

Paracetamol related deaths in England and Wales, 1993–97

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INTRODUCTION

There are about 2,500 deaths from overdose and poisoning in England and Wales every year.¹ Many of these deaths are likely to be preventable and hence action aimed at reducing such deaths could bring significant public health benefits. The most common cause of non-opiate related deaths is paracetamol, which can cause fatal liver disease if taken either intentionally or unintentionally in too high a dose (Box one). Intentional overdosage of paracetamol is thought to cause about 100–200 deaths per year in England and Wales.^{2,3}

In *Our Healthier Nation*, the Department of Health set a target to reduce the death rate from suicide and undetermined injury by 20 per cent by 2010.⁴ Many people who commit suicide do so by taking a drug overdose, for example, an analgesic such as paracetamol. To try to limit the number of people who use an overdose of paracetamol as the method of suicide, in November 1998 the Medicines Control Agency restricted the quantity of paracetamol that can be bought in one purchase.⁵ The effect this intervention has had on deaths from paracetamol is not yet known.

Previous estimates of deaths caused by paracetamol have been based on local studies which may not give the true national picture or national studies which are based on data which have had a number of limitations.^{6,7} Until 1992, figures on deaths from overdose and poisoning in England and Wales were extracted manually from the registration forms received by the Office of Population Censuses and Surveys. This was a very cumbersome process and was made even more difficult because drugs were listed exactly as they were recorded on the coroner's certificate. Hence, drugs could be listed under either their trade or brand name. Many drugs are also part of compound preparations. This made it difficult to ensure that all deaths due to a

Paracetamol can cause fatal liver disease if taken, either intentionally or unintentionally in too high a dose. Using a newly developed database of deaths from overdose and poisoning, we examined the mortality associated with paracetamol in England and Wales between 1993–97. In total, there were 2,499 deaths during this period in which preparations containing paracetamol were among the drugs taken, an average of about 500 deaths per year and about 20 per cent of all deaths from overdose and poisoning. Paracetamol was the only drug taken in 873 deaths, an average of about 175 deaths per year; this figure probably provides a better estimate of the true mortality associated with paracetamol than all deaths from overdose and poisoning in which paracetamol was taken. There were 488 deaths in which liver failure was specifically mentioned. The most commonly used preparations of paracetamol were paracetamol alone (1,451 deaths) and coproxamol (991 deaths). The study confirms that paracetamol is one of the important causes of deaths from overdose and poisoning and shows the value of the new database for monitoring trends in these deaths.

specific drug had been identified. This was particularly a problem for paracetamol which is sold under many different brand names and is also found in several different compound preparations.

Box one

WHY PARACETAMOL CAN BE DANGEROUS

Taken in its normal dosage, paracetamol is a safe and effective painkiller. It can also reduce the temperature of children and adults with fever, and is commonly used for this purpose. Taken in too high a dose, however, paracetamol can be dangerous and can cause fatal liver disease. Metabolites of paracetamol have a toxic effect on the cells of the liver (hepatocytes). This toxic effect may be caused by as few as twelve tablets of paracetamol. However it may take several days before symptoms develop. The widespread availability of paracetamol makes it a commonly used means of committing suicide. In addition, a lack of awareness of the potential dangers of exceeding the recommended dose means that accidental poisoning is also an important cause of death from paracetamol.

CLINICAL FEATURES OF PARACETAMOL POISONING

Initial symptoms after taking more than the recommended dosage are often no more than mild nausea and vomiting. As liver damage develops over the following days, right sided abdominal pain may be experienced. If no treatment is given to halt or reverse the liver failure then a build up of toxins in the body can lead to confusion, jaundice, an inability to clot blood, swelling of the brain and subsequent death. Because paracetamol by itself does not immediately cause drowsiness or unconsciousness, and the delay in developing serious symptoms, both reduce the likelihood of help being sought at an early stage. Establishing paracetamol poisoning as early as possible is vital because it is possible to prevent liver damage by administering an antidote. If treatment is given within six hours of taking paracetamol, death can usually be prevented.

TREATMENT

The first aim of treatment is to prevent paracetamol from being absorbed from the digestive system. If the person arrives at the hospital within an hour of taking the overdose, a special activated charcoal in liquid form can be swallowed and stop the tablets being absorbed into the body. An antidote is also available to halt or reverse the damaging effects of paracetamol on the liver. This works by stopping toxic metabolites of paracetamol from attaching to liver proteins and thus causing damage to liver cells. This treatment should be started as early as possible and ideally within the first six hours. If liver failure cannot be reversed or halted, liver transplantation remains the only option available. However this option is not suitable for every-one and will depend on the clinical condition of the patient and will depend on the availability of a liver from a suitable donor. Further information on the treatment of paracetamol poisoning is available from the National Poison's Unit at Guy's Hospital in London.

From 1993 onwards, data from the registration forms have been stored electronically with the relevant drugs stored as a textual entry. Since 1993, it has been possible to perform electronic searches of the information transcribed from the registration form. This has simplified the identification of deaths from overdose and poisoning but does not overcome the problem of ensuring that all the different brand names of a drug such as paracetamol are identified. To overcome this problem, all drugs on the electronic record have been coded to British National Formulary (BNF) categories. All preparations containing paracetamol have also been identified. These developments now allow information on the number of deaths associated with a specific drug to be extracted more easily than in the past. Information can also be extracted on deaths where more than one drug was used. The new database also makes it possible to look at deaths from overdose and poisoning in relation to other factors such as age, sex and other diagnoses recorded on the death certificate.

A further problem which is specific to paracetamol-related deaths is how we define these deaths. Ideally, only deaths where liver disease occurred after ingesting paracetamol would be included in the definition of paracetamol-related deaths. A broader definition would include deaths in which paracetamol has been mentioned on the registration form or detected either alone or in combination with other drugs on toxicological analysis regardless of whether or not liver disease was noted.

Because of the difficulties in obtaining accurate national data on deaths associated with paracetamol, there have been only a few national studies and none which have been carried out recently.^{2,7} In this article, we use the newly-enhanced database of deaths from overdose and poisoning to examine the epidemiology of deaths associated with the ingestion of paracetamol, and compare the results with those published previously by other researchers.

METHODS

Definition of deaths from overdose and poisoning

Deaths which are not due to natural causes or where the cause of death is not known must be referred to the coroner for further investigation.⁸ In such cases, the coroner may order a post-mortem and then hold an inquest. Any sudden, unexpected deaths in which a drug is involved fall into this category; in virtually all of such deaths the coroner orders an inquest and carries out a post-mortem. The coroner uses information from the post-mortem and any additional information available to decide the cause of death and to give a verdict. The coroner then certifies the death and sends a certificate to the registrar of births and deaths who completes a registration form. Part V of the certificate issued by the coroner provides details about the circumstances surrounding accidental deaths. This section must be completed compulsorily for accidental deaths and may also be filled in for non-accidental deaths.⁹ The registrar then sends information on the registration form and Part V of the coroner's certificate to the Office for National Statistics for coding.

The underlying cause of death in all people dying in England and Wales is classified using the Ninth Revision of the International Classification of Diseases (ICD9). With two exceptions, deaths from overdose and poisoning are coded by the Office of National Statistics to a number of ICD9 codes (Box two). The first exception is deaths due to an adverse reaction from a drug used for therapeutic purposes (i.e. deaths from the side-effects of a drug). Information on these deaths is collected and monitored by the Medicines Control Agency. The second exception is deaths due to tobacco or alcohol, which are not classified as drug-related. The presence of alcohol is however noted on the database of deaths from overdose and poisoning if it has been mentioned on the coroner's certificate.

Box two

ICD9 CODES USED TO CLASSIFY DEATHS FROM OVERDOSE AND POISONING

ICD9 code	Description
304	Drug dependence
305.2 - 305.9	Non-dependent abuse of drugs
E850 - 858	Accidental poisoning by drugs, medicaments and biologicals
E950.0 - E950.5	Suicide and self-inflicted poisoning by solid or liquid substances
E962.0	Assault by poisoning
E980.0 - E980.5	Poisoning by solid or liquid substances, undetermined whether accidentally or purposely inflicted

After classification as a death from overdose and poisoning, information on these deaths is entered onto an Access database, using data from both the registration form and the coroner's certificate. The information recorded includes administrative data such as age, sex and postcode; the cause of death; and any intermediate causes of death mentioned on the death certificate (such as respiratory or liver failure). Additional information recorded on the database includes the name of any drug mentioned on the registration form or on the coroner's certificate, the BNF codes of the drugs taken, and whether any of the drugs taken contained paracetamol or aspirin. Information is now available on the database for all deaths from overdose and poisoning between 1993–97.

Definition of paracetamol-related deaths

Paracetamol-related deaths were defined as any deaths in which paracetamol, or a compound preparation containing paracetamol, was mentioned as one of the drugs taken in a drug-related death. Paracetamol may have been the only drug taken; it may have been part of a compound preparation; or it may have been taken with one or more other drugs.

A text search of the database was undertaken to identify any paracetamol related deaths associated with liver disease (defined as liver failure, liver necrosis, hepatic failure, hepatic necrosis, fatty change in liver, hepatorenal failure and multi-organ failure). There is considerable variation in the terminology used for death certification and a certain number of deaths may not be included had the analysis been based on a manual search for deaths. Deaths from alcoholic liver disease were excluded from the analysis because we were interested only in acute or recent changes to the liver which may be ascribed to the ingestion of paracetamol rather than the chronic or long term changes caused by the ingestion of excess alcohol over a long period of time. Using the information available on the database, we examined the demographic characteristics of deaths associated with the ingestion of paracetamol in terms of the presence or absence of liver disease. We then compared deaths involving paracetamol as the only drug with deaths in which paracetamol was taken either in combination with at least one other drug or as part of a compound preparation.

RESULTS

There were 2,499 paracetamol-related deaths during the period 1993–97, an average of about 500 deaths per year and about 20 per cent of all

deaths from overdose and poisoning during this period. The most commonly used preparations were paracetamol (1,451 deaths) and coproxamol (991 deaths) (Table 2). Of the other commonly available compound preparations containing paracetamol, cocodamol was associated with 44 deaths and codydramol with 35 deaths. Paracetamol was the only drug taken in 873 deaths, an average of about 175 deaths per year (Table 1). This figure of 175 deaths per year is likely to be a better estimate of the true mortality associated with paracetamol than the figure based on all deaths where paracetamol was one of the drugs taken.

Table 1 Paracetamol-related deaths in England and Wales, 1993–97

	Number of deaths
Paracetamol taken alone or with one or more other drugs or in compound	2,449
Paracetamol taken as an opiate-based compound only	875
Paracetamol taken alone	873
Paracetamol taken with one or more other drugs and liver disease	488
Paracetamol taken alone and liver disease	449
Paracetamol taken in a compound preparation with no other drugs and liver disease	14

Table 2 Preparations of paracetamol taken in paracetamol associated deaths

Preparation	Prescription only	Number of deaths
Paracetamol	No	1,451
Coproxamol	Yes	991
Paracetamol (325mg) and Dextropropoxyphene (32.5mg) E.g.: Distalgesic, Fortagesic		
Co-codamol	Yes	44
Paracetamol (500mg; 1000mg) and Codeine (8mg; 30mg; 60mg) E.g.: Kapake; Migraleve; Tylex; Solpadol; Solpadeine.		
Co-dydramol	Yes	35
Paracetamol (500mg) and Dihydrocodeine Tartrate (10mg; 20 mg, 30mg) E.g.: Paramol; ¹ Remedeine		

¹Paramol (paracetamol 500mg and dihydrocodeine 7.46mg) can be bought without a prescription.

The number of paracetamol associated deaths per year increased from 463 in 1993 to 562 in 1997. The number of deaths was similar in men and women and differs from deaths from overdose and poisoning overall in which the deaths in men exceed the deaths in women by a ratio of 2:1. The mean age of death overall is 47 years with deaths occurring at a younger age in males (44 years) than in females (50 years). The number of paracetamol related deaths was highest in people aged 30–44 years (751 deaths) followed by the age group 45–59 years (563 deaths) and lowest in people aged 75 years and over (excluding children aged 0–14 years). However using age group specific mortality rates, people aged over 75 years have the highest rate of death in women and the second highest rates of death in men (Table 3).

There were 488 deaths associated with liver disease or liver failure (Table 4). In over 90 per cent (449) of these deaths, paracetamol was taken alone. More female deaths have a record of liver disease than males (280 versus 208). Overall the mean age of these deaths was 44 years. There was little difference in the age of death in males (44.0 years) and females (44.2 years). The age group with the highest number of deaths associated with documented liver failure were 30–44 years olds.

Table 3 Numbers of paracetamol related deaths and annual death rates by age and sex in England and Wales, 1993–97

Age group	Males		Females	
	Number	Rate per million	Number	Rate per million
0–14	3	0.12	9	0.37
15–29	290	10.65	214	8.26
30–44	437	15.36	314	11.29
45–59	292	12.66	271	11.70
60–74	169	10.30	241	12.92
75 and over	84	13.17	175	14.51
Total	1,275	10.03	1,224	9.28

The verdicts on intent following the inquest into paracetamol-related deaths are shown in Table 5. Of these deaths, 78 per cent were either of undetermined intent or suicide, the two categories usually used to define suicide. In about 20 per cent of deaths, the verdict was accidental poisoning. For deaths where paracetamol was the only drug taken, about 74 per cent were either suicide or of undetermined intent. Where liver disease or liver failure was mentioned, 65 per cent of paracetamol related deaths were due to either suicide or undetermined intent.

Table 4 Numbers of paracetamol related deaths associated with liver disease and annual rates by age and sex in England and Wales, 1993–97

Age group	Males		Females	
	Number	Rate per million	Number	Rate per million
0–14	2	0.08	3	0.12
15–29	34	1.25	65	2.51
30–44	77	2.71	94	3.38
45–59	59	2.56	54	2.33
60–74	26	1.58	43	2.30
75 and over	10	1.57	21	1.74
Total	208	1.64	280	2.12

DISCUSSION

This study confirms that paracetamol-associated deaths are an important cause of mortality. Paracetamol is an easily available drug and can be bought as an 'over the counter' medicine. Its ready availability may explain the frequency of its use in deaths from overdose and poisoning. The Medicines Control Agency reduced the maximum number of tablets of paracetamol that can be bought in one purchase to 32 in November 1998 but it remains too early to examine the effect of this on paracetamol-associated deaths. This will be investigated once the data for 1999 are available for analysis.

The average annual number of deaths from paracetamol varies considerably, depending on how the death is defined, ranging from 500 deaths per year for all deaths from overdose and poisoning in which paracetamol was mentioned, to 175 deaths per year where paracetamol was the only drug taken, and to about 90 deaths per year when liver disease has been documented and paracetamol was the only drug taken. The true mortality associated with paracetamol is likely to be around the 175 deaths per year where paracetamol was the only drug taken. Paracetamol-only preparations are the most commonly named drugs

Table 5 Deaths by category of intent associated with the ingestion of paracetamol

ICD 9 code	Intent	Total number of deaths	Percentage of total paracetamol related deaths	Deaths with liver disease	Percentage of total paracetamol related deaths
E980	Undetermined Intent	1,119	44.8	184	7.36
E950	Suicide	831	33.3	134	5.36
E850–858	Accidental	503	20.1	158	6.32
304	Drug dependence	14	0.6	2	0.08
305	Non-dependent abuse	31	1.3	10	0.40
962	Homicide	1	0.04	-	-
	Total	2,499	100.0	488	19.5

associated with these deaths. The most commonly taken compound preparation of paracetamol is co-proxamol, which is made up of paracetamol and dextropropoxythene. Either of these two components can cause death; paracetamol causes a long-drawn out death whereas dextropropoxythene causes rapid death.

The number of deaths involving paracetamol in men and women is similar. This differs from deaths from overdose and poisoning overall where approximately two-thirds of the deaths occur in males. The highest number of deaths occur in the age group 30–44 years in both men and women. In women, the age specific mortality rate is highest in those over 75 years age. More women are reported as having died with liver disease than men but there is little difference in their respective mean ages.

The verdict after inquest is slightly more likely to be suicides in males (46 per cent of male deaths as opposed to 43 per cent of female deaths). By contrast slightly more women are given an open verdict than men (35 per cent versus 32 per cent). In the majority of these deaths the coroner's verdict is either suicide or undetermined intent. In contrast the majority of deaths with liver disease have a verdict of either undetermined or accidental intent. The relative risk of deaths from accidental intent in the people with liver failure was 1.90 (95% CI = 1.62–2.24). This may reflect the delay in seeking medical assistance and a lack of awareness of the potential danger of exceeding the stated dose of paracetamol.

Strengths and weaknesses of the study

The number of deaths associated with paracetamol varies according to how the death is defined. There is a five-fold difference in the number of deaths between the strictest definition when there is liver disease and paracetamol is the only drug recorded, and the broadest definition of a paracetamol-related death, where paracetamol may be found alone, as part of a compound preparation or in the presence of one or more other drugs. It is therefore important when monitoring deaths from paracetamol that the definition of a paracetamol-related death is precise.

There are variations that exist in the amount of additional information available on deaths from overdose and poisoning.⁹ They include variability in drug testing in hospitals and in the information noted and recorded on the coroner's certificate. Not every unexpected death will be tested for the presence of drugs and where testing is undertaken, testing for one specific drug is often encouraged. Where more than one drug is identified at the time of death it can be difficult to ascribe the primary cause of death to one particular drug. There is also considerable variability in the drug names recorded in the database of deaths from overdose and poisoning. This is firstly an indication of the

many different paracetamol-containing compounds are available on prescription and over the counter. Secondly, it indicates the variation in information recorded and transcribed from the death certificate and registration documents and the coroners certificate.

Despite these concerns, previously unused information about deaths from overdose and poisoning is now available and accessible from the new database. There is no upper limit to the number of drugs recorded for each death and at present, seven is maximum number of drugs recorded on the database. Data can be extracted using a range of variables including specific drug names, BNF code, age, sex, and geographical area. The database provides comprehensive information on deaths from overdose and poisoning for the whole of England and Wales and enables districts and regions to make comparisons to the national data. Information is currently available for five consecutive years and hence a more precise calculation of mortality rates is feasible than the local studies previously undertaken. Information from the coroner's inquest ensures that as much as possible of the details surrounding the death are accessible from the database to allow more accurate recording of drugs present at the time of death and the circumstances surrounding the death. Additional information on the dose of drug taken would also be useful as this would help establish how safe paracetamol is in therapeutic doses and in patients who may be predisposed to liver damage, such as those taking enzyme inducing drugs or who are malnourished.

Comparison with other studies

There is little current data available on deaths from overdose and poisoning in the published literature with the most recent articles using data from before 1990. Hence, the data described here are the most recent available. The most common ranges for the number of deaths attributable to paracetamol is 100–200 deaths per year. This study shows the mean annual number of deaths of deaths ranges from 90 to 500 deaths per year, depending on how a paracetamol-related death is defined.

Harvey and Spooner analysed deaths relating to paracetamol in 1978.¹⁰ They found the number of deaths in which paracetamol is identified as the cause of death alone or with other drugs is 212. Of these deaths, 105 were associated with paracetamol alone. Their final figure for deaths definitely due to paracetamol is 64, thirty percent of the deaths thought initially to be related to paracetamol. This definition of a death caused by paracetamol includes only those deaths where liver disease has occurred. A more recent analysis by the same authors looking at paracetamol deaths in 1990 identify 547 deaths from coroners returns in which paracetamol has been mentioned.² Of these, 150 deaths were considered to be caused as a result of acute liver failure following the ingestion of paracetamol.

By comparison, over the five years for which data are available on the database of deaths from overdose and poisoning, an average of about 290 deaths per year were associated with paracetamol alone or with paracetamol in a combined preparation. Of these deaths, paracetamol alone was recorded in about 175 deaths per year and liver disease recorded as the cause of death in about 92 deaths per year.

Unanswered questions and future research

Monitoring deaths associated with taking paracetamol provides an indication of the level of problem and a means of assessing the impact of interventions and policies aimed at reducing deaths by suicide or accidental poisoning. An accurate estimate of the deaths due to paracetamol is required to do this. As discussed earlier, there is a lack of clarity about how a paracetamol-related death should be defined. The data now available will help improve how such deaths are defined and

allow an assessment of the impact of restricting sales of paracetamol on deaths from accidental and intentional overdose. Annual updating of deaths from overdose and poisoning on the database provides a powerful tool to monitor trends in all deaths from overdose and poisoning which have been investigated by coroners' offices.

Key points

- Paracetamol can cause fatal liver disease if taken, either intentionally or unintentionally, in too high a dose.
- Between 1993–1997, there were 2,499 deaths in which preparations containing paracetamol were among the drugs taken, an average of about 500 deaths per year.
- Paracetamol was the only drug taken in 873 deaths, an average of about 175 deaths per year; this figure probably provides the best estimate of the true mortality associated with paracetamol overdosage and poisoning.
- There were 488 deaths associated with paracetamol in which liver failure was mentioned.
- The most commonly used preparations of paracetamol were paracetamol alone (1,451 deaths) and coproxamol (991 deaths).

REFERENCES

- 1 ONS Drug-related Deaths Database: first results for England and Wales, 1993–97. *Health Statistics Quarterly* 5 (2000), 57–60.
- 2 Spooner JB and Harvey JG. Paracetamol overdosage - facts not misconceptions. *Pharm J* 250 (1993), 706–7.
- 3 Fagan E, Wannan G. Reducing Paracetamol Overdoses. *British Medical Journal* 313 (1996), 1417–1418.
- 4 Department of Health. *Saving Lives: our healthier nation* (CM 4386). TSO (London: 1999).
- 5 Committee on Safety of Medicines, Medicines Control Agency. *Paracetamol and Aspirin. Current Problems in Pharmacovigilance*. 1997 (September); 23:9.
- 6 Hails FG and Whittington RM. Distalgesic and Paracetamol Poisoning. *British Medical Journal* 2 (6151) (1978), 1569–70.
- 7 Gunnell D, Hawton K and Murray V. Use of Paracetamol for Suicide and Non-fatal Poisoning in the UK and France: are restrictions on availability justified? *Journal of Epidemiology and Community Health* 51 (1997), 175–179.
- 8 Ashley J and Devis T. Death Certification from the Point of view of the Epidemiologist. *Population Trends* 67 (1992), 22–28.
- 9 Christophersen O, Rooney C and Kelly S. Drug-Related Mortality: Methods and Trends. *Population Trends* 93 (1998).
- 10 Harvey JG and Spooner JB. Paracetamol Poisoning. *British Medical Journal* 2 (1978), 832–3.

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