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Adverse drug reactions in a hospital general medical unit meriting notification to the Committee on Safety of Medicines

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1 We have retrospectively analysed data collected by a local adverse drug reactions reporting scheme in an acute hospital medical setting and have determined the numbers and types of reactions that would have merited notification as yellow card reports according to the guidelines of the Committee on Safety of Medicines.

2 The data related to 20 695 consecutive acute general medical admissions on seven general medical wards (140 beds) and were collected over 3 years, from April 1990 to March 1993.

3 Over 3 years there were 1420 reports of suspected adverse drug reactions, a rate of 68.7 per 1000 admissions.

4 If the guidelines for reporting issued by the Committee on Safety of Medicines had been strictly followed, 477 yellow cards would have been sent (23.1 per 1000 admissions). In 357 of these reports (74.8%), the reaction had caused admission to hospital. Only 31 of the 477 potential cards (6.5%) involved black triangle drugs and 10 of these were for minor reactions.

5 Only 30 of the 477 potential yellow cards (6.3%) were known to have been sent. The majority of those reactions not reported were for drug-related admissions, most of which were for well-known reactions to established drugs.

6 We have confirmed and quantified the extent of under-reporting of serious suspected adverse drug reactions to the Committee on Safety of Medicines from our hospital medical unit.

Keywords adverse drug reactions Committee on Safety of Medicines yellow cards

Introduction

There is a high level of under-reporting of suspected adverse drug reactions (ADRs) to the Yellow Card Scheme of the Committee on Safety of Medicines (CSM) in the UK [1, 2], and according to the 1993/94 annual report of the Medicines Control Agency (MCA) [3] this appears to be getting worse, since the number of yellow cards sent by doctors during the year dealt with by the report had fallen by 17%. It has been suggested that at most only 14% of all suspected ADRs are reported in General Practice [4], and reporting from hospitals appears to be worse [5], even though they presumably see more serious reactions. However, there are no published data that confirm the degree of under-reporting from hospitals in the UK.

From 1988 to 1995 we ran a local ADR reporting scheme to investigate patients being treated on the general medical unit of the John Radcliffe Hospital. This research project was established in order to monitor and assess suspected ADRs, to highlight local prescribing problems, and to give feedback to doctors, nurses, and pharmacists.

As part of our general analysis of suspected ADRs

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reported to the Oxford Scheme, we retrospectively determined the numbers and types of reactions that would have merited notification as yellow card reports according to the guidelines of the CSM, and have compared them with the suspected adverse reactions for which yellow cards were known to have been sent. We present here data collected over 3 years relating to 20 695 consecutive acute general medical admissions.

Methods

The Oxford Adverse Drug Reactions Scheme operated on seven acute general medical wards (140 beds) in the John Radcliffe Hospital, including one specialist gastroenterology ward. The scheme was run by a part-time research pharmacist. Any health-care professional could initiate a report on a suspected ADR, either by writing the suspected drug, the adverse event, and the reporter's name on a form kept at the end of each bed, or by contacting the ADR research pharmacist, who visited the wards regularly and investigated and evaluated the reports. Deliberate overdoses were excluded. When a rare or unusual reaction occurred, doctors were asked to sign a yellow card which had been completed in detail by the ADR research pharmacist. These methods have previously been reported [6, 7].

The reactions were classified by their occurrence before or during the current hospital admission. Reactions that occurred before the admission were further classified according to whether they caused the admission or were coincidental. All reactions were given a severity score (Table 1) and causality was assessed subjectively by the same experienced pharmacist, with help when necessary from a clinical pharmacologist. The suspected drugs were categorized according to the BNF and to whether they were black triangle drugs or not. The suspected reaction was coded according to the 1990 CSM's computerized database of adverse events. The mechanism of each drug reaction was classified as dose-related, non-dose-related, long-term, or unknown, using published evidence to make the classification.

Data were stored in the form of records relating to reactions and reports in a database developed in 'dbase'. It is important to recognise the difference between records, reactions, and reports in this system. For example, a rash that could have been caused by either of two co-administered antibiotics, amoxycillin or flucloxacillin, would be represented by *two records,* one for each drug, but by only *one reaction* and *one report*. However, should two different reactions occur at the same time they would be classified as *two reactions* but only *one report*.

The CSM requests in the BNF that the following types of reactions be reported on yellow cards:

> 'NEWER DRUGS. These are indicated by the sign ▼. Doctors are asked to report *all* suspected reactions (i.e. any adverse or any unexpected event, however minor, which could conceivably be attributed to the drug). Reports should be made despite uncertainty about a causal relationship, irrespective of whether the reaction is well recognized, and even if other drugs have been given concurrently.'
>
> 'ESTABLISHED DRUGS. Doctors are asked to report *all* serious suspected reactions, including those that are fatal, life-threatening, disabling, incapacitating, or which result in or prolong hospitalisation; they should be reported even if the effect is well recognised.'

Using these criteria for this study, we have flagged the following reactions on our database that would have merited a yellow card:

- Any suspected adverse reaction attributed to a black triangle drug.
- Any suspected adverse reaction, attributed to an established drug, that caused the hospital admission (severity scores 3, 4, or 5).
- Any suspected adverse reaction, attributed to an established drug, that was serious and occurred during an in-patient stay (severity scores 4 or 5).

We asked the CSM for information on the number of

Table 1 Criteria for determining the severity of an adverse drug reaction

Severity score	*Description of the reaction*	*Criteria*	*Examples*
1	Trivial	Inconvenient Withdrawal not necessary	Transient nausea
2	Minor	More uncomfortable Withdrawal will depend on the patient's tolerance of the reaction	Vomiting Headache
3	Significant	More serious Usually requires withdrawal	Rash Thrombocytopenia
4	Serious	Life-threatening Requires immediate withdrawal	Anaphylaxis Stevens–Johnson syndrome
5	Death-related	May have caused death or contributed to it	

yellow cards that had originated from the medical wards of the John Radcliffe Hospital during this period and comparative figures for the whole John Radcliffe Hospital and similar teaching hospitals.

The data from April 1990 to March 1993 were analysed using Epi Info, a word-processing, database and statistics system for epidemiological research.

Results

Total number of suspected ADRs

During the 3-year study period, there were 20 695 admissions to the medical wards covered by the Oxford Scheme and 1420 reports of suspected ADRs. This is equivalent to 68.7 reports per 1000 admissions (Table 2) or about 1 report per 15 admissions. One-third were present on admission and two-thirds occurred after admission. Only 2.3% of all reports involved a black triangle drug.

Suspected reactions meriting yellow cards

If the CSM's guidelines for reporting had been strictly followed, 477 reports on the scheme would have been identified as meriting yellow cards. The reporting rate for yellow cards would have been 23.1 per 1000 admissions (Table 2), i.e. one-third of all the reports collected. The largest component, 357 reports (74.8%), was for reactions causing an admission (17.3 reports per 1000 admissions), 347 due to established drugs and 10 due to black triangle drugs. Reactions occurring after admission accounted for 120 potential yellow cards, 99 serious reactions to established drugs, and 21 reactions due to black triangle drugs. Only six of these 21 black triangle reactions were classified as serious. In all, 105 serious reactions occurred after admission, a rate of 5.1 reports per 1000 admissions. This is equivalent to about 1 serious drug-related reaction during 200 admissions. During the 3 years two deaths were attributed to an ADR (a rate of 1 per 10 000 admissions).

Established drugs accounted for 446 (94%) of the 477 potential yellow cards. Only 31 of the potential yellow cards (6.5%) involved a black triangle drug (1.49 reports per 1000 admissions), 10 of these being for minor or trivial reactions.

In all, 477 potential yellow cards were retrospectively identified (123 in 1990/1, 203 in 1991/2, and 151 in 1992/3), but only 30 (6.3%) were known to have been sent. Details of these 30 yellow cards are shown in Table 3. Data provided by the CSM suggested that the scheme was responsible for almost all of the yellow cards received from the medical unit of the John Radcliffe Hospital, and the overall reporting for the hospital was similar to or better than other teaching hospitals. However, the CSM has emphasized that this information may be incomplete.

Types of ADRs detected

The 477 potential yellow cards involved 130 different types of suspected adverse reactions and 179 different drugs. Three groups of ADRs contributed to one-third of all reactions meriting a yellow card. These were

Table 2 Relation of adverse drug reaction to hospital admission

		Reporting rates per 1000 admissions (numbers of reports/records in parenthesis)						
Analysis	*Relation of ADR to hospital admission*	*All*		*Potential yellow cards*		*Yellow cards*		*Potential yellow cards (%) of total*
Reports	*(i) Black triangle drugs*							
	Present on admission	0.48	(10)	0.48	(10)	0.048	(1)	100
	Occurred after admission	1.01	(21)	1.01	(21)	0.097	(2)	100
	(ii) Established drugs							
	Present on admission	22.28	(461)	16.77	(347)	0.82	(17)	75
	Occurred after admission	44.84	(928)	4.78	(99)	0.48	(10)	11
	Total reports	68.66	(1420)	23.05	(477)	1.45	(30)	34
Records	*(i) Black triangle drugs*							
	Present on admission	1.16	(13)	1.16	(13)	0.14	(3)	100
	Occurred after admission	2.07	(43)	2.03	(43)	0.14	(3)	100
	(ii) Established drugs							
	Present on admission	36.43	(754)	27.98	(579)	1.55	(32)	77
	Occurred after admission	77.84	(1611)	8.36	(173)	0.48	(10)	11
	Total records	116.98	(2421)	39.04	(808)	2.32	(48)	33

Table 3 Details of the yellow cards sent to the Committee on Safety of Medicines

Reaction	*Suspected drugs*
INR > 15, GI haemorrhage	Warfarin + azapropazone
INR > 15, GI haemorrhage	Warfarin + azapropazone
INR > 15, haematoma	Warfarin + azapropazone
Anaphylactoid reaction	Phytomenadione
Anaphylactoid reaction	Phytomenadione
Back pain	Phytomenadione
Back pain	Streptokinase
Bronchospasm	Multivitamins
Serum sickness	Ampicillin
Muscle spasm	Azathioprine
Rash/neutropenia	Sulphasalazine
Stevens–Johnson syndrome	Phenytoin, enalapril
Nephrotic syndrome	Tiaprofenic acid
Abnormal renal function deteriorated	Enalapril*, indomethacin
Acute renal failure	Streptokinase
Acute renal tubular necrosis	Iopamidol
Jaundice	Streptokinase
Jaundice	Fluconazole*, imipramine
Cholestatic jaundice	Flucloxacillin
Jaundice/abnormal liver function	Amoxycillin, clavulanic acid
Hepatitis/rash	Sulphasalazine
Hepatitis/cholestasis	Dextropropoxyphene, paracetamol
Thrombocytopenia**	Levodopa, carbidopa
Thrombocytopenia	Captopril*
Pancreatitis**	Azathioprine
Antidiuretic hormone disorder	Glibenclamide, tolbutamide
Extrapyramidal disorder/confusion	Trifluoperazine
Cardiomyopathy	Doxorubicin
Myositis	Fluoxetine
Supraventricular tachycardia	Amiodarone

*Black triangle drug at time of report.
**Fatal reaction.

gastrointestinal haemorrhage, toxicity from drugs with a low therapeutic index (e.g. warfarin, digoxin), and impaired renal function (e.g. due to diuretics, ACE inhibitors). Gastrointestinal haemorrhage was the most frequent (15% of potential yellow cards); aspirin, responsible for 27% of these records, was the single drug most often implicated, and the non-aspirin non-steroidal anti-inflammatory drugs (NSAIDs) were responsible for 50%. We have reported elsewhere the data on individual NSAIDs [8].

Mechanism of event

Most of the reactions reported to the scheme were dose-related (Table 4), accounting for 80.3% of all records. This pattern was also observed with potential yellow cards (72.3% of records). This is in contrast to the pattern seen among yellow cards that were known to have been sent to the CSM, where the numbers of dose-related and non-dose-related reactions were similar.

Drug interactions causing ADRs

Drug interactions caused ADRs in only 31 of the 1420 reports (1.50 per 1000 admissions). Twenty-two were serious enough to merit a potential yellow card (1.06 per 1000 admissions) and three were known to have been been reported as yellow cards (0.14 per 1000 admissions). None of these interactions was novel and all involved drugs with a low therapeutic index; warfarin, the most frequent, was implicated in 19 of the 31 reports, 14 of the 22 potential yellow cards, and all three actual yellow cards. The other drugs with a low therapeutic index implicated in the interactions were aminophylline, carbamazepine, cyclosporin, digoxin, lithium, and phenytoin.

Groups detecting ADRs

The two main groups of health-care professionals who detected suspected ADRs on the Oxford scheme

Table 4 Adverse drug reactions classified by mechanism of events, BNF classification of suspected drug, and body system affected (CSM classification) (analysis is by record only, as reports can contain more than one suspected drug and more than one event)

		Reporting rates per 1000 admissions (numbers of records in parenthesis)						
		All		*Potential yellow cards*		*Yellow cards*		*Potential yellow cards (%) of total*
Analysis	*Classification*							
Records	*(i) Mechanism of event*							
	Dose-related	93.98	(1945)	28.22	(584)	0.97	(20)	30
	Non-dose related	18.85	(390)	8.94	(185)	1.21	(25)	47
	Long-term	1.30	(27)	0.48	(10)	0.00	(0)	37
	Unclassified (unknown)	2.85	(59)	1.40	(29)	0.14	(3)	49
Records	*(ii) BNF class of suspected drug*							
	Cardiovascular	49.82	(1031)	16.28	(337)	0.48	(10)	33
	Infections	22.71	(470)	4.30	(89)	0.29	(6)	19
	Central nervous system	19.23	(398)	7.01	(145)	0.63	(13)	36
	Musculoskeletal system	7.68	(159)	5.22	(108)	0.24	(5)	68
	Endocrine	4.98	(103)	22.28	(46)	0.10	(2)	45
	Others	12.56	(260)	4.01	(83)	0.58	(12)	32
Records	*(iii) Body system affected*							
	Gastrointestinal system	30.01	(621)	8.94	(185)	0.10	(2)	30
	Autonomic	17.30	(358)	3.82	(79)	0.10	(2)	22
	Central nervous system	13.58	(281)	3.14	(65)	0.14	(3)	23
	General disorders	11.16	(231)	6.23	(129)	0.68	(14)	56
	Others	44.94	(930)	16.91	(350)	1.30	(27)	38
	Total records	116.98	(2421)	39.04	(808)	2.32	(48)	33

(Table 5) were nurses (702 reactions, 49.4%), and pharmacists (635 reactions, 44.7%). The ADR research pharmacist detected 465 of the 635 pharmacist reports. Doctors detected 83 reactions (5.9%). Pharmacists detected 240 reactions meriting a potential yellow card (50.4%), of which the ADR research pharmacist was responsible for 144 reactions; nurses detected 189 (39.6%) and doctors detected 48 (10.1%). Of the 30 yellow cards known to have been sent, 15 (50%) were initiated by pharmacists, 9 (30%) by doctors, and 6 (20%) by nurses.

Efficacy of the scheme to detect reactions meriting a yellow card

In a parallel study in the John Radcliffe Hospital (HMP, unpublished observations), 1071 acute medical admissions were systematically reviewed in search of ADRs recorded in the medical notes. In all, 36 significant reactions resulting in admission were identified (33.6 reports per 1000 admissions), including one reaction attributed to a black triangle drug. A review of 871 of these patients identified four serious reactions that

Table 5 Adverse drug reactions classified by reporter

		Reporting rates per 1000 admissions (numbers of reports/records in parenthesis)						
		All		*Potential yellow cards*		*Yellow cards*		*Potential yellow cards (%) of total*
Analysis	*Reporter*							
Reports	Nurse	33.92	(702)	9.13	(189)	0.29	(6)	27
	Pharmacist	30.68	(635)	11.60	(240)	0.72	(15)	38
	Doctor	4.01	(83)	2.32	(48)	0.43	(9)	58
	Total reports	68.62	(1420)	23.05	(477)	1.45	(30)	34
Records	Nurse	57.79	(1196)	14.59	(302)	0.43	(9)	25
	Pharmacist	51.90	(1074)	19.81	(410)	1.30	(27)	38
	Doctor	7.30	(151)	4.64	(96)	0.58	(12)	64
	Total records	116.98	(2421)	39.04	(808)	2.32	(48)	33

occurred during their in-patient stay (4.6 reports per 1000 admissions). This gives an overall rate of 38.2 potential yellow card reports per 1000 admissions, compared with a rate of 23.1 reports per 1000 admissions reported to the Oxford Scheme. Thus, the estimated efficacy of the Oxford Scheme to detect reactions meriting a yellow card is 60.3%.

Discussion

The Yellow Card Scheme of the CSM is vital for the identification of previously unknown ADRs, for example blood dyscrasias with mianserin [9], the hepatotoxicity of amiodarone [10], and cardiac arrhythmias with terodiline [11]. The data are also used to assess the risk : benefit profile of both new and established drugs.

The CSM asks for ADR reports of two types: all reactions to black triangle drugs and serious reactions to established drugs. Recognising the difficulties in categorizing serious ADRs, the Committee has issued guidance on which ADRs to report [12]. For the purposes of this study we designated as serious those reactions that caused admission to hospital or were potentially life-threatening reactions occurring in hospital. Certainly not every case of, for example, 'hypokalaemia', 'renal dysfunction', or 'hypotension' was a serious reaction.

The CSM emphasizes that for yellow card reporting proven causality is not essential. Validation of ADRs is contentious, and even standardized assessment methods, such as algorithms and decision tables, produce disagreement amongst experts, particularly in attributing cause to the drug rather than other factors [13]. Subjective validation by experienced pharmacists and clinicians, as we have used, is therefore still used by many workers [14].

Using the Oxford Scheme we have analysed 1420 spontaneous reports of ADRs derived from 20 695 medical admissions over a 3-year period. Using the guidelines produced by the CSM, we have retrospectively identified 477 reactions that merited a potential yellow card (23.1 per 1000 admissions). Of these potential yellow cards, 357 (74.8%) were reactions causing admission to hospital. The total number of drug-related admissions found in the present study (2.3%) is similar to that found in other studies [15]. Only 129 potential yellow cards (25.2%) were for reactions that occurred in hospital; 99 of these were serious reactions to established drugs and 21 were reactions to black triangle drugs, of which only 6 were serious.

Most of the reactions in the reports identified as potential yellow cards were dose-related (72.3% of records). Many of these were well-known reactions resulting from either the primary or secondary pharmacological action of the drug, such as gastrointestinal haemorrhage, toxicity from drugs with a low therapeutic index, and impairment of renal function. However, of the actual yellow cards known to have been sent, only 41.7% were for dose-related reactions.

There were few reported reactions to black triangle drugs (31 reports). This probably reflected the low usage of these drugs in Oxford at the time of the study, although it may be that the newer drugs were safer.

Although there are many documented drug interactions, our data suggest that they do not often cause adverse drug reactions. Only 31 suspected adverse interactions were reported to the scheme, but 22 were serious enough to merit a potential yellow card, all involving drugs with a low therapeutic index. Over a period of 1 month yellow cards were sent for three patients admitted to hospital with haemorrhage and an INR greater than 15 as a result of the interaction between azapropazone and warfarin. These cases prompted joint letters from us and the local FHSA medical adviser to all local GPs and Community Pharmacists, warning them of this contraindication, and an educational presentation was made at a medical grand round.

Although nurses made 702 reports to the scheme, only 189 (27%) were serious enough to merit a potential yellow card. Pharmacists made slightly fewer reports to the scheme, 635, but 240 of these (38%) were serious enough to merit a potential yellow card. Although doctors were responsible for only 48 of the potential yellow cards, these represented 58% of their reports to the scheme, indicating the more serious nature of their reports.

The number of yellow cards submitted by our scheme is comparable with other schemes. The Green Card Scheme in Liverpool [16] resulted in 176 yellow cards from about 28 000 admissions per year over 3 years (2.1 per 1000 admissions); these cards originated from specialties throughout the hospital. In Oxford 30 completed cards resulted over 3 years from about 7000 admissions per year on the medical wards alone (1.5 per 1000 admissions). In a pilot study in the former Northern Region [17], in which hospital pharmacists signed yellow cards with the doctor's approval, 145 yellow cards were sent during the first year by 47 pharmacists in 13 of the Region's 15 Districts. In the second year 142 yellow cards were sent [Northern Regional Drug and Therapeutics Centre, personal communication]. However, no data were readily available to correlate the number of yellow card reports with the number of admissions in this study.

Under-reporting to the Oxford Scheme

We have estimated that the overall efficacy of the Oxford Scheme for detecting potential yellow cards was 60%. The scheme appeared to detect serious reactions that occurred during the in-patient stay and most of the reports implicated a black triangle drug. However, only about half of the significant reactions resulting in admission were reported to the scheme, which may reflect a greater emphasis by clinical staff on reporting events that occurred in hospital.

Under-reporting of ADRs to the CSM

Completion of yellow cards for reactions that fulfil the CSM's guidelines was low from the medical unit of the John Radcliffe Hospital (6.3% of reports on the Oxford Scheme and only 3.8% of ADRs recorded in the medical notes). We believe that the reporting rate of yellow cards from the whole of the John Radcliffe Hospital is comparable with similar hospitals in the UK (CSM, personal communication). This degree of under-reporting of hospital ADRs in the UK is seen elsewhere; for example, in a Danish study of 1999 consecutive admissions to medical wards, 157 admissions were related to ADRs, but only one case was reported to the national regulatory authority (0.6%) [18]. This was one-tenth of the rate observed in our study.

There are many reasons for the under-reporting of suspected adverse reactions to the CSM. These include lack of time [19, 20]; for example, it has been reported that doctors from a low-reporting area wrote more prescriptions per day and had more clinical contact than doctors from a high-reporting area [20]. In addition, doctors seem unaware of the need to report well-known serious reactions and need more guidance on what to report. However, it is difficult to persuade doctors to sign yellow cards for trivial or minor reactions to black triangle drugs. Under-reporting may also occur because doctors are under the misconception that they need to be absolutely confident in the cause-and-effect relation between drug and presumed adverse reaction before reporting it [20].

The main reason for the low proportion of yellow card reporting in our study is that the CSM asks for all reactions resulting in admission to hospital. These reactions, by definition, are serious, but the majority are for well-known reactions to established drugs and are therefore often not reported. If all such drug-related admissions were reported to the CSM from all the acute hospitals in the UK, we estimate that this would generate in excess of 20 000 additional yellow cards per year.

Conclusions

We have confirmed and quantified the suspected very low level of reporting of yellow cards from a hospital medical unit. We have shown that there is the potential for a large number of yellow cards to be reported to the CSM from a hospital medical unit, but that the majority of these are for drug-related admissions, most of which are due to well-known reactions to established drugs.

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