription compound analgesics. These increases were due to similar increases of 45-47% (from 2003-2005 to 2006-2007) in the rate of IDO presentations involving Kapake, Solpadol and Tylex. The rate of presentations involving any paracetamol-containing drug was 15% and 18% lower in 2006 and 2007, respectively. The decreases in the overall rate of paracetamol-related IDO presentations were similar in magnitude to the net decrease in the rates of presentations involving distalgesic and other prescription compound analgesics.

The median number of distalgesic tablets taken in IDO presentations involving the drug was 20 (Interquartile (IQ) range = 10-30), with men, on average, taking more distalgesic tablets in IDO acts than women (Mann-Whitney U = 106,194, p < 0.001; Male median (IQ range) = 20 (12-39); Female median (IQ range) = 18 (10-28)). There was some evidence that the median
number of distalgesic tablets varied by year (Median test chi-square = 9.80, df = 4, p = 0.044). As can be seen from Figure 4, the number of distalgesic tablets taken in IDO presentations was relatively constant in 2003-2006 but decreased in 2007. This decrease in 2007 compared to preceding years was only associated with female IDO acts (Mann-Whitney U = 11,349, p = 0.050; 2003-2006 median (IQ range) = 18 (10-30); 2007 median (IQ range) = 15 (7-20)).

Discussion
The withdrawal of distalgesic from the Irish market in January 2006 resulted in an immediate reduction in sales to pharmacies from about 40 million tablets in 2005 to 500,000 tablets in 2006. The rate of intentional drug overdose (IDO) presentations to hospital involving distalgesic in 2006 and 2007, respectively, was just 28% and 16% of the rate in the three years pre-withdrawal. The magnitude of the impact of the withdrawal is in line with effects of the withdrawal of distalgesic (co-proxamol) on drug-related suicide mortality in Scotland [9] and in England and Wales [4].

The 48% jump in sales of the other prescription compound analgesics between 2005 and 2006 was likely to be due to doctors prescribing these drugs because of the withdrawal of distalgesic. The 11% increase in sales of solpadeine and 22% increase in sales of other paracetamol-containing medicines may have been partially related to the withdrawal of distalgesic. There was evidence of a substitution effect whereby the increased availability of the other prescription compound analgesics resulted in a significant increase in the rate of IDO presentations to hospital involving these drugs. The total rate of IDO presentations to hospital and the rate of paracetamol-related presentations decreased across the five years, 2003-2007. The decrease in the rate of paracetamol-related presentations was particularly marked between 2005 and 2006, which may be primarily due to the withdrawal of distalgesic.
Similar experiences have been reported by studies assessing the impact of distalgesic (codeproxamol) withdrawal on suicide mortality [3, 4, 9].

We found evidence of a time lag in the effect of the withdrawal of distalgesic on IDO presentations. Sales of the drug to pharmacies in 2006 were approximately 1% of sales in 2005 whereas the rate of distalgesic-related IDO presentations decreased to 28% of the pre-withdrawal rate and the evidence of a reduction in the number of distalgesic tablets taken in overdose acts was limited and only apparent in 2007 and even then half of those presentations involved more than 17 tablets. These findings reflect the availability of distalgesic from already-filled prescriptions and a gradual reduction in household stocks. The Dispose of Unused Medicines Properly (DUMP) campaign is a separate initiative also aimed at restricting access to means of suicidal behaviour (http://www.imt.ie/opinion/2009/05/dumping_drugs_saves_lives.html). Carried out in a number of areas across Ireland, the DUMP campaign may have accelerated the disposal of distalgesic from the homes of patients. However, it may have more effective had the DUMP campaign been adopted nationally and promoted in conjunction with the withdrawal of distalgesic. In relation to future preventive initiatives, there is a need for greater awareness and promotion of existing initiatives that have the potential to be complimentary.

The study had a number of strengths and limitations. We were able to examine data relating to IDO presentations to the vast majority, though not all, of the hospitals in Ireland. In line with recommendations for the evaluation of initiatives restricting access to means of suicidal behaviour [10], we examined data from the three years before and the two years after the withdrawal of distalgesic. We examined sales to pharmacy data to assess changes in the availability of the relevant drugs. Changes in presentation rates and the number of tablets taken were examined for IDO presentations involving distalgesic and other relevant drugs. Substitution to other methods of self-poisoning or self harm was not examined. Legislation restricting pack-sizes of paracetamol-only drugs was implemented during the study period.
This may explain the decrease in the rate of paracetamol-related IDO presentations and may have partially confounded the impact of the withdrawal of distalgesic on this rate.

Conclusions

The withdrawal of distalgesic from the Irish market resulted in a marked reduction in the rate of IDO presentations to hospital involving the drug, which in turn may have caused the reduction in the rate of all paracetamol-related IDO presentations. The smaller increase in IDO presentations involving other prescription compound analgesics constituted evidence of substitution. However, the withdrawal of distalgesic in Ireland can be considered a positive measure in the prevention of non-fatal suicidal behaviour, which is likely also to have an effect on suicide.
Competing interests

The authors declare that they have no competing interests.

Authors’ contributions

PC and EA designed the study with contributions from UR. PC, EA and UR drafted the manuscript. PC and UR carried out the data analyses. HSK and IJP were involved in the conception of the Registry upon which the study was based and contributed to revisions of the manuscript. KH provided advice and commented on various drafts of the manuscript. All authors read and approved the final manuscript.
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References


Figure 1. National rate of intentional drug overdose presentations (all and those involving a paracetamol-containing drug) to hospital in Ireland, 2003-2007

Note: Error bars represent the 95% confidence intervals for the rates.
Figure 2. Trends in sales to pharmacies in Ireland of paracetamol-containing medicines, 1998-2007
Figure 3. National rate of intentional drug overdose presentations to hospital in Ireland involving distalgesic, other prescription compound analgesics and solpadeine, 2003-2007

Note: Error bars represent the 95% confidence intervals for the rates.
Figure 4. Median number of distalgesic tablets taken in intentional drug overdose presentations to hospital in Ireland, 2003-2007

Note: Error bars represent the interquartile range.
Table 1. National rate of intentional drug overdose presentations to hospital in Ireland involving distalgesic, other prescription compound analgesics, solpadeine and any paracetamol-containing drug and change associated with withdrawal of distalgesic

<table>
<thead>
<tr>
<th>Drug involved in presentations</th>
<th>Age-standardised rate per 100,000</th>
<th>2006 vs. 2003-2005</th>
<th>Rate change</th>
<th>IRR¹ (95% CI)</th>
<th>2007 vs. 2003-2005</th>
<th>Rate change</th>
<th>IRR¹ (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Distalgesic</td>
<td>10.1</td>
<td>2.8</td>
<td>1.6</td>
<td>-7.3</td>
<td>0.28*** (0.24-0.34)</td>
<td>-8.5</td>
<td>0.16*** (0.13-0.20)</td>
</tr>
<tr>
<td>Other prescription compound analgesics</td>
<td>4.2</td>
<td>5.2</td>
<td>6.5</td>
<td>1.0</td>
<td>1.26** (1.08-1.47)</td>
<td>2.3</td>
<td>1.55*** (1.35-1.79)</td>
</tr>
<tr>
<td>Solpadeine</td>
<td>6.3</td>
<td>6.6</td>
<td>5.7</td>
<td>0.3</td>
<td>1.05 (0.92-1.19)</td>
<td>-0.6</td>
<td>0.90 (0.78-1.03)</td>
</tr>
<tr>
<td>Any paracetamol</td>
<td>61.6</td>
<td>56.0</td>
<td>54.6</td>
<td>-5.6</td>
<td>0.85*** (0.81-0.88)</td>
<td>-7.0</td>
<td>0.82*** (0.79-0.86)</td>
</tr>
</tbody>
</table>

¹ Incidence rate ratio after adjustment for age

* p < 0.05, ** p < 0.01, *** p < 0.001
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