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Relative toxicity of analgesics commonly used for intentional self-poisoning: a study of case fatality based on fatal and non-fatal overdoses

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ABSTRACT

Background: Analgesics are used most frequently in fatal and non-fatal medicinal self-poisonings. Knowledge about their relative toxicity in overdose is important for clinicians and regulatory agencies.

Methods: Using data for 2005-2012 we investigated case fatality (number of suicides relative to number of non-fatal self-poisonings) of paracetamol, aspirin, codeine, dihydrocodeine, tramadol, paracetamol with codeine (co-codamol), paracetamol with dihydrocodeine (co-dydramol), ibuprofen and co-proxamol (paracetamol plus dextropropoxyphene; withdrawn in the UK in 2008 due to high toxicity). Data on suicides obtained from the Office for National Statistics and on non-fatal self-poisonings from the Multicentre Study of Self-harm in England. Case fatality was estimated for each drug, using paracetamol as the reference category.

Results: Compared to paracetamol and based on single drug deaths the case fatality index of dihydrocodeine was considerably elevated (odds ratio (OR) 12.81, 95% Confidence Interval (CI) 10.19 – 16.12). Case fatality indices for tramadol (OR 4.05, 95% CI 3.38 – 4.85) and codeine (OR 2.21, 95% CI 1.81 - 2.70) were also significantly higher than for paracetamol. The results when multiple drug deaths were included produced similar results. The relative toxicity of co-proxamol far exceeded that of the other analgesics.

Limitations: Data on fatal self-poisonings were based on national data, whereas those for non-fatal poisonings were based on local data.

Conclusions: Dihydrocodeine and tramadol are particularly toxic in overdose and codeine is also relatively toxic. They should be prescribed with caution, particularly to individuals at risk of self-harm.

Introduction

Self-poisoning is a common method used for suicide, especially in females (Office for National Statistics, 2017) and is the most frequent reason for hospital presentation for non-fatal self-harm (Geulayov, et al., 2016). Analgesics are the most common group of drugs involved in both intentional fatal (Värnik, et al., 2011) and non-fatal self-poisonings in the UK (Geulayov, et al., 2016; Prescott, et al., 2009). Some of the analgesic preparations used in overdoses are available for purchase over the counter (OTC) as well as on prescription, while others can only be obtained through prescription (e.g. codeine products). In the UK, paracetamol is the most common single drug used for non-fatal self-poisoning (Geulayov, et al., 2016; Prescott, et al., 2009). It is also responsible for a considerable number of fatal intentional self-poisonings, although this number has decreased since the introduction of reduced pack sizes (Hawton, et al., 2013; Hawton, et al., 2004). Ready availability is probably a major reason why analgesics, especially paracetamol (Hawton, et al., 1995), are commonly used for self-poisoning. However, the recognised association between pain and risk of suicidal behaviour (Tang & Crane, 2006; Theodolou, et al., 2005) and the particular availability of analgesics to those suffering pain are also likely to be relevant.

It is important to assess the relative toxicity of individual analgesics in order to provide information to assist clinicians making decisions about which drugs to prescribe, especially to patients at possible increased risk of self-poisoning. Such

information is also important for regulatory agencies responsible for issuing safety messages and for controlling availability of drugs. Furthermore, it is relevant to suicide prevention policy. Finally, it may assist pathologists and coroners when making decisions about likely causes of death by poisoning.

In an earlier study we used the case fatality approach, in which the rate of death involving specific drugs is compared to the rate of their use in non-fatal self-poisoning (Rose & Unis, 2000; White, et al., 2008) to study the relative toxicity of the analgesic co-proxamol (paracetamol combined with dextropropoxyphene). Co-proxamol appeared to be 28 times more toxic than paracetamol (Hawton, Simkin, et al., 2003). This finding, together with evidence of a large number of fatal intentional poisonings with the drug, resulted in an investigation by the Medicines and Health products Regulatory Agency (MHRA) and the subsequent decision to withdraw co-proxamol in the UK, an initiative which appears to have prevented a large number of deaths from analgesic overdoses (Hawton, et al., 2009; Hawton, et al., 2012). We have also previously used the case fatality approach to assess relative toxicity of antidepressants (Hawton, et al., 2010).

We have employed the case fatality approach to investigate the relative toxicity of analgesics currently most commonly used for fatal and non-fatal self-poisoning in the UK.

Methods

Study analgesics

The analgesics we investigated in this study were paracetamol (acetaminophen in the USA), aspirin (acetylsalicylic acid), codeine, dihydrocodeine, tramadol, paracetamol with codeine (co-codamol), paracetamol with dihydrocodeine (co-dydramol) and ibuprofen. All except paracetamol, aspirin and ibuprofen are only available on prescription. The period covered by the study was 2005-2012. We also included the analgesic co-proxamol (paracetamol plus dextropropoxyphene) because, although it was withdrawn for reasons of high toxicity at the end of 2008 (Committee on Safety of Medicines, 2006; Medicines & Healthcare products Regulatory Agency, 2005), it provided a useful comparison for the toxicity findings of the other relatively toxic analgesics.

Deaths

Information on drug poisoning deaths receiving a coroner's verdict of intentional self-poisoning or death of undetermined intent (open verdict) that involved the analgesics under investigation was provided by the Office of National Statistics based on year of death during 2005-2012 in England, including deaths which were registered up to the end of 2013. We included open verdicts because this is current policy with regard to suicide statistics and research in the UK as it is recognised that such deaths are often likely to have been intentionally self-inflicted (Gunnell, et al., 2013; Office for National Statistics, 2015b). Intentional self-poisonings and open verdicts are henceforth termed 'suicides'. Death data were obtained for males and females separately for all drugs.

At the inquests coroners would have had full access to pathology findings from the post mortem examinations including, for example, results of blood tests.

Non-fatal self-poisoning

Self-poisoning data were obtained from the three centres currently involved in the Multicentre Study of Self-harm in England (Geulayov, et al., 2016; Hawton, et al., 2007). In this study data are collected on all people who present with self-harm to emergency departments at general hospitals in Oxford (one hospital), Manchester (three hospitals) and Derby (two hospitals until 2009, subsequently merged into one hospital). Self-harm is defined as intentional non-fatal self-poisoning or self-injury irrespective of degree of suicidal intent or other motives (Hawton, Harriss, et al., 2003; National Institute for Health and Clinical Excellence (NICE), 2011). Self-poisoning with drugs includes the intentional ingestion of more than the prescribed amount of any drug, whether or not there is evidence that the act was intended to result in death. In the Multicentre Study, data are collected on gender, age, date and method of self-harm, including the specific drugs ingested. Results of blood tests would have been available to clinicians. The analyses for non-fatal self-poisoning were based on all non-fatal overdoses involving the analgesics under investigation, including those with other drugs (with or without alcohol).

Episodes of self-poisoning resulting in hospital presentation involving the study analgesics in people aged 15 years and over in the defined population areas of Oxford City, Manchester City and Derby Unitary area were included in the study. Mid-year population estimates for these areas for 2005-2012 were obtained from the

Office for National Statistics. Rates of self-poisoning per 100,000 person-years were calculated for these areas combined.

Alcohol involvement

Information on the presence of alcohol in cases of fatal self-poisoning was obtained from ONS records and was based on the coroner's toxicology report.

Statistical analysis

We calculated rates of suicide by self-poisoning per 100,000 person-years using England's mid-year population estimates for 2005-2012 obtained from the Office for National Statistics (Office for National Statistics, 2016). Rates of non-fatal self-poisoning were based on the number of episodes of non-fatal self-poisoning per 100,000 person-years using mid-year population estimates obtained from ONS (Office for National Statistics, 2016) for 2005-2012 for the geographical areas covered by the Multicentre Study of Self-harm (Oxford City, the City of Manchester, and Derby Unitary area

Case fatality for specific drugs was calculated as the ratio between the number of deaths involving each drug to the total number of episodes of non-fatal self-poisoning with each drug. These were related to case fatality for paracetamol (reference drug). Paracetamol was chosen as the reference drug because it has a long history of extensive use in the UK (and other countries), including for intentional poisoning (Hawton et al, 2013). Confidence intervals for case fatality indices were calculated using the Poisson distribution.

We conducted two analyses. The first included only deaths involving single drugs. The second included these deaths plus cases where multiple drugs were recorded but the study analgesic was the first drug listed by the coroner. We did this on the basis that the first recorded drug was likely to be the most important in contributing to the death. In cases where the first drug was a combination of paracetamol and another analgesic (e.g. paracetamol and codeine) the drug was identified as the single combination drug (as per Office for National Statistics policy).

We stratified the analysis by gender and also examined fatal self-poisoning by alcohol involvement.

Statistical analysis was carried out using Stata 14.1.

Ethical approval

The monitoring systems for self-harm in Oxford and Derby have approval from local Health/Psychiatric Research Ethics Committees to collect data on self-harm for local and multicentre projects. Self-harm monitoring in Manchester is part of a clinical audit system, and has been ratified by the local Research Ethics Committee. All three monitoring systems are fully compliant with the Data Protection Act (1998). All centres have approval under Section 251 of the National Health Services (NHS) Act (2006) to collect patient identifiable information without explicit patient consent.

We obtained specific approval from ONS to obtain mortality data.

Results

Fatal and non-fatal poisonings

Table 1 shows the numbers of suicide deaths involving each of the study drugs in 2005-2012 in England where these were recorded as single drug deaths as well as multiple drugs deaths in which the study drug was the first drug recorded (with or without alcohol), together with the suicide death rate for each drug per 100,000 person-years. During the eight year study period there were 1462 single-drug suicide deaths by poisoning involving the analgesics included in this study (excluding co-proxamol). As can be seen in Table 1, the most frequently involved analgesic was paracetamol, with relatively large numbers also for tramadol, dihydrocodeine, and co-codamol. There were a further 471 deaths in which multiple drugs were identified and one of the study analgesics was listed first on the death certificates. There was also a relatively large number of deaths involving co-proxamol, but this was withdrawn in the UK at the end of 2008.

Also shown in Table 1 is the number of non-fatal self-poisoning episodes involving each analgesic from the Multicentre Study of Self-harm in England, together with the population-based rates for each drug. By far the highest rates were for paracetamol, with relatively high rates also for ibuprofen and co-codamol.

(Table 1 about here)

Case fatality

The ratios of suicide poisonings to non-fatal poisonings for each of the study analgesics relative to paracetamol (reference drug) are shown in Table 2. Overdoses of dihydrocodeine and tramadol were both considerably more likely to result in death compared to paracetamol. The relative toxicity of dihydrocodeine was particularly marked, with a ratio nearly 13 times that of paracetamol. For tramadol the figure was more than four times greater. For dihydrocodeine the relative toxicity index appeared greater in females, although no formal gender comparison was conducted. Codeine also appeared more toxic in overdose relative to paracetamol.

The findings for co-proxamol shown in Table 2 confirmed the well-recognised very high relative toxicity for this drug.

(Table 2 about here)

When the suicide death data were based on one of the study analgesics being the first-named drug in multiple drug deaths (together with the data for single drug deaths) there was a very similar pattern of findings; overdoses of dihydrocodeine and tramadol were approximately 17 and six times, respectively, more likely to result in death than an overdose of paracetamol while an overdose of codeine was almost three times more likely to result in death relative to paracetamol. However, the toxicity indices in this analysis appeared higher than those calculated including only single-drug fatal overdoses (see Table 3), although the models were not compared directly.

(Table 3 about here)

There were few deaths involving ibuprofen and its case fatality was very low (Tables 2 and 3).

Alcohol

We examined alcohol involvement in fatal single drug overdoses, as this would provide the best evidence for any interaction with specific analgesics. The number and percentage of fatal single drug overdoses in which there was evidence of alcohol involvement were, in order of relative percentages (n, %): aspirin (3, 7.9%); tramadol (27, 14.0%); paracetamol (81, 16.2%); dihydrocodeine (28, 18.7%); paracetamol and dihydrocodeine (6, 20.7%); ibuprofen (3 25.0%); paracetamol and codeine (35, 25.2%) and codeine (37, 27.6%). While there were differences between the study analgesics in terms of the proportion of alcohol involvement these do not seem to suggest major specific interactions consistent with the increases in toxicity. The equivalent figures for the two analgesics associated with higher toxicity indices were similar (18.7% for dihydrocodeine and 14.0% for tramadol). For co-proxamol the figures were 53 and 19.9%.

Discussion

Analgesics are the drugs which are most frequently used for both fatal and non-fatal intentional self-poisoning in the UK (Geulayov, et al., 2016; Prescott, et al., 2009; Värnik, et al., 2011). It is therefore important to assess which analgesics are the most toxic as this can aid prescribing practices and also inform regulatory agencies. We have assessed relative toxicity of analgesics commonly used for fatal and/or

non-fatal self-poisoning in the UK by assessing case fatality based on numbers of fatal to non-fatal self-poisonings. We have previously used this approach in assessing the relative toxicity of co-proxamol (Hawton, Simkin, et al., 2003) and antidepressants (Hawton, et al., 2010). For antidepressants we have previously shown that the case fatality approach produced similar findings to those derived from evaluating the toxicity of antidepressants in terms of rates of death relative to rates of prescribing (i.e. fatal toxicity approach) (Hawton, et al., 2010). However, the latter approach could not be used here as some of the study drugs are mostly sold over the counter rather than obtained by prescription.

The results have highlighted the relatively high toxicity of dihydrocodeine and tramadol, and to a lesser extent codeine. These are prescription-only drugs in the UK. Relative high fatal toxicity of both tramadol and codeine was also found in a study in Finland based on deaths related to overall consumption of these drugs (Ojanpera, et al., 2016). In 2009 the UK Medicines and Health Products Regulatory Agency issued warnings about analgesics containing codeine or dihydrocodeine (Medicines and Health Products Regulatory Agency, 2009). In 2015 the UK Office for National Statistics reported steadily rising numbers of poisoning deaths involving tramadol between 2010 and 2014 in England and Wales, with a total of 240 deaths registered in 2014 in which tramadol was mentioned on death certificates (not all being recorded as suicides) (Office for National Statistics, 2015a). In 2016 184 poisoning deaths and in 2017 185 deaths were attributed to tramadol (Office for National Statistics, 2018). Toxicity of tramadol appears to be related to its tendency to cause seizures and respiratory depression (Ryan & Isbister, 2015). The numbers of deaths from poisoning with dihydrocodeine in England and Wales were 100 in

2016 and 94 in 2017 (The Statistics Portal, 2018). Poisoning deaths involving codeine have risen in England and Wales in recent years, with 131 deaths recorded in 2016 and 156 in 2017 (Office for National Statistics, 2018). It is interesting to note that the considerably elevated toxicity of dihydrocodeine and codeine was not found where these drugs were combined with paracetamol. This raises the question of whether there may be confounding factors which influence access to larger amounts of codeine or dihydrocodeine which might affect risk of fatal poisoning in some individuals, such as drug misuse and chronic pain.

It should be noted that the toxicity of co-proxamol, which we previously showed to be high using the case fatality approach (Hawton, Simkin, et al., 2003) and which was followed by announcement of withdrawal of this drug in 2005 (Committee on Safety of Medicines, 2006; Medicines & Healthcare products Regulatory Agency, 2005), was much greater in this study than the toxicity of either dihydrocodeine or tramadol. Nevertheless, the findings from the present study highlight the need for caution in the prescribing of these latter two drugs, and also codeine, especially in patients who might be at risk of self-harm (e.g. previous history of self-harm, family history of suicidal behaviour, depression, alcohol misuse).

We also found low case fatality for ibuprofen. While this drug is frequently used in non-fatal self-poisoning it is rarely a cause of death from overdose. It does, however, carry significant risk of gastric bleeding, especially in chronic use (Garcia Rodriguez & Jick, 1994).

There was no indication from the single drug deaths analysis that the potential interaction between the study drugs and alcohol was a major contributory factor to the increase in deaths involving specific drugs. However, involvement of alcohol in overdoses of drugs which are likely to cause respiratory depression, especially opiates, would be expected to increase the risk of death.

In terms of the contribution of specific analgesics to fatal poisonings, the relatively large number of deaths involving paracetamol should be noted. This reflects the very high rate of use of this drug for self-poisoning in the UK (Geulayov, et al., 2016; Prescott, et al., 2009). Thus, while paracetamol is clearly less toxic than several other analgesics, strategies to reduce the extent of its use for poisoning, especially in large amounts, and to improve treatment where substantial numbers of tablets are consumed, are clearly extremely important.

Strengths and limitations

The fact that study spans eight years of data allowed us to include a large number of suicide deaths (N = 1462 in total) and of non-fatal self-poisoning episodes (N = 2169 per year) (excluding co-proxamol).

The suicide figures were based on national data, whereas those for non-fatal self-poisoning were based on local data collected in three research centres which form the Multicentre Study of Self-harm in England. While one might question the extent to which the latter data are nationally representative, the centres are based in communities with diverse populations in terms of socio-economic characteristics and rates of self-harm (Geulayov, et al., 2016).

A substantial number of the deaths involved ingestion of multiple drugs, for which there must be uncertainty in some cases about which drugs were most likely to have contributed to death and the effect of possible interactions between drugs. Interactions between analgesics (especially opioids) and, for example, benzodiazepines and non-benzodiazepine hypnotics, may contribute to toxicity (Hakkinen, et al., 2012). But similar results were obtained when we analysed case fatality based on single drug deaths and when multiple drug deaths were used but the study drugs were the first listed on the death certificates. This was based on the assumption that the first listed drug would have been the main contributor to death. For non-fatal poisonings we included all drugs ingested in multiple drug overdoses as we had no indication of what would have been the "main" drug. Also, in the Multicentre Study of Self-harm database we cannot isolate the drug of interest from the possibility that the person had consumed other medications and therefore cannot provide the proportion of single drug non-fatal overdoses in the same way that we have for the ONS data. Furthermore, we had no information on dosages of drugs and number of tablets consumed in either fatal or non-fatal overdoses.

We included fatal poisonings where alcohol was ingested but have no reason to believe that there were major differences between the drugs in this respect. Indeed, for all the analgesics alcohol was recorded as being present in the deceased's blood in fewer than 30% of the single drug deaths. Also, there were no difference between the analgesics that suggested an association with relative toxicity, making it unlikely that it was a significant contributor to the findings.

Generalisability of the findings to other countries has some limitations. This particularly applies to the USA. While the relative toxicity findings for the analgesics we have studied are likely to be applicable there, the most significant problem regarding analgesic poisonings in the USA concerns the major increases in deaths involving other opioids, such as oxycodone (The Lancet, 2017).

Conclusions

Applying a previously used measure of relative toxicity (case fatality) we have shown that of analgesics commonly used for fatal and/or non-fatal self-poisoning, dihydrocodeine and tramadol were more toxic in overdose, and to a lesser extent codeine, relative to paracetamol. While these drugs may have important roles in pain management, caution clearly needs to be exercised in prescribing them, especially for individuals who may be at risk of self-poisoning.

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Competing interests

KH has provided evidence to the Medicines and Health Products Regulatory Agency regarding paracetamol and co-proxamol.

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KH and DG are NIHR Senior Investigators

Table 1 Total numbers and rates of deaths by intentional self-poisoning and undetermined intent ('suicides') in England, and the numbers of non-fatal self-poisoning episodes per year, involving each analgesic, with rates of non-fatal self-poisoning in the Multicentre Study of Self-harm in England in persons aged 15 years and over, 2005–2012

	Single-drug deaths in England, total n	Death rate per 100,000, population	First-listed drug deaths in England, total n	Total single and first-listed drug deaths in England, total n	Death rate per 100,000 population	Total N of non-fatal self-poisonings in the Multicentre Study [average n per year]	Self-poisoning rate per 100,000 population
Paracetamol	500	0.146	81	581	0.170	8671 [1084]	151.3
Aspirin	38	0.011	9	47	0.014	811 [101]	14.1
Codeine	134	0.039	73	207	0.061	1052 [132]	18.4
Dihydrocodeine	150	0.044	78	228	0.067	203 [25]	3.5
Tramadol	193	0.056	131	324	0.095	827 [103]	14.4
Paracetamol with codeine (co-codamol)	139	0.040	55	194	0.057	2241 [280]	39.1
Paracetamol with dihydrocodeine (co-dydramol)	29	0.009	15	44	0.013	367 [46]	6.4
Ibuprophen	12	0.004	1	13	0.004	3185 [398]	55.5
Co-proxamol (paracetamol plus dextropropoxyphene)*	267	0.078	28	295	0.086	75 [9]	1.3

* Withdrawn in the UK at the end of 2008

Table 2 Case fatality: the ratio of the number of suicides involving each drug to the number of non-fatal self-poisoning episodes relative to the equivalent ratio for paracetamol: single-drug only, by gender

	Odds ratios (95% CI)		
	All	Males	Females
Paracetamol	Reference	Reference	Reference
Aspirin	0.81 (0.58-1.14)	1.03 (0.69-1.55)	0.47 (0.25-0.89)
Codeine	2.21 (1.81-2.70)	2.37 (1.79-3.12)	1.98 (1.47-2.67)
Dihydrocodeine	12.81 (10.19-16.12)	9.45 (6.90-12.93)	16.29 (11.62-22.80)
Tramadol	4.05 (3.38-4.85)	3.93 (3.07-5.05)	3.87 (2.97-5.05)
Paracetamol with codeine (co-codamol)	1.08 (0.89-1.31)	1.24 (0.96-1.61)	0.89 (0.67-1.20)
Paracetamol with dihydrocodeine (co-dydramol)	1.37 (0.93-2.02)	1.62 (0.99-2.65)	1.01 (0.53-1.93)
Ibuprofen	0.07 (0.04-0.12)	0.08 (0.03-0.17)	0.06 (0.03-0.14)
Co-proxamol (paracetamol plus dextropropoxyphene)*	61.74 (47.06-81.00)	70.95 (46.16-109.06)	53.81 (37.61-76.99)

*Withdrawn in the UK at the end of 2008

Table 3 Case fatality: the ratio of the number of suicides involving each drug to the number of non-fatal self-poisoning episodes relative to the equivalent ratio for paracetamol: single-drug overdoses combined with multiple drug overdoses where the study analgesic the first listed drug, by gender

	Odds ratio (95% CI)		
	All	Males	Females
Paracetamol	Reference	Reference	Reference
Aspirin	0.87 (0.64-1.17)	1.08 (0.74-1.56)	0.53 (0.30-0.93)
Codeine	2.94 (2.48-3.49)	3.10 (2.44-3.93)	2.68 (2.09-3.44)
Dihydrocodeine	16.76 (13.63-20.62)	12.01 (9.04-15.97)	21.98 (16.25-29.73)
Tramadol	5.85 (5.02-6.82)	5.59 (4.51-6.93)	5.72 (6.10-9.63)
Paracetamol with codeine (co-codamol)	1.29 (1.09-1.53)	1.44 (1.14-1.82)	1.12 (0.87-1.44)
Paracetamol with dihydrocodeine (co-dydramol)	1.79 (1.30-2.47)	1.76 (1.12-2.74)	1.74 (1.09-2.80)
Ibuprofen	0.06 (0.04-0.11)	0.08 (0.04-0.16)	0.05 (0.02-0.12)
Co-proxamol (paracetamol plus dextropropoxyphene)*	58.70 (44.95-75.67)	65.45 (42.78-100.14)	53.05 (37.40-75.24)

*Withdrawn in the UK at the end of 2008

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