DOI:10.1111/j.1365-2125.2004.02236.x

Hospital admissions for 'drug-induced' disorders in England: a study using the Hospital Episodes Statistics (HES) database

Patrick Waller,[1] Mary Shaw,[2,3] Davidson Ho,[2,3] Saad Shakir[1,4] & Shah Ebrahim[3]

[1]Drug Safety Research Unit, Southampton, [2]South West Public Health Observatory, Bristol, [3]Department of Social Medicine, University of Bristol, Bristol, and [4]University of Portsmouth, Portsmouth, UK

Correspondence
Dr Patrick Waller, Drug Safety Research Unit, Bursledon Hall, Blundell Lane, Southampton SO31 1AA, UK.
Tel: +44 1489 798107
Fax: +44 1489 690016
E-mail: patrick.waller@btinternet.com

Keywords
adverse drug reaction, drug safety, HES data, hospital admission, pharmacovigilance

Received
22 April 2004
Accepted
2 July 2004

Aims
To review Hospital Episode Statistics (HES) data for England coded as being 'drug induced' during 1996–2000 and to consider their potential utility for assessing the public health burden of adverse drug reactions (ADRs) and studying drug safety.

Methods
ICD-10 codes including the words 'drug-induced' or 'due to' a medicine or which are recognized to be invariably caused by a drug were extracted along with external cause codes indicating that a drug was implicated (i.e. Y40-59 in ICD-10). We also calculated the proportions of patients with each 'drug-induced' code for whom an external cause code had been applied.

Results
During the 5-year study period there were almost 53.8 million hospital admissions in England, of which 44 411 (0.083%) were coded as 'drug-induced' and 168 958 (0.314%) were associated with a relevant external cause code. The numbers of patients with 'drug-induced' codes used were generally stable during the study period (range 7454–8860 per year) but the application of external cause codes increased in each year and by 40% overall (from 24 786 in 1996 to 34 843 in 2000). The overall proportion of 'drug-induced' codes associated with a relevant external cause code was quite low (12–15%) but there was considerable variation between codes.

Conclusions
Comparisons with published studies indicate that HES data grossly underestimate the burden of drug-induced disorders as a cause of hospital admission. There are likely to be multiple underlying reasons including under-recognition, under-recording and limitations of the coding system. The potential of these data for identifying previously unrecognized serious ADRs is limited by constraints on the availability of detailed data regarding individual cases.

Introduction

Adverse reactions to medicinal drugs are an important cause of morbidity and mortality in the developed world [1, 2]. In 1998 a meta-analysis of 39 US studies of hospitalized patients estimated the frequency of serious adverse drug reactions (ADRs) to be 6.7% and fatal ADRs 0.32% [3]. Based on these findings, it was suggested that ADRs were between the fourth and sixth leading cause of death. In the UK, a study conducted in Oxford in the early 1990s estimated an overall ADR

frequency of 6.9% in hospitalized patients [4], one-third having been present on admission. There have been many such studies around the world and, in general, it seems that ADRs may be considered responsible for about 3–6% of hospital admissions [2].

The methodologies used for estimating the incidence of ADRs in the hospital setting invariably require systematic review of large numbers of cases and are highly resource intensive. Routinely collected diagnostic data would be expected to underestimate the incidence of ADRs because of under-recognition. Nevertheless, it would be of interest to know to what extent such data can quantify ADRs and whether or not they are of potential value for studying drug safety, given that other systems in routine use such as spontaneous ADR reporting have similar limitations [5].

The Department of Health's Hospital Episodes Statistics (HES) system is a very large database containing personal, medical and administrative details of all patients admitted to, and treated in, NHS hospitals in England. This information has many uses including health and fiscal policy, performance management and health services research. HES data are split into years running from 1 April to 31 March in the following year; over 12 million HES records are generated each year. The 10th International Classification of Diseases (ICD-10) [6] is used for coding. Further information on HES is available on the Department of Health's website [7].

Since HES data are a comprehensive record of hospital admissions and any disorder leading to hospital admission is considered 'serious' by definition [8], they are potentially a useful routine source of information on serious ADRs. However, as far as we are aware, only one relevant study, covering one hospital, has previously been published [9]. A search of Medline from 1989 to December 2003 found nothing else directly relevant.

The objectives of this study were to review and describe HES data for England coded as being 'drug-induced' for the period 1996–2000, to assess their potential value for assessing the public health impact of ADRs and for research into the safety of medicines.

Methods

We used an extract of the Department of Health's HES database held at the University of Bristol containing records with admission dates from 1 April 1996 to 31 March 2001. A complex encryption procedure is applied to this extract in order to protect the identity of individual patients. Duplicate records were removed by matching date of birth, postcode, sex, provider code, date of admission, date of discharge, episode start date and episode end date, i.e. if two records were identical on all of these variables then the duplicate was removed.

In the HES data, an 'episode' is defined as a period of continuous treatment in the care of a particular consultant in a single NHS hospital. A person going into hospital may have more than one episode of care before they are discharged but by taking the 'admission episode' only the first episode is counted. In order to account for the problem of multiple admissions of the same patient for the same diagnosis we used the variables date of birth, postcode and sex to create a dataset of individual patients.

We studied the five most recent years for which HES data were available (1996–2000), selecting all ICD-10 codes which included the words 'drug-induced' or which indicated that the diagnosis was 'due to' a drug, and codes which clearly implied an adverse drug reaction (e.g. neuroleptic malignant syndrome). These codes are referred to below as being 'drug-induced'. Data for codes which were closely related (i.e. where there was more than one relevant code beyond the decimal point in ICD-10) were combined. We did not include codes for which other causes might have been responsible for some of the cases, even though most would have been expected to be drug-induced (e.g. toxic epidermal necrolysis). We recognized that the codes we included would sometimes be an imperfect match for ADRs in either direction (which is an inherent limitation of ICD-10) but we avoided applying our judgements in the selection of data for inclusion. Thus we included all codes that indicated that an admission was 'drug-induced' and then attempted to consider the limitations of these data as a proxy for ADRs.

We also studied ICD codes Y40-59, which are the additional codes used to indicate an 'external cause' relevant to drugs, grouped into 20 broad categories. Finally, we investigated the extent to which patients with each 'drug-induced' code also had a relevant external cause code applied to their records.

Results

The numbers of episodes and admissions during the period 1996–2000 for all diagnoses are provided in Table 1, along with the numbers of episodes, admissions and patients with 'drug-induced' codes and those for which a relevant external cause code was applied. During this period there were 53 847 408 hospital admissions of which 44 411 (0.083%) were coded as 'drug-induced' and 168 958 (0.314%) were associated with a relevant external cause code. The overall proportion of patients admitted with a 'drug-induced' and/or a relevant external cause code was 0.35%.

Table 1
Hospital Episode Statistics (England); total numbers of episodes and admissions (any diagnosis), and numbers of episodes, admissions and patients with 'drug-induced' codes and for whom external cause codes Y40–Y59 were applied

Year	1996	1997	1998	1999	2000	Total
*Episodes**						
Total	11080026	11544549	11984728	12196271	12265485	59071059
No. with 'drug-induced codes'	8837	9493	10403	9984	9773	48490
No. with cause codes (Y40–Y59)	32582	37994	42263	47164	49729	209732
Admissions						
Total	10239806	10463971	11005351	11137174	11001106	53847408
No. with 'drug-induced codes'	8176	8839	9677	9159	8560	44411
No. with cause codes (Y40–Y59)	27172	30845	34439	37809	38693	168958
Patients (primary diagnosis)						
No. with 'drug-induced codes'	7454	8083	8860	8430	7857	40684
No. with cause codes (Y40–Y59)	24786	27638	30952	33924	34843	152143

**An episode is a period of continuous treatment in the care of a particular consultant speciality in a single hospital (see Methods for further explanation of the difference between an episode and an admission). Source: HES – Department of Health.*

Table 2 provides counts of patients for all the selected ICD-10 codes with the numbers of fatalities given in parentheses. The total numbers of patients with 'drug-induced' codes ranged from 7454 to 8860 per year. The two largest categories by far were 'mental disorders due to opioids' and 'mental disorders due to multiple psychoactive drugs'. When combined with 'mental disorders due to sedatives/hypnotics' these three codes accounted for 74–78% of the total number of 'drug-induced' codes in each year. In general, the numbers of cases for each code remained fairly stable during the 5-year study period, although there are some 'outliers', most notably the data for malignant hyperthermia due to anaesthesia (25 cases in the first year of study falling to one the following year and thereafter remaining in single figures).

Regarding fatalities, the total numbers of patients per year with 'drug-induced' codes ranged from 45 to 96. The largest fatal category was liver disease, accounting for 42–65% of the total. The data for this code appear to indicate a downward trend in the last 2 years of the study period, from about 90 deaths in total in the first 3 years to 64 in 1999 and 45 in 2000. Most of this reduction can be attributed to a fall in fatal drug-induced liver disease, from about 60 in the first 3 years to 27 and 22 deaths in 1999 and 2000, respectively.

Table 3 provides counts of patients for whom codes Y40-Y59 were applied with the numbers of fatalities given in parentheses. There were about three to four times as many relevant Y code applications as 'drug-induced' codes in each year, with the overall totals ranging from 24 786 to 34 843. The largest single category (with almost 6000 applications and over 200 fatalities in 2000) was Y43, 'primarily systemic agents', which includes antineoplastic and immunosuppressive drugs. The next largest was Y45, analgesics, antipyretics and anti-inflammatories. The number of codes Y40-59 applied increased each year of the study period and during 5 years there was an overall rise of 40%. This trend seemed to apply to most of the individual codes. Fatalities also increased each year, with an overall rise from 619 to 936 (51%).

Table 4 shows the percentages of patients with individual 'drug-induced' codes for whom codes Y40-Y59 were also applied. Overall, 13–15% of 'drug-induced' codes were associated with the application of a relevant Y code. The highest figures were for drug-induced aplastic anaemia (84–94%) and the lowest for mental disorders due to opioids (0% in each year), with the data generally being stable for specific codes. Because mental disorders form a large proportion of the total (about three-quarters), the overall figures of 12–15% obscure rates which are generally much higher for most of the codes. When the three codes for mental disorders were excluded from the calculations, the overall annual proportions of 'drug-induced' codes associated with the application of a relevant Y code ranged from 55 to 62%.

Table 2
Hospital Episode Statistics (England); primary diagnosis : number of patients admitted for 'drug-induced' ICD-10 codes (no. fatal)

ICD-10 code	Diagnosis	1996	1997	1998	1999	2000
D61.1	Drug-induced aplastic anaemia	94 (5)	89 (3)	67 (3)	74 (2)	72 (5)
D59.0/2	Drug-induced haemolytic anaemia	31 (0)	14 (0)	10 (0)	19 (1)	19 (0)
E03.2	Hypothyroidism due to medicaments	12 (0)	14 (0)	19 (1)	17 (1)	11 (0)
E27.3	Drug-induced adrenocortical failure	7 (0)	16 (0)	19 (1)	18 (0)	16 (0)
F11	Mental disorders due to opioids	2712 (3)	3303 (7)	3796 (3)	3764 (5)	3680 (3)
F13	Mental disorders due to sedatives/hypnotics	298 (0)	248 (0)	247 (0)	223 (0)	189 (0)
F19	Mental disorders due to multiple psychoactive drugs	2559 (1)	2684 (3)	2899 (5)	2562 (3)	2134 (2)
G21.0	Malignant neuroleptic syndrome	59 (3)	53 (2)	63 (5)	53 (5)	61 (7)
G21.1	Drug-induced Parkinsonism	107 (2)	86 (4)	94 (3)	77 (2)	80 (0)
G24.0	Drug-induced dystonia	140 (1)	146 (1)	124 (0)	110 (0)	108 (2)
G25.0/4/6	Drug-induced extrapyramidal syndrome/chorea/tics	106 (0)	114 (0)	106 (0)	117 (0)	83 (0)
G72.0	Drug-induced myopathy	34 (0)	35 (2)	39 (2)	44 (1)	34 (1)
H91.0	Ototoxic hearing loss	0 (0)	1 (0)	2 (0)	5 (0)	3 (0)
I42.7	Drug-induced cardiomyopathy	14 (0)	21 (4)	16 (1)	17 (3)	30 (1)
J70.2/3/4	Drug-induced interstitial lung disorders	18 (1)	20 (2)	33 (3)	29 (2)	27 (1)
K71	Drug-induced liver disease	321 (57)	304 (61)	306 (57)	228 (27)	251 (22)
L56.0/1	Drug-induced phototoxicity	5 (0)	6 (0)	2 (0)	4 (0)	2 (0)
M10.2	Drug-induced gout	24 (1)	22 (0)	19 (1)	20 (0)	11 (0)
M32.0	Drug-induced systemic lupus erythematosus	9 (0)	10 (0)	14 (0)	10 (0)	10 (0)
M34.2	Drug-induced systemic sclerosis	2 (0)	2 (0)	2 (0)	3 (0)	4 (0)
N14.0/1/2	Drug-induced nephropathy	35 (3)	47 (2)	36 (5)	46 (1)	61 (1)
T88.3	Malignant hyperthermia due to anaesthesia	25 (0)	1 (0)	3 (0)	5 (0)	7 (0)
T88.6	Drug-induced anaphylaxis	270 (2)	280 (1)	321 (2)	376 (6)	345 (0)
T88.7	Unspecified adverse drug effect	572 (9)	567 (4)	623 (1)	609 (5)	619 (0)
Totals		7454 (88)	8083 (96)	8860 (93)	8430 (64)	7857 (45)

Source: HES – Department of Health.

Discussion

As expected, estimates of the overall frequency of 'drug-induced' disorders from HES data were much lower than those seen in published systematic studies. When the data for 'drug-induced' codes (applied to 0.083% of admissions) and external cause codes (applied to 0.314% of admissions) were considered together (and account taken of patients for whom both were applied), 0.35% of hospital admissions were coded as being drug-related. Based on published comparisons (more direct data being unavailable), this is an order of magnitude less than would be expected if these data were a complete and accurate source of information on ADRs leading to hospital admission [2]. The main reasons are likely to be under-recognition of ADRs, under-recording and limitations of the coding system. In particular, the 24 ICD-10 codes which clearly define a 'drug-induced' diagnosis are clearly not comprehensive in their scope. We excluded some codes for which a drug cause was likely in the majority of cases (e.g. toxic epidermal necrolysis, bleeding peptic ulcer), but these cases will have been captured by the external cause (Y) codes where they were applied.

Although HES data clearly underestimate the overall scale of the problem of ADRs leading to hospital admission, it should also be recognized that some cases within the drug-induced categories and/or who have a relevant external cause code may not be ADRs, as generally defined [8]. In particular, drug abuse and overdose are generally excluded and it seems likely that some of the F codes (drug-induced mental disorders) relate to the former and some cases (for example, of liver disease, code K71) will relate to the latter. Notably, the F codes accounted for a large proportion of the 'drug-induced codes' in Table 2. If they had been excluded, the annual totals would have ranged from 1848 to 1918 cases and the overall proportion of admissions which were drug-induced would have been reduced from 0.083% to 0.017%. However, since the majority of codes implying a drug-induced event were Y codes, the overall propor-

Table 3
Hospital Episode Statistics (England); number of patients admitted with external cause codes Y40–Y59 applied (no. fatal)

ICD-10 code	Drug group	1996	1997	1998	1999	2000
Y40	Systemic antibiotics	2782 (44)	3016 (57)	3270 (58)	3243 (66)	3462 (56)
Y41	Other systemic anti-infectives/antiparasitics	543 (12)	608 (10)	666 (9)	638 (11)	726 (7)
Y42	Hormones (including synthetic, antagonists)	2608 (66)	2919 (98)	3537 (87)	3897 (102)	3625 (94)
Y43	Primarily systemic agents*	3202 (128)	4082 (151)	4953 (189)	5340 (215)	5935 (231)
Y44	Agents primarily affecting blood constituents	2060 (92)	2212 (117)	2735 (145)	2916 (143)	2998 (158)
Y45	Analgesics/antipyretics/anti-inflammatories	3197 (82)	3673 (98)	4189 (128)	4557 (131)	4532 (134)
Y46	Antiepileptics/antiParkinsonism drugs	852 (4)	871 (7)	899 (10)	934 (11)	846 (6)
Y47	Sedatives, hypnotics, antianxiety drugs	261 (3)	275 (5)	291 (4)	309 (1)	345 (7)
Y48	Anaesthetics, therapeutic gases	375 (4)	379 (5)	352 (3)	439 (10)	427 (0)
Y49	Psychotropic drugs	1132 (14)	1234 (21)	1242 (23)	1294 (30)	1386 (27)
Y50	CNS stimulants	40 (0)	44 (0)	39 (0)	49 (1)	54 (0)
Y51	Drugs affecting autonomic nervous system	1097 (9)	1258 (6)	1308 (9)	1583 (7)	1697 (16)
Y52	Agents primarily affecting cardiovascular system	2511 (65)	2735 (77)	2976 (84)	3342 (81)	3627 (82)
Y53	Agents primarily affecting gastrointestinal system	239 (5)	275 (3)	310 (4)	334 (6)	354 (5)
Y54	Agents affecting water/mineral balance/uric acid	1254 (39)	1392 (41)	1534 (38)	1855 (47)	1987 (59)
Y55	Agents affecting muscle/respiratory system	281 (7)	232 (8)	233 (9)	244 (6)	261 (9)
Y56	Topical agents affecting skin, ENT, dental	831 (23)	816 (25)	783 (24)	880 (32)	692 (25)
Y57	Other and unspecified medicaments	1085 (22)	1175 (18)	1189 (25)	1391 (22)	1357 (19)
Y58	Bacterial vaccines	213 (0)	212 (1)	205 (0)	322 (0)	235 (0)
Y59	Other vaccines/biologicals	223 (0)	230 (2)	241 (1)	357 (1)	297 (1)
Totals		24786 (619)	27638 (750)	30952 (850)	33924 (923)	34843 (936)

**Includes, inter alia, antineoplastics and immunosuppressives. Source: HES – Department of Health.*

tion of admissions with relevant codes would be reduced only slightly (from 0.35% to 0.33%) and thus our main result is not greatly sensitive to their inclusion or exclusion.

Important limitations of the external cause codes are the lack of specification that a particular drug was considered responsible and the very broad groupings of drugs used (e.g. antineoplastics and immunosuppressives are grouped together under code Y43). However, many more external cause codes were applied than 'drug-induced' codes and use of these codes increased by 40% during the study period. The reason for this increase is unclear.

The data for 'drug-induced' codes were fairly stable over a 5-year period but there appears to have been a significant fall in liver disease between 1998–1999 and 1999–2000, and particularly in fatal cases. This could relate to regulatory measures taken to reduce pack sizes of paracetamol (and therefore inhibit overdose) in September 1998 [10]. This is not supported by any reduction in use of code Y45 (which includes analgesics), but the underlying trend for increased use of external cause codes needs to be borne in mind. There was also a marked fall in cases of malignant hyperthermia due to anaesthesia after the first year, but there are no data indicating prior stability and it is possible that the figure for 1996 was artefactually high.

Ideally, all 'drug-induced' codes should also be associated with a relevant external cause (Y) code indicating which group of drugs was considered responsible. However, the data in Table 4 show that there was considerable variation in the application of Y codes between 'drug-induced' codes. The overall annual proportions of 'drug-induced' codes associated with a relevant Y code were low (12–15%) but were highly influenced by the F codes (drug-induced mental disorders). These contain the two largest single 'drug-induced' categories and for both these codes an additional external cause code was almost invariably not applied. The data for the F codes contrast with much higher proportions of additional Y code applications for most other 'drug-induced' codes. The 'drug-induced' code with highest proportion of Y codes applied was aplastic anaemia, for which it ranged from 84 to 94% during the study period (Table 4). When

Table 4
Hospital Episode Statistics (England); primary diagnosis: % patients admitted for 'drug-induced' ICD-10 codes for which an external cause code Y40-Y59 was applied

ICD-10 code	Diagnosis	1996	1997	1998	1999	2000
D61.1	Drug-induced aplastic anaemia	94	84	88	85	86
D59.0/2	Drug-induced haemolytic anaemia	58	57	30	63	47
E03.2	Hypothyroidism due to medicaments	92	79	63	71	73
E27.3	Drug-induced adrenocortical failure	71	50	58	67	56
F11	Mental disorders due to opioids	0	0	0	0	0
F13	Mental disorders due to sedatives/hypnotics	0	1	1	2	1
F19	Mental disorders due to multiple psychoactive drugs	0	0	0	0	0
G21.0	Malignant neuroleptic syndrome	19	34	30	19	20
G21.1	Drug-induced Parkinsonism	42	33	36	44	45
G24.0	Drug-induced dystonia	60	68	74	70	77
G25.0/4/6	Drug-induced extrapyramidal syndrome/chorea/tics	4	4	7	5	0
G72.0	Drug-induced myopathy	71	74	69	61	82
H91.0	Ototoxic hearing loss	0	100	50	40	67
I42.7	Drug-induced cardiomyopathy	64	52	50	53	63
J70.2/3/4	Drug-induced interstitial lung disorders	50	55	64	76	78
K71	Drug-induced liver disease	16	19	20	22	24
L56.0/1	Drug-induced phototoxicity	60	83	100	75	50
M10.2	Drug-induced gout	50	77	63	75	82
M32.0	Drug-induced systemic lupus erythematosus	33	20	36	20	20
M34.2	Drug-induced systemic sclerosis	0	0	0	0	25
N14.0/1/2	Drug-induced nephropathy	60	55	61	78	67
T88.3	Malignant hyperthermia due to anaesthesia	0	100	0	0	29
T88.6	Drug-induced anaphylaxis	77	80	83	83	87
T88.7	Unspecified adverse drug effect	63	69	66	73	71
	% of total for all codes in each year	13	13	12	14	15

the three F codes were excluded and the overall annual proportions recalculated, they varied from 55 to 62%. The proportions for the amalgamated G25 codes (drug-induced extrapyramidal disorders, chorea and tics) were surprisingly low (0–7%) by comparison with the figures for similar conditions, i.e. Parkinsonism (33–45%) and dystonias (60–77%). The reasons for these variations are unclear.

One further line of analysis which we have not yet pursued would be to start with the patients who had relevant Y codes and to see what were the most common associated primary diagnoses. For example, it might be expected that a considerable proportion of patients whose admissions were coded with Y45 – analgesics, antipyretics and anti-inflammatories – would have diagnoses relating to the upper gastrointestinal tract. Such an analysis is also likely to be the most effective way of exploring HES data for rare adverse events which are usually but not invariably drug-induced (e.g. toxic epidermal necrolysis).

HES data on adverse reactions share some characteristics of spontaneous ADR reporting data in that they are dependent on a clinical diagnosis of an adverse reaction being made and recorded. However, it is possible that clinicians may apply different levels of diagnostic certainty to the two systems. In the UK, the yellow card scheme [11] requests reports of serious and nonserious ADRs for new drugs and serious reactions only for established drugs. In total about 20 000 reports are received per annum and it is well recognized that there is inherent and substantial under-reporting [5]. In principle, HES data are more systematic and should be more complete than yellow card data for ADRs leading to hospitalization. Ultimately, however, any value of HES data in supplementing spontaneous ADR reporting would be severely limited by a lack of specific information on the drugs involved and also by a time lag of about 2 years before they become available. Comparisons of the HES data presented here with yellow card data for the same time period and geographical area would be of interest.

In conclusion, HES data considerably underestimate

the public health burden of 'drug-induced' disease. The lack of specific information on the drugs implicated and the unavailability of detailed individual case records (for reasons of confidentiality) mean that, unless these barriers can be removed and a different coding system more pertinent to the study of ADRs applied [12], they would have only limited usefulness for the purpose of studying drug safety.

We thank Hilary Pearce for helpful comments on an earlier draft of this paper. The Drug Safety Research Unit is a charitable trust which receives unconditional grants from the pharmaceutical industry. No specific funding was received for this study. M.S. and D.H. are funded by the South West Public Health Observatory. HES analyses conducted within the Department of Social Medicine are supported by the South West Public Health Observatory. The Hospital Episodes Statistics (HES) data were made available by the Department of Health. Conflicts of interest: none.

References

1 Bates DW. Drugs and adverse drug reactions. How worried should we be? JAMA 1998; 279: 1216–17.

2 Stephens MDB. Introduction. In Stephens' Detection of New Adverse Drug Reactions, eds Talbot J, Waller P. Chichester: Wiley, 2004; 17–30.

3 Lazarou J, Pomeranz BH, Corey PN. Incidence of adverse drug reactions in hospitalized patients. JAMA 1998; 279: 1200–5.

4 Smith CC, Bennett PM, Pearce HM et al. Adverse drug reactions in a hospital general medical unit meriting notification to the Committee on Safety of Medicines. Br J Clin Pharmacol 1996; 42: 423–9.

5 Stephens MDB. Introduction. In Stephens' Detection of New Adverse Drug Reactions, eds Talbot J, Waller P. Chichester: Wiley, 2004; 10–17.

6 International Statistical Classification of Diseases and Health Problems, 10th revision. Geneva: World Health Organisation, 1992.

7 http://www.dh.gov.uk/PublicationsAndStatistics/Statistics/HospitalEpisodeStatistics/fs/en (accessed 6 October 2004).

8 Arnold BDC. Regulatory aspects of pharmacovigilance. In Stephens' Detection of New Adverse Drug Reactions, eds Talbot J, Waller P. Chichester: Wiley, 2004; 382–4.

9 Cox AR, Anton C, Goh CHF, Easter M, Langford NJ, Ferner R. Adverse drug reactions in patients admitted to hospital identified by discharge ICD-10 codes and by spontaneous reports. Br J Clin Pharmacol 2001; 52: 337–9.

10 Hawton K, Townsend E, Deeks J et al. Effects of legislation restricting pack sizes of paracetamol and salicylate on self poisoning in the United Kingdom: before and after study. BMJ 2001; 322: 1203–7.

11 Davis S, Raine JM. Spontaneous reporting – UK. In Pharmacovigilance, eds Mann R, Andrews E. Chichester: Wiley, 2002; 195–207.

12 Brown EG. Dictionaries and coding in pharmacovigilance. In Stephens' Detection of New Adverse Drug Reactions, eds Talbot J, Waller P. Chichester: Wiley, 2004; 533–57.