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How good are articles on adverse drug reactions?

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Abstract

A study was carried out of the quality and completeness of articles on adverse drug reactions: 5737 articles from 80 countries published between 1972 and 1979 were studied. Only 61% of the articles included information on the number of patients treated and the number with adverse drug reactions, yet these are essential for calculating the incidence of adverse reactions. In only 55% could the incidence of a particular adverse reaction be calculated.

Great importance is placed on articles on adverse reactions, particularly those that report on many patients. Authors and editors should ensure that articles include the following information: drug regimens,

numbers of patients treated, numbers of patients developing adverse reactions, and nature and incidence of adverse reactions.

Introduction

Published articles on adverse drug reactions are considered to be important, particularly for regulatory agencies and drug companies, as both have to rely heavily on worldwide experience by independent investigators in "daily life." It is important to know not only what adverse reactions occur but how often they occur, and this cannot be determined from individual case reports. Studies of large groups of patients are therefore especially important in providing quantitative information. But how good are articles at giving information on adverse drug reactions?

One review of 23 papers on adverse drug reactions published in a reputable medical journal showed serious shortcomings in most of them: in 14 articles the number of patients affected by particular symptoms was missing, and nine articles contained no information on dosage or duration of treatment.¹ Similar inadequacies were found in 1600 clinical trials submitted by drug companies to licensing authorities²: in 80% of the trials adverse reactions were referred to, but in only 44% was the number of different types of adverse reactions given and in only 13% was

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the incidence of adverse reactions given. Other authors have confirmed these inadequacies.³⁻⁵

To study further the quality of articles reporting adverse drug reactions we looked at articles that related to Ciba-Geigy products. As these products are used in all branches of medicine all over the world articles relating to them are likely to be representative of all articles on adverse drug reactions.

Methods

We classified articles on adverse drug reactions into three types: reports on not more than five patients; review articles of many authors' experience; and articles on authors' own experience with many patients. The third type are particularly interesting as they give some idea of the incidence of adverse drug reactions. We consider here only this third type. There were 5737 such articles from 80 countries published between 1972 and 1979. They included articles ranging from those relating to formal clinical trials to unsolicited accounts of experience with treatment.

Microfiches of all publications are kept in our files, but some information is extracted from them and stored in computer files. The following is among the information stored in the computer: name of Ciba-Geigy drug (or of its generic equivalent); galenic form (reported or deduced); daily dose (or range thereof); duration of treatment (or range thereof); names of other drugs given at the same time; number of patients treated; patients' ages (or range thereof); reason for using the drug; number of patients with adverse reactions; list of adverse reactions seen; number of adverse reactions; name of author and country of origin of publication; publication's references; internal referee's assessment of usefulness made at time of entering the paper into the computer.

We analysed these data to determine how many of the articles contained particular types of information.

Results

Countries where 100 or more publications originated during 1972-9 were the USA (828 publications), France (771), Great Britain (694), the German Federal Republic (459), Italy (343), Japan (313), Switzerland (257), Sweden (234), Spain (134), Brazil (127), Austria (110), Finland (107), Denmark (102), and India (100). Table I shows the type of information contained in the 5737 articles studied. Only 19% of the articles (column L) contained information on the number of patients treated, the number of patients who had adverse drug

reactions, the number of adverse drug reactions, the age of the patients, the dose of drug used, the duration of treatment, and the galenic form of the drug. Only 61% of the articles (column D) included information on the number of patients treated and the number with adverse drug reactions, yet these are essential for calculating the incidence of adverse reactions. In only 55% was there sufficient information for the incidence of particular adverse reactions to be calculated (column G). Furthermore, a comparison of the information contained in articles published from 1972 to 1975 with those published from 1975 to 1979 showed no significant change.

Table II shows the type of information contained in articles from countries where more than 200 such articles originated. There were considerable variations, and articles from Japan, France, and Italy seemed to be the most complete.

Table III shows the type of information contained in articles from particular journals. In general, journals particularly devoted to therapeutic research (9, 10, 11, 14, 18, 19, 29, 30) tended to publish fairly complete papers. A group of more general medical journals (1, 2, 4, 5, 17, 20, 21), however, some of them from Third World countries, also published papers with remarkably complete data.

We also looked indirectly at whether the specialty of the author affected the type of information contained in the articles. We did this by looking at articles on drugs used mainly in particular specialties: diclofenac, used mainly in rheumatology; maprotiline, used mainly in psychiatry; and oxprenolol, used mainly in cardiology. No significant differences emerged.

Discussion

Our results show that many articles on large numbers of patients treated with a particular drug and containing information on adverse drug reactions lack important data. We think that most researchers would have basic information on the numbers of patients treated, the numbers who had adverse drug reactions, the number of adverse reactions, the age of the patients, the dose of the drug, the duration of treatment, and the galenic form of the drug, yet only 19% of the articles contained all this information. Nor could we find any evidence that things are improving. Our results also show that this is a problem in all countries where large numbers of studies are undertaken, and in most international journals. Some journals are better than others, but whether this reflects the kind of papers received or the editorial policy we cannot say. We also have circumstantial evidence that no one specialty is better than another.

Do these findings matter? Yes, they do, because published

TABLE I—Availability of relevant data in 5737 medical publications (1972-9)

Type of information:	A	B	C	D	E	F	G	H	I	J	K	L
No of patients treated	+			+	+		+	+	+	+	+	+
No of patients with adverse reaction		+		+		+	+	+	+	+	+	+
No of adverse reactions			+		+	+	+					+
Any information on age								+				+
Any information on dose									+			+
Any information on duration of treatment										+		+
Any information on galenic form											+	+
No (%) of publications giving these data	5135 (90)	3791 (66)	3909 (68)	3517 (61)	3609 (63)	3431 (60)	3173 (55)	1844 (32)	2505 (44)	2239 (39)	3517 (61)	1094 (19)

TABLE II—Availability of relevant data in medical publications originating from selected countries (1972-9). (Figures in lower part of table are numbers (%) of publications)

Type of information	A	B	C	D	E	F	G	H	I	J	K	L
No of patients treated	+			+	+		+	+	+	+	+	+
No of patients with adverse reaction		+		+		+	+	+	+	+	+	+
No of adverse reactions			+		+	+	+					+
Any information on age								+				+
Any information on dose									+			+
Any information on duration of treatment										+		+
Any information on galenic form											+	+
Switzerland (n = 257)	221 (86)	159 (62)	163 (63)	137 (53)	142 (55)	141 (55)	120 (47)	61 (24)	71 (28)	75 (29)	137 (53)	27 (11)
German Federal Republic (n = 459)	394 (86)	305 (66)	292 (64)	276 (60)	261 (57)	268 (58)	239 (52)	115 (25)	181 (39)	162 (35)	276 (60)	56 (12)
France (n = 771)	713 (92)	538 (70)	559 (73)	509 (66)	529 (69)	493 (64)	466 (60)	311 (40)	380 (49)	338 (44)	509 (66)	177 (23)
Great Britain (n = 694)	631 (91)	403 (58)	427 (62)	379 (55)	400 (58)	344 (50)	322 (46)	163 (23)	280 (40)	223 (32)	379 (55)	95 (14)
Sweden (n = 234)	197 (84)	167 (71)	162 (69)	147 (63)	140 (60)	155 (66)	137 (59)	69 (29)	90 (38)	79 (34)	147 (63)	41 (18)
USA (n = 828)	690 (83)	503 (61)	514 (62)	446 (54)	448 (54)	449 (54)	394 (48)	221 (27)	297 (36)	267 (32)	446 (54)	113 (14)
Italy (n = 343)	317 (92)	235 (69)	243 (71)	217 (63)	228 (66)	221 (64)	206 (60)	131 (38)	165 (48)	159 (46)	217 (63)	79 (23)
Japan (n = 313)	293 (94)	250 (80)	249 (80)	245 (78)	242 (77)	234 (75)	230 (73)	177 (57)	218 (70)	190 (61)	245 (78)	146 (47)

TABLE III—Availability of relevant data in publications from selected medical journals (1972-9). (Figures in lower part of table are numbers (%) of publications)

Type of information	A	B	C	D	E	F	G	H	I	J	K	L
No of patients treated	+			+	+		+	+	+	+	+	+
No of patients with adverse reaction		+		+		+	+	+	+	+	+	+
No of adverse reactions			+		+	+	+					+
Any information on age								+				+
Any information on dose									+			+
Any information on duration										+		+
Any information on galenic form											+	+
Australia:												
1 <i>Medical Journal of Australia</i> (n = 34)	29 (85)	20 (59)	24 (71)	18 (53)	21 (62)	19 (56)	17 (50)	12 (35)	15 (44)	12 (35)	18 (53)	9 (26)
Brazil:												
2 <i>Folha Médica</i> (n = 48)	48 (100)	40 (83)	41 (85)	40 (83)	41 (85)	37 (77)	37 (77)	29 (60)	31 (65)	37 (77)	40 (83)	18 (38)
Denmark:												
3 <i>Ugeskrift for Laeger</i> (n = 24)	20 (83)	17 (71)	21 (88)	14 (58)	17 (71)	17 (71)	14 (58)	4 (17)	9 (38)	4 (17)	14 (58)	0
Egypt:												
4 <i>Ain Shams Medical Journal</i> (n = 20)	20 (100)	14 (70)	15 (75)	14 (70)	15 (75)	13 (65)	13 (65)	8 (40)	13 (65)	13 (65)	14 (70)	6 (30)
France:												
7 <i>Gazette Médicale de France</i> (n = 37)	36 (97)	27 (73)	29 (78)	27 (73)	29 (78)	27 (73)	27 (73)	15 (41)	21 (57)	20 (54)	27 (73)	11 (30)
6 <i>Nouvelle Presse Médicale</i> (n = 15)	14 (93)	10 (67)	11 (73)	9 (60)	10 (67)	10 (67)	9 (60)	5 (33)	9 (60)	6 (40)	9 (60)	3 (20)
German Federal Republic:												
7 <i>Deutsche Medizinische Wochenschrift</i> (n = 18)	15 (83)	14 (78)	14 (78)	13 (72)	13 (72)	14 (78)	13 (72)	4 (22)	8 (44)	4 (22)	13 (72)	2 (11)
8 <i>Therapiewoche</i> (n = 48)	44 (92)	37 (77)	27 (56)	35 (73)	25 (52)	26 (54)	24 (50)	16 (33)	31 (65)	29 (60)	35 (73)	8 (17)
9 <i>European Journal of Clinical Pharmacology</i> (n = 31)	30 (97)	20 (65)	18 (58)	19 (61)	17 (55)	17 (55)	16 (52)	13 (42)	16 (52)	11 (35)	19 (61)	8 (26)
10 <i>International Journal of Clinical Pharmacology and Biopharmacy</i> (n = 8)	8 (100)	7 (88)	8 (100)	7 (88)	8 (100)	7 (88)	7 (88)	5 (63)	7 (88)	5 (63)	7 (88)	3 (38)
11 <i>Arzneimittel-Forschung</i> (n = 27)	27 (100)	17 (63)	16 (59)	17 (63)	16 (59)	16 (59)	16 (59)	11 (41)	16 (59)	14 (52)	17 (63)	10 (37)
12 <i>Medizinische Welt</i> (n = 23)	22 (96)	16 (70)	17 (74)	16 (70)	17 (74)	14 (61)	14 (61)	6 (26)	10 (43)	9 (39)	16 (70)	2 (9)
Great Britain:												
13 <i>British Medical Journal</i> (n = 59)	49 (83)	40 (68)	43 (73)	34 (58)	36 (61)	34 (58)	29 (49)	11 (19)	21 (36)	15 (25)	34 (58)	6 (10)
14 <i>British Journal of Clinical Pharmacology</i> (n = 36)	36 (100)	24 (67)	25 (69)	24 (67)	25 (69)	21 (58)	21 (58)	16 (44)	19 (53)	19 (53)	24 (67)	11 (31)
15 <i>Journal of International Medical Research</i> (n = 99)	93 (94)	52 (53)	53 (54)	51 (52)	51 (52)	40 (40)	39 (39)	36 (36)	46 (47)	39 (39)	51 (52)	21 (21)
16 <i>Lancet</i> (n = 49)	44 (90)	43 (88)	39 (80)	38 (78)	35 (71)	38 (78)	34 (69)	16 (33)	23 (47)	19 (39)	38 (78)	9 (18)
Italy:												
17 <i>Minerva Medica</i> (n = 24)	22 (92)	17 (71)	17 (71)	15 (63)	15 (63)	16 (67)	14 (58)	11 (46)	12 (50)	13 (54)	15 (63)	7 (29)
18 <i>Clinica Terapeutica</i> (n = 27)	24 (89)	19 (70)	18 (67)	17 (63)	18 (67)	17 (63)	17 (63)	10 (37)	14 (52)	15 (56)	17 (63)	8 (30)
Japan:												
19 <i>Chemotherapy</i> (n = 139)	135 (97)	122 (88)	123 (88)	120 (86)	121 (87)	121 (87)	119 (86)	101 (73)	111 (80)	103 (74)	120 (86)	88 (63)
20 <i>Shinryo To Shinyaku</i> (n = 22)	22 (100)	21 (95)	17 (77)	21 (95)	17 (77)	17 (77)	17 (77)	16 (73)	21 (95)	20 (91)	21 (95)	12 (55)
Mexico:												
21 <i>Prensa Medica Mexicana</i> (n = 12)	12 (100)	10 (83)	9 (75)	10 (83)	9 (75)	9 (75)	9 (75)	9 (75)	8 (67)	5 (42)	10 (83)	4 (33)
New Zealand:												
22 <i>New Zealand Medical Journal</i> (n = 29)	22 (76)	20 (69)	19 (66)	17 (59)	17 (59)	17 (59)	15 (52)	3 (10)	5 (17)	4 (14)	17 (59)	2 (7)
Norway:												
23 <i>Tidsskrift for den Norske Lægeforening</i> (n = 13)	10 (77)	7 (54)	10 (77)	6 (46)	7 (54)	7 (54)	6 (46)	2 (15)	3 (23)	2 (15)	6 (46)	2 (15)
South Africa:												
24 <i>South African Medical Journal</i> (n = 31)	30 (97)	20 (65)	22 (71)	20 (65)	22 (71)	18 (58)	18 (58)	7 (23)	16 (52)	11 (35)	20 (65)	4 (13)
Sweden:												
25 <i>Acta Medica Scandinavica</i> (n = 43)	32 (74)	31 (72)	29 (67)	22 (51)	21 (49)	29 (67)	21 (49)	13 (30)	13 (30)	8 (19)	22 (51)	5 (12)
26 <i>Läkartidningen</i> (n = 26)	17 (65)	18 (69)	19 (73)	13 (50)	13 (50)	18 (69)	13 (50)	2 (8)	3 (12)	3 (12)	13 (50)	1 (4)
Switzerland:												
27 <i>Schweizerische Medizinische Wochenschrift</i> (n = 31)	26 (84)	22 (71)	19 (61)	18 (58)	15 (48)	18 (58)	14 (45)	8 (26)	7 (23)	9 (29)	18 (58)	4 (13)
28 <i>Schweizer Rundschau</i> (n = 22)	20 (91)	12 (55)	12 (55)	10 (45)	10 (45)	10 (45)	8 (36)	6 (27)	8 (36)	7 (32)	10 (45)	3 (14)
USA:												
29 <i>Clinical Pharmacology and Therapeutics</i> (n = 33)	29 (88)	16 (48)	19 (58)	14 (42)	17 (52)	16 (48)	14 (42)	7 (21)	13 (39)	12 (36)	14 (42)	7 (21)
30 <i>Current Therapeutic Research</i> (n = 68)	65 (96)	37 (54)	36 (53)	37 (54)	36 (53)	29 (43)	29 (43)	32 (47)	36 (53)	34 (50)	37 (54)	22 (32)
31 <i>Journal of the American Medical Association</i> (n = 19)	17 (89)	14 (74)	14 (74)	12 (63)	12 (63)	14 (74)	12 (63)	8 (42)	6 (32)	7 (37)	12 (63)	4 (21)

articles, particularly those that report on large numbers of patients, are a unique source of data. They are essential for assessing the importance and incidence of adverse reactions, which in its turn is obviously essential for rational prescribing. It is striking that while so much importance is placed on published articles the quality of so many is so poor.

There is obviously a need to improve the quality of articles containing information on adverse drug reactions, but how can this be done? The responsibility clearly lies with both authors and editors. One important way in which authors can help is by not publishing information in more than one journal without acknowledging that it has been published elsewhere. In our study we came across many examples of authors doing exactly this. This is an important problem that others have recognised.^{6, 7} Authors should always include information on drug regimens, numbers of patients treated, numbers of patients developing adverse drug reactions, and the nature and incidence of the reactions, and editors should insist that this minimum information is included. Lock has written on the responsibility of the medical press,⁸ and we agree with Altman that, "The ultimate responsibility for the general standard of published research rests with the medical journals. Perhaps unwillingly the journals

have the role of guardian of quality."⁹ But the authors should not make this task too difficult.

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