

Effects of legislation restricting pack sizes of paracetamol and salicylate on self poisoning in the United Kingdom: before and after study

Keith Hawton, Ellen Townsend, Jonathan Deeks, Louis Appleby, David Gunnell, Olive Bennewith, Jayne Cooper

Abstract

Objective To evaluate the effects on suicidal behaviour of legislation limiting the size of packs of paracetamol and salicylates sold over the counter.

Setting UK population, with detailed monitoring of data from five liver units and seven general hospitals, between September 1996 and September 1999.

Subjects People who died by suicidal or accidental overdose with paracetamol or salicylates, or who died of undetermined causes; patients admitted to liver units with hepatic paracetamol poisoning; patients presenting to general hospitals with self poisoning after taking paracetamol or salicylates.

Main outcome measures Mortality from paracetamol or salicylate overdose; numbers of patients referred to liver units or listed for liver transplant; numbers of transplantations; numbers of overdoses and tablets taken; blood concentrations of the drugs; prothrombin times; sales to pharmacies and other outlets of paracetamol and salicylates.

Results Numbers of tablets per pack of paracetamol and salicylates decreased markedly in the year after the change in legislation on 16 September 1998. The annual number of deaths from paracetamol poisoning decreased by 21% (95% confidence interval 5% to 34%) and the number from salicylates decreased by 48% (11% to 70%). Liver transplant rates after paracetamol poisoning decreased by 66% (55% to 74%). The rate of non-fatal self poisoning with paracetamol in any form decreased by 11% (5% to 16%), mainly because of a 15% (8% to 21%) reduction in overdoses of paracetamol in non-compound form. The average number of tablets taken in paracetamol overdoses decreased by 7% (0% to 12%), and the proportion involving > 32 tablets decreased by 17% (4% to 28%). The average number of tablets taken in salicylate overdoses did not decrease, but 34% fewer (2% to 56%) salicylate overdoses involved > 32 tablets. After the legislation mean blood concentrations of salicylates after overdose decreased, as did prothrombin times; mean blood concentrations of paracetamol did not change.

Conclusion Legislation restricting pack sizes of paracetamol and salicylates in the United Kingdom

Legislation on packaging of paracetamol and salicylates (16 September 1998)

- Pharmacies can sell a maximum of 32 tablets per sale (previously there was no limit), although they can still sell up to 100 tablets in justifiable circumstances
- Other retail outlets can sell a maximum of 16 tablets (the previous limit was 24)
- Specific warnings of the dangers of paracetamol overdose are now printed on packets and on leaflets in packets

has had substantial beneficial effects on mortality and morbidity associated with self poisoning using these drugs.

Introduction

Deliberate self poisoning with non-opiate analgesics, especially paracetamol, is common in the United Kingdom, resulting in a substantial number of deaths each year.¹⁻⁴ The increasing misuse of paracetamol has paralleled a rise in sales, and by implication greater availability, of the drug.⁵ Paracetamol is also responsible for approximately half of all cases of liver failure in the United Kingdom.⁶

On 16 September 1998 legislation was introduced in the United Kingdom limiting pack sizes of paracetamol, salicylates, and their compounds sold over the counter (box).⁷ The justification for the legislation was that analgesic self poisoning is often highly impulsive and associated with both low suicidal intent and limited knowledge of the possible consequences.^{8,9} There is evidence that mortality from paracetamol self poisoning is lower in countries with smaller maximum pack sizes than in the United Kingdom.⁵

We conducted a prospective study to assess the impact of this legislation on mortality from paracetamol and salicylate overdose; cases of liver poisoning after paracetamol overdose, as reflected in numbers of liver transplantations, referrals to liver units, and abnormal liver function tests; number and nature of cases of paracetamol and salicylate overdose; and sales of paracetamol and salicylates.

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Methods

Mortality from overdoses of paracetamol and salicylates

The Office for National Statistics supplied data on drug related deaths and deaths from undetermined cause in England and Wales for September 1996 to September 1999.¹⁰ The data for 1996 to 1998 indicated that data for 1999 required adjustment of 4.5% to account for cases still under coroner's review.

Liver transplantation and referrals to liver transplant units

Data on numbers of admissions after paracetamol overdose, patients listed for liver transplantation, and patients receiving transplants were supplied by five liver units in England for October 1996 to September 1999.

Non-fatal self poisoning with paracetamol and salicylates

Data were collected in Oxford (one hospital), Bristol and Bath (four hospitals), and Manchester (two hospitals) on all presentations with self poisoning between 16 September 1997 and 15 September 1999. Information was not available for Manchester for all salicylate overdoses. The number of tablets taken in each overdose was recorded. Data on blood paracetamol and salicylate concentrations and prothrombin times were recorded where such investigations occurred.

Sales data

Intercontinental Medical Statistics supplied data for September 1996 to September 1999 on monthly sales of paracetamol and salicylate preparations to pharmacies and other outlets in the United Kingdom. These data cover 97% of sales to pharmacies, including Boots (but excluding its brand name products). Because manufacturers were given 12 months' notification of the legislation, sales in the 12 months after the new legislation were compared with those in the penultimate 12 months before legislation.

Statistical analyses

Rates of death, non-fatal self poisoning, admission to liver units, listing for liver transplantation, and transplantation were calculated separately for periods of 12 months before and after the new legislation. Relative incidence rates are ratios of the rate after the new legislation to the rate before legislation and are

expressed as percentage increases or decreases. The proportions of deaths and non-fatal self poisonings attributed to each drug (and to combinations of drugs) before and after the legislation were compared as risk ratios, the changes being expressed as percentage increases or decreases.

The biochemical data and numbers of tablets taken in each overdose were summarised using geometric means. Changes were expressed as percentage increases or decreases, their significance being estimated from *t* tests. We analysed sales data using *t* tests.

Data on transplantations, non-fatal self poisonings, and biochemical concentrations were stratified according to centre (Oxford, Bristol and Bath, and Manchester) and analysed using inverse variance and Mantel-Haenszel methods.

Results

Mortality from paracetamol and salicylate overdoses in England and Wales

After the introduction of the new law the proportion of all relevant drug related deaths that were attributable to paracetamol or salicylates on their own decreased significantly (table 1).

Admissions to liver units and numbers of liver transplantations in England

After the legislation the annual number of admissions with hepatic paracetamol poisoning to liver units declined by 30% (95% confidence interval 22% to 37%) compared with the two years before the legislation. Significant reductions occurred in all five units (data for one centre have already been published).¹¹ Across the five units the annual number of admissions decreased from 310 in the 24 months before the change to 193 in the 12 months after.

The total number of listings for four liver units in the 12 months after the legislation decreased by 59% (47% to 67%) compared with the annual number for the 24 months before the legislation, and in two of the units the numbers were significantly reduced. After the legislation 66% fewer patients (55% to 74%) in the five units underwent liver transplantation because of paracetamol poisoning of the liver, compared with the annual number for the two years before the change (figure). The reduction in four of the five units was significant: average annual transplant rates decreased from 25 to 12 per year.

Table 1 Numbers of suicides, undetermined deaths, and deaths resulting from accidental poisoning attributable to paracetamol and salicylates among people aged 12 years and over in England and Wales before and after the change in law on packaging*

Drug	No (%) of deaths			% change in incidence‡ (95% CI)	P value	% change in proportional incidence‡ (95% CI)	P value
	Penultimate 12 months before change (n=2255)	12 months before change (n=2234)	12 months after change (n=2086)†				
Paracetamol:							
Alone	203 (9.0)	185 (8.3)	147 (7.0)	-21 (-34 to -5)	0.01	-18 (-33 to -1)	0.04
With other drugs	59 (2.6)	56 (2.5)	56 (2.7)	2 (-26 to 39)	0.9	5 (-24 to 44)	0.8
Salicylates:							
Alone	35 (1.6)	29 (1.3)	16 (0.8)	-48 (-70 to -11)	0.02	-46 (-69 to -7)	0.03
With other drugs	4 (0.2)	8 (0.4)	3 (0.1)	-48 (-85 to 81)	0.3	-46 (-85 to 91)	0.3
Paracetamol and salicylates	11 (0.5)	5 (0.2)	9 (0.4)	18 (-47 to 163)	0.7	21 (-47 to 174)	0.6

*16 September 1998.

†These numbers were increased by 4.5% in the analyses. (See methods section for explanation.)

‡Comparison of 12 months after the change with the average of the two years before.

Non-fatal self poisoning with paracetamol and salicylates

Although overdoses involving paracetamol of any kind as a proportion of the total number of cases of self poisoning did not change, the absolute number decreased significantly by 11% (5% to 16%). The proportion of cases in which paracetamol alone was used (the most common type of paracetamol overdose) also decreased significantly (10% (4% to 15%)).

After the legislation there was a small but significant increase in the proportion in which paracetamol was involved with other drugs, but no significant change in the absolute number. Numbers of cases in which salicylates were taken with other drugs did not change.

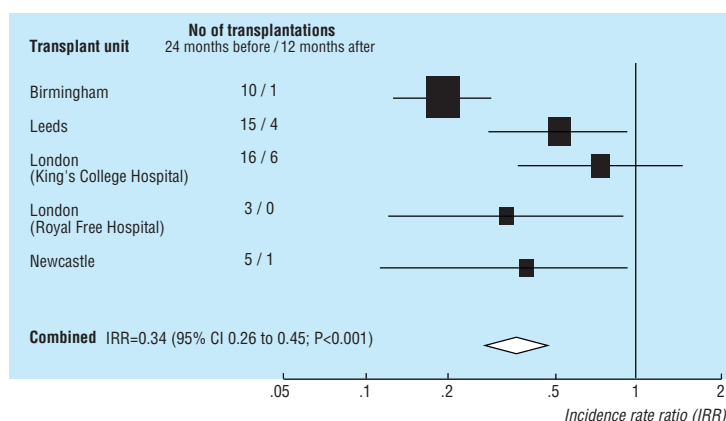
The mean number of tablets taken per paracetamol overdose decreased slightly in the 12 months after the legislation compared with the previous 12 months, but the decrease was significant only in Bristol and Bath (a decrease of 9% (2% to 16%)). The proportion of overdoses in which more than 32 tablets were taken decreased significantly, for both paracetamol (decrease of 17% (4% to 28%) and salicylates (34% (2% to 56%)).

Biochemical data and results of tests of liver function

The mean individual highest blood paracetamol concentrations recorded in Oxford, Bristol and Bath, and Manchester did not change after the legislation, but the mean highest prothrombin times decreased slightly (-2% (0% to -4%)). The mean highest salicylate concentrations recorded in Oxford and Bristol also decreased (-17% (-11% to -21%)).

Sales data

The mean numbers of tablets per pack of paracetamol and salicylates sold to pharmacies in the United Kingdom decreased markedly in the 12 months after the legislation compared with the penultimate 12 months before. There was, however, a compensatory increase in the number of packs sold of paracetamol, such that the total number of tablets of paracetamol sold did not



Number of liver transplants undertaken after paracetamol poisoning before and after the change in law

change (table 2). The total numbers of tablets of paracetamol compounds, salicylates, and salicylate compounds sold to pharmacies decreased significantly. The numbers of tablets sold of preparations combining both paracetamol and salicylates did not change significantly.

Discussion

Although interpreting results from a study with a simple before and after design is problematic,¹² the evidence for a causal relation between the legislation and the changes in mortality and morbidity is strong, especially because the decrease in the number of cases of self poisoning with paracetamol alone and in the resulting mortality came after several years of successively increasing numbers of paracetamol overdoses and related deaths.^{1 2 13} The effects of the legislation on mortality, numbers of cases of self poisoning, morbidity, and drug sales were consistent for both paracetamol and salicylates.

Table 2 Quantities (95% confidence interval) of paracetamol and salicylates sold to pharmacies and other retail outlets in the United Kingdom for sales over the counter before and after the change in law*

Drug	Penultimate 12 months before change	12 months after change	Difference (95% CI)	% change	P value
Paracetamol:					
Mean No of tablets per packet sold	32.6 (26.1 to 39.1)	24.2 (23.5 to 24.9)	-8.4 (-14.6 to -2.2)	-26	0.01
No of packets (millions)	1 280 (1 210 to 1 351)	1 614 (1 402 to 1 825)	333 (124 to 543)	26	0.003
No of tablets (millions)	42 169 (33 394 to 50 945)	38 986 (33 974 to 44 000)	-3 182 (-6 340 to 12 705)	-8	0.5
Paracetamol compounds:					
Mean No of tablets per packet sold	39.5 (31.6 to 47.4)	30.1 (29.5 to 30.6)	-9.4 (-16.8 to -1.9)	-24	0.02
No of packets (millions)	2 032 (1 895 to 2 169)	1 502 (1 422 to 1 581)	-530 (-680 to -381)	-26	<0.0001
No of tablets (millions)	81 265 (64 073 to 98 456)	45 110 (43 049 to 47 172)	-36 155 (-52 469 to -19 840)	-44	0.0001
Salicylates:					
Mean No of tablets per packet sold	56.5 (45.2 to 67.9)	26.1 (25.5 to 26.6)	-30.5 (-41.2 to -19.8)	-54	<0.0001
No of packets (millions)	952 (878 to 1 026)	647 (575 to 720)	-304 (-402 to -207)	-32	<0.0001
No of tablets (millions)	54 736 (43 084 to 66 388)	16 901 (14 915 to 18 887)	-37 835 (-48 972 to -26 698)	-69	<0.0001
Salicylate compounds:					
Mean No of tablets per packet sold	29.2 (23.1 to 35.2)	13.1 (12.3 to 13.8)	-16.1 (-21.8 to -10.3)	-55	<0.0001
No of packets (millions)	335 (316 to 3 54)	484 (139 to 396)	150 (64 to 235)	-45	0.001
No of tablets (millions)	9 610 (7 559 to 11 662)	6 233 (5 332 to 7 135)	-3 377 (-5 488 to -1 266)	-35	0.003
Paracetamol and salicylate compounds:					
Mean No of tablets per packet sold	61.0 (48.7 to 73.2)	15.3 (14.8 to 15.7)	-45.7 (-57.2 to -34.2)	-75	<0.0001
No of packets (millions)	262 (245 to 280)	1 075 (877 to 1 273)	812 (625 to 999)	310	<0.0001
No of tablets (millions)	15 699 (12 434 to 18 964)	16 292 (13 503 to 19 080)	592 (-3 453 to 4 638)	4	0.8

*16 September 1998.

Methodological issues

It is important to consider the possibility of incomplete or inconsistently recorded data when interpreting the results of before and after studies. We made an adjustment to account for the incompleteness of mortality data for 1999. However, the degree of undercounting was small and had been consistent over the three previous years. Our investigation of trends in self poisoning was based on routinely collected data from seven hospitals. Although clinicians in these centres were aware of the introduction of the legislation, there is no reason to believe that this would have affected their recording of routine clinical information. Another potential limitation of before and after studies is the difficulty of accounting for underlying trends in the outcomes; analysis based on proportional incidence counters this. Also, we are not aware of any changes in policy on blood testing in cases of overdose during the study period. One liver unit did not provide data for inclusion in the analyses, but there is no reason to expect that the pattern in this centre would have been any different from that in the other centres.

Mortality and morbidity

The number of deaths from self poisoning with paracetamol alone went down by 40 from the 12 months before the law change to the 12 months after, and the corresponding figure for salicylates was about 15. This reduction in mortality from paracetamol self poisoning was reflected in reduced morbidity. The reduction in the number of admissions to liver units because of paracetamol poisoning has already been highlighted.¹¹ Our analysis of data from five liver units shows that there was an even greater reduction in the number of these admissions that progressed to liver transplantation.

Non-fatal self poisoning

These trends were also reflected in a reduction in the number and proportion of overdoses in which paracetamol was taken alone, the predominant type of overdose involving paracetamol. The small but significant increase in overdoses in which paracetamol compounds or paracetamol together with other drugs were taken may be a result of the decreased availability of paracetamol and consequent use of other drugs to increase the size of the overdose. Also, although the maximum blood concentrations of paracetamol in patients in whom measurements were taken did not change overall, there was a small decrease in the proportion of patients with abnormal prothrombin times—a sensitive measure of liver poisoning.¹⁴

A reduction in the frequency and severity of paracetamol self poisoning after the legislation has been reported in a London hospital.¹⁵ We also noted a reduction in the number of large overdoses of salicylates and in maximum blood salicylate concentrations.

Sales of paracetamol and salicylates

Trends in the nature and number of paracetamol and salicylate overdoses and their consequences are compatible with sales data, which showed a marked reduction in the mean number of tablets per pack sold to pharmacies and some other outlets for all relevant preparations in the 12 months after the new legislation compared with the penultimate 12 months before. Although increases in the number of packs sold of

What is already known on this topic

Paracetamol and salicylate overdoses are very common in the United Kingdom and are associated with high levels of mortality and morbidity

International comparison shows that national mortality from paracetamol overdose may be related to the maximum number of tablets in individual preparations

Legislation to limit the size of packs of paracetamol and salicylates was introduced in the United Kingdom in September 1998

What this study adds

The number of tablets in packets of paracetamol and salicylate preparations decreased markedly in the 12 months after the legislation

The number of deaths from self poisoning with paracetamol alone and with salicylates alone decreased after the legislation

There was also a decrease in the number of liver transplants and admissions to liver units with hepatic paracetamol poisoning and in the number of overdoses of paracetamol and salicylates in which large numbers of tablets were taken

paracetamol and paracetamol-salicylate compounds seemed to compensate for these decreases, the net effect would have been a reduction in the maximum number of tablets in households.

Conclusion

The legislation has been relatively successful, in that it was followed by a marked reduction in the number of deaths resulting from overdoses of paracetamol and salicylates and by fewer liver transplantations and reduction in other indices of morbidity associated with paracetamol self poisoning. The results indicate that the main factor was the reduction in the number of tablets per pack. Elsewhere we have shown that stronger warnings on labels are unlikely to have much impact.⁸

Since the new legislation, pharmacies and other retail outlets have usually allowed only one pack to be bought per transaction. Although this does not prevent a customer visiting several outlets to amass a large supply of the drugs, the general effect of the legislation is to reduce the maximum number of analgesic tablets available for impulsive self poisoning. An even smaller maximum pack size for pharmacy sales, such as the 8 g limit in France, might have had a greater impact still.

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Contributors: KH initiated the study and contributed to the design, interpretation, and reporting. ET coordinated the collection of the data and contributed to the study design, interpretation, and reporting. JD conducted the statistical analyses and contributed to the interpretation and reporting. LA and DG contributed to the design of the study, data collection, interpretation, and reporting. JC and OB contributed to database design, data collection, and reporting. KH is guarantor for the study.

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Antipsychotic drugs and heart muscle disorder in international pharmacovigilance: data mining study

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Abstract

Objectives To examine the relation between antipsychotic drugs and myocarditis and cardiomyopathy.

Design Data mining using bayesian statistics implemented in a neural network architecture.

Setting International database on adverse drug reactions run by the World Health Organization programme for international drug monitoring.

Main outcome measures Reports mentioning antipsychotic drugs, cardiomyopathy, or myocarditis.

Results A strong signal existed for an association between clozapine and cardiomyopathy and myocarditis. An association was also seen with other antipsychotics as a group. The association was based on sufficient cases with adequate documentation and apparent lack of confounding to constitute a signal. Associations between myocarditis or cardiomyopathy and lithium, chlorpromazine, fluphenazine, haloperidol, and risperidone need further investigation.

Conclusions Some antipsychotic drugs seem to be linked to cardiomyopathy and myocarditis. The study shows the potential of bayesian neural networks in analysing data on drug safety.

Introduction

The antipsychotic drug clozapine has been reported to cause myocarditis or cardiomyopathy.^{1,2} Other drugs in the same therapeutic class may share similar toxicity. Data mining of a large database of suspected adverse

reactions can find such new signals. As part of the World Health Organization's programme for international drug monitoring, national pharmacovigilance centres in 60 countries report adverse reactions to a central database maintained by the Uppsala Monitoring Centre in Sweden.³

To analyse this large database an approach using bayesian statistics implemented in a neural network architecture has been developed. The approach is able to look for new adverse reactions from combinations of drugs and also to identify previously unknown patterns, such as risk factors for adverse events with specific drugs—for example, patient age, underlying diseases, and drug interactions. We used the bayesian approach to look for cardiac effects related to antipsychotic drugs in the WHO database of adverse reactions.

Methods

We used the bayesian confidence propagation network, which implements bayesian statistics in a neural network architecture, in the WHO database. The network was used to test reports of clozapine and all other antipsychotic drugs suspected of causing myocarditis or cardiomyopathy against a background of all reports in the database. We calculated the strength of dependency between a drug (or drug group) and adverse reaction using a logarithmic measure of disproportionality called the information component.⁴ An association between the drug and the reaction was considered significant if the information component minus 2 standard deviations was positive. The value of the information compo-

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