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Comparison of hospital episodes with 'drug-induced' disorders and spontaneously reported adverse drug reactions

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Aims
To compare Hospital Episode Statistics for 'drug-related' admissions with spontaneously reported adverse drug reactions (ADRs) using UK Yellow Card data for the period 1996–2000.

Methods
This was a descriptive study for which we matched the relevant datasets in respect of time, place, evidence of hospitalization and disease terminology. The principal outcome was the ratio of ADRs leading to hospitalization which had been reported spontaneously during the whole study period.

Results
Twenty types of ADR were included and between them there was a wide spread of overall ratios (range 0–130%). The general tendency was for under-reporting on Yellow Cards but for ADRs with a fatal outcome this appeared to be less (range 7–168%).

Conclusions
This study provides some broad indications of the degree of under-reporting of ADRs that occurs despite a clinical diagnosis of a serious ADR being made and recorded.

Introduction

A recent study of Hospital Episode Statistics (HES) data for England coded as being 'drug-induced' [1] indicated that HES data grossly underestimate the burden of these disorders as a cause of hospital admission. There were likely to be multiple underlying reasons including under-recognition, under-recording and limitations of the coding system. Approximately 40 000 patients per year were identified from HES data as having a 'drug-induced' admission during the late 1990s.

HES data for the relevant codes share some characteristics of spontaneous adverse drug reaction (ADR) reporting data in that they are dependent on a clinical diagnosis of an adverse reaction being made and recorded. In the UK, the Yellow Card Scheme [2] requests reports of serious and non-serious ADRs for new drugs and serious reactions only for established drugs. In total, about 20 000 reports are received per annum [2]. It is well-recognized that there is substantial under-reporting in all spontaneous ADR reporting schemes [3–9].

Despite their limitations, HES data are more systematic and are likely to be more complete than Yellow Card data for ADRs leading to hospitalization.

The objective of this study was to compare HES data for 'drug-induced' disorders with spontaneous ADR data for the same reactions during the period 1996–2000.

Methods

This is a descriptive comparative study. For HES data we used Table 2 of the published paper by Waller *et al*. [1] giving, for each year, the numbers of patients admitted and numbers of fatal outcomes for all International Classification of Diseases (ICD) codes explicitly indicating that the event was drug induced.

Patients identified from Yellow Card data from the UK spontaneous ADR reporting system coded using the Medical Dictionary for Regulatory Activities (MedDRA) [10] were identified for the relevant HES discharge diagnoses coded using the International Classification of Diseases volume 10 (ICD-10) (see below). To account for the fact that not all reported ADRs necessarily result in hospitalization, we included only cases where hospitalization or prolongation of hospitalization was indicated in a tick box or the text on the Yellow Card. In order to match time periods, the date of the event was used wherever it was available. Where it was not available, the date of receipt of the report was used. HES data relate to financial years [1] and the same time periods were therefore used for Yellow Cards. Although it is possible that a suspected ADR may be reported by both the referring and admitting physicians, such duplicates are routinely merged during a duplicate control programme. Potential duplicate Yellow Cards are identified by matching suspect drugs, patient identification details and reporter details. Duplicates had also been removed from HES data, as described previously [1]. The Yellow Card data include the whole UK, which is a wider population than HES data (which are from England only). We therefore applied a correction factor representing the proportion of the UK population which resides in England widely used by the Office of National Statistics from 2001 census data (i.e. 0.84 [11]). All ratios are expressed as percentages. Detailed statistical analyses were not carried out as we considered these data to be primarily descriptive.

ICD-10 codes were matched to the MedDRA dictionary [10] used for coding of Yellow Cards according the following principles. The most appropriate level was generally considered to be at high-level term (HLT). However, if the ICD-10 code was synonymous with a preferred term (PT) in MedDRA and there were no other PTs considered likely to be used for that diagnosis, then that PT was used. Conglomeration of more than one PT within an HLT was also allowed if some PTs within an HLT were clearly inappropriate. Some 'drug-induced' disorders implied a range of disorders across more than one HLT (e.g. nephropathies) or high-level group terms (e.g. drug-induced liver disorders), and this was also allowed. In the previous study [1], only ICD codes which exclusively imply a drug cause were included. Thus, as there is no specific ICD-10 code referring to 'drug-induced' gastrointestinal bleeding we were not able to include this ADR in the study, despite its importance. The following 'drug-induced' codes could not sensibly be matched and were excluded: F11 Mental disorders due to opioids, F13 Mental disorders due to sedatives/hypnotics, F19 Mental disorders due to multiple psychoactive drugs, T88.7 Unspecified adverse drug effect. A detailed matching of codes between ICD-10 and MedDRA is available from the authors.

Results

Table 1 shows the comparison of numbers of Yellow Cards with evidence of hospitalization and numbers of cases appearing in the HES data for the period 1996–2000. This table has been ordered by the overall (i.e. average per year) ratios with the highest at the top. The overall range of ratios was from 0 to 130% and for all but one ADR type (ototoxic hearing loss) was less than 100%, indicating that these ADRs are more likely to be recorded in the HES database than in the Yellow Card database. Table 2 provides the numbers of cases in Table 1 which resulted in fatalities (similarly ordered). Types of ADR appearing in Table 1 for which no fatal cases were reported are excluded here. The overall range of ratios was from 7 to 168% and all but one fatal ADR type (drug-induced haemolytic anaemia) was less than 100%. For some ADR types there were large variations in ratios between years but these are generally based on small numbers and no clear time trends were apparent.

Discussion

As expected, there was a general tendency for fewer Yellow Card reports than records of drug-induced hospital admission but this was less pronounced for fatal outcomes. Only for ototoxic hearing loss and fatal haemolytic anaemia did the numbers of Yellow Cards exceed the number of admissions recorded as 'drug-induced' and there were very small numbers of such cases in both databases. The considerable range of overall ratios between terms was unexpected. For example, for liver disease the ratio was 58%, whereas for aplastic anaemia it was only 8%. Even more striking was the variation within the same system organ class for

Table 1
Numbers of cases of suspected adverse drug reactions (ADRs) reported spontaneously through the UK Yellow Card Scheme where the reaction resulted in or prolonged hospitalization, compared with the numbers of cases appearing the Hospital Episode Statistics (HES) data for the period 1996–2000

		Year																	
		1996			1997			1998			1999			2000			Average per year		
ICD10 code	Diagnosis	ADR cases	HES cases	Ratio (%)	ADR cases	HES cases	Ratio (%)	ADR cases	HES cases	Ratio (%)	ADR cases	HES cases	Ratio (%)	ADR cases	HES cases	Ratio (%)	ADR cases	HES cases	Ratio (%)
H91.0	Ototoxic hearing loss	4	0	–	1	1	84	4	2	168	4	5	67	4	3	112	3	2	130
L56.0/1	Drug-induced phototoxicity	6	5	101	4	6	56	3	2	126	6	4	126	2	2	84	4	4	93
D59.0/2	Drug-induced haemolytic anaemia	7	31	19	19	14	114	18	10	151	12	19	53	11	19	49	13	19	61
K71	Drug-induced liver disease	160	321	42	218	304	60	205	306	56	185	228	68	213	251	71	196	282	58
G25.0/4/6	Drug-induced extrapyramidal syndrome/chorea/tics	53	106	42	66	114	49	71	106	56	81	117	58	82	83	83	71	105	56
G72.0	Drug-induced myopathy	14	34	35	21	35	50	18	39	39	24	44	46	31	34	77	22	37	49
N14.0/1/2	Drug-induced nephropathy	13	35	31	29	47	52	12	36	28	29	46	53	25	61	34	22	45	40
G21.0	Malignant neuroleptic syndrome	14	59	20	21	53	33	31	63	41	27	53	43	27	61	37	24	58	35
J70.2/3/4	Drug-induced interstitial lung disorders	13	18	61	11	20	46	14	33	36	7	29	20	7	27	22	10	25	34
I42.7	Drug-induced cardiomyopathy	4	14	24	6	21	24	7	16	37	10	17	49	12	30	34	8	20	33
M32.2	Drug-induced systemic lupus erythematosus	1	9	9	5	10	42	7	14	42	4	10	34	4	10	34	4	11	33
T88.6	Drug-induced anaphylaxis	65	270	20	97	280	29	119	321	31	126	376	28	112	345	27	104	318	27
E27.3	Drug-induced adrenocortical failure	4	7	48	2	16	11	6	19	27	4	18	19	3	16	16	4	15	21
G24.0	Drug-induced dystonia	26	140	16	23	146	13	35	124	24	25	110	19	28	108	22	27	126	18
E03.2	Hypothyroidism due to medicaments	1	12	7	3	14	18	1	19	4	4	17	20	2	11	15	2	15	13
D61.1	Drug-induced aplastic anaemia	8	94	7	5	89	5	8	67	10	6	74	7	9	72	11	7	79	8
M10.2	Drug-induced gout	0	24	0	0	22	0	2	19	9	4	20	17	2	11	15	2	19	7
T88.3	Malignant hyperthermia due to anaesthesia	0	25	0	0	1	0	1	3	28	1	5	17	1	7	12	1	8	6
G21.1	Drug-induced Parkinsonism	4	107	3	10	86	10	4	94	4	6	77	7	3	80	3	5	89	5
M34.2	Drug-induced systemic sclerosis	0	2	0	0	2	0	0	2	0	0	3	0	0	4	0	0	3	0

Since the Yellow Card Scheme applies to the UK and HES data derive only from England, all ratios have accordingly been adjusted by a factor of 0.84 [11].

Table 2
Numbers of fatal cases of suspected adverse drug reactions (ADRs) reported spontaneously through the UK Yellow Card Scheme where the reaction resulted in or prolonged hospitalization, compared with the numbers of cases appearing in the Hospital Episode Statistics (HES) data for the period 1996–2000

		Year																	
		1996			1997			1998			1999			2000			Average per year		
ICD10 code	Diagnosis	ADR cases	HES cases	Ratio (%)	ADR cases	HES cases	Ratio (%)	ADR cases	HES cases	Ratio (%)	ADR cases	HES cases	Ratio (%)	ADR cases	HES cases	Ratio (%)	ADR cases	HES cases	Ratio (%)
D59.0/2	Drug-induced haemolytic anaemia	0	0	–	1	0	–	1	0	–	0	1	0	0	0	–	0.4	0.2	168
D61.1	Drug-induced aplastic anaemia	4	5	67	3	3	84	1	3	28	4	2	168	2	5	34	2.8	3.6	65
J70.2/3/4	Drug-induced interstitial lung disorders	2	1	168	2	2	84	3	3	84	0	2	0	0	1	0	1.4	1.8	65
T88.6	Drug-induced anaphylaxis	1	2	42	3	1	252	2	2	84	1	6	14	1	0	–	1.6	2.2	61
K71	Drug-induced liver disease	11	57	16	21	61	29	22	57	32	15	27	47	16	22	61	17.0	44.8	32
G21.0	Malignant neuroleptic syndrome	1	3	28	2	2	84	2	5	34	2	5	34	1	7	12	1.6	4.4	31
G72.0	Drug-induced myopathy	0	0	–	0	2	0	1	2	42	0	1	0	0	1	0	0.2	1.2	14
N14.0/1/2	Drug-induced nephropathy	0	3	0	1	2	42	0	5	0	0	1	0	0	1	0	0.2	2.4	7

Since the Yellow Card Scheme applies to the UK and HES data derive only from England, all ratios have accordingly been adjusted by a factor of 0.84 [11].

extrapyramidal ADRs, chorea and tics (56%) compared with Parkinsonism (5%). The reasons for such variations are unclear. In neither dataset did there appear to be important time trends over the 5-year study period. There were some large variations in ratios within codes across the years, but only for those ADRs associated with very small numbers of cases.

The intention of this study was essentially exploratory rather than to provide precise estimates and there are several important limitations. It was not possible to cover the whole clinical spectrum of ADRs or, therefore, to provide an overall estimate of under-reporting on Yellow Cards relative to HES data. Despite the public health impact of some important ADRs (e.g. 'drug-induced' gastrointestinal bleeding), it was not possible to study these because of the limitations of the coding system used for HES data. There are well-recognized limitations to both the datasets used [1, 3] and our matching of them in terms of time, place and codes was inevitably imperfect. The likely most important specific limitation of the comparison made relates to the use of tick boxes on the Yellow Card to indicate hospitalization. This tick box does not allow differentiation between hospital admission and prolongation of hospitalization as it is selected to indicate both circumstances. In addition, to the (unknown) extent that these tick boxes are underused, the degree of under-reporting on Yellow Cards will have been overestimated. We would expect that most of the individual hospitalized cases reported on Yellow Cards from England would be present in the HES data but, because of data confidentiality restrictions, specific Yellow Card data could not be linked to specific HES admission data at the patient level. Furthermore, part of the observed differences between the databases may relate to differing thresholds of suspicion required to consider a case as 'drug-induced' in HES data compared with Yellow Card data for which only a suspected association is sufficient.

Further analyses and studies could compare reporting rates according to source of Yellow Card reports (e.g. hospital and non-hospital) and comparisons of HES data with analogous information from other countries would be of interest.

In conclusion, this study provides some broad indications of the degree of under-reporting of ADRs that occurs in the UK despite a clinical diagnosis of a serious ADR being made and recorded. There appear to be large variations in the degree of such under-reporting between ADR type or for the same ADR type over the study time period. The reasons for this may in part relate to methodological issues but there seems to be some dependence on the nature of the ADR. Our study highlights the importance of physicians including 'drug-induced' causation in the differential diagnosis list for many diseases. Spontaneous ADR reporting schemes should emphasize this point in their promotional activities.

Conflict of interest

P.B. and L.W. are current employees of the Medicines and Healthcare products Regulatory Agency (MHRA) which operates the UK Yellow Card Scheme. P.W. was employed by its predecessor from 1990 to 2002 and holds a contract to consult for the MHRA. The views expressed here are those of the authors and not necessarily the official position of the MHRA.

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