

Quality of the Publication of Adverse Drug Reactions in the Letters to the Editor Section of Four Spanish Internal Medicine and General Medicine Journals

E. Sempere,^a V. Palop,^b A. Bayón,^c R. Sorando,^d and I. Martínez-Mir^e

Objective. To assess the quality and relevance of adverse drug reactions (ADRs) published as Letters to the Editor (LE) in Spanish medical journals.

Design. Observational study.

Participants. LE on adverse drug reactions published over 5 years (1994–98).

Setting. Four Spanish medical journals (*Medicina Clínica*, *Revista Clínica Española*, *ATENCIÓN PRIMARIA* and *Anales de Medicina Interna*).

Main measurements. Patient characteristics, drugs, ADR, causality algorithm, minimum criteria, and publication relevance.

Results. Out of 2244 LE, 204 (9.1%) reported ADRs, which included 235 cases. The therapeutic subgroups most commonly implicated were anticoagulants and antiplatelet drugs, antibiotics, and antineoplastic agents; 20.4% of the drugs were recently marketed. ADRs most commonly involved the nervous system (13.6%), liver (10.2%), skin and appendages (9.8%), general reactions (9.8%), and the digestive system (8.1%). The reactions were moderate in 50.2% of cases and severe/fatal in 34%. The mean causality algorithm value (5.9 ± 2.2) was similar among journals. Of the ADRs, 28 (11.9%) were definitive, 182 (77%) possible or probable, and 26 (11.1%) improbable or conditional; 10.2% were unknown. There were no differences in the mean minimum publication criteria (9.5 ± 1.2). Publication relevance was 3.2 ± 1.6 points, and higher in *Medicina Clínica*.

Conclusions. ADRs constitute an important part of LE in the journals studied. The causal relationship is acceptable, the documentation quality is high, with few unknown reactions and ADRs to recently marketed drugs. Relevance is generally low, although greater in *Medicina Clínica*.

Key words: Adverse drug reactions. Quality. Criteria.

CALIDAD DE LA PUBLICACIÓN DE REACCIONES ADVERSAS A MEDICAMENTOS EN LA SECCIÓN DE CARTAS AL DIRECTOR DE CUATRO REVISTAS ESPAÑOLAS DE MEDICINA INTERNA Y MEDICINA GENERAL

Objetivo. Conocer la calidad y la relevancia de las reacciones adversas a medicamentos (RAM) publicadas como Cartas al Director en las revistas médicas españolas.

Diseño. Estudio descriptivo.

Participantes. Cartas al director sobre RAM aparecidas durante 5 años (1994–98).

Emplazamiento. Cuatro revistas españolas (*Medicina Clínica*, *Revista Clínica Española*, *ATENCIÓN PRIMARIA* y *Anales de Medicina Interna*).

Mediciones principales. Las características de los pacientes, de los medicamentos, de las reacciones adversas, el algoritmo de causalidad, los criterios mínimos y la relevancia de la publicación.

Resultados. De 2.244 cartas, 204 (9,1%) se referían a RAM e incluían 235 casos. Los subgrupos terapéuticos más implicados fueron: anticoagulantes y antiplaquetarios, antibióticos y antineoplásicos. El 20,4% de los medicamentos era reciente. Las RAM más frecuentes afectaron al sistema nervioso (13,6%), el hígado (10,2%), la piel y anejos (9,8%), reacciones generales (9,8%) y aparato digestivo (8,1%). El 50,2% fueron moderadas y el 34%, graves/mortales. El valor medio ($5,9 \pm 2,2$) del algoritmo de causalidad fue similar entre revistas; las RAM fueron: 28 (11,9%) definidas, 182 (77%) posibles o probables y 26 (11,1%) improbables o condicionales; el 10,2% eran desconocidas. No se detectaron diferencias en la media ($9,5 \pm 1,2$) de criterios mínimos de publicación. La relevancia de la publicación fue de $3,2 \pm 1,6$ puntos, superior en *Medicina Clínica*.

Conclusiones. La publicación de RAM supone una parte importante de la sección de Cartas al Director en las revistas estudiadas. La relación de casualidad es aceptable y la calidad documental elevada, con pocas reacciones desconocidas y a medicamentos recientes. La relevancia ha sido escasa, aunque superior en *Medicina Clínica*.

Palabras clave: Reacciones adversas a medicamentos. Calidad. Criterios.

Spanish version available at
www.atencionprimaria.com/84.260

A commentary follow
 this article
 (pág.193)

^aCentro de Salud de Paterna, Valencia, Spain.

^bSubdirección de Atención Primaria. Hospital de la Ribera de Alzira, Valencia, Spain.

^cCentro de Salud Trinidad, Valencia, Spain.

^dServicio de Urgencias, Hospital Arnau de Vilanova, Valencia, Spain.

^eDirección de Área de Servicios Médicos, Consorcio Hospital General Universitario de Valencia, Fundación HGU, Valencia, Spain.

Correspondence:
 E. Sempere Verdú.
 Centro de Salud de Paterna.
 Conselleria de Sanitat. Valencia.
 Clot de Joan, s/n. 46980 Paterna.
 Valencia, España.
 E-mail: mere@comv.es

Manuscript received September 9, 2004.
 Manuscript accepted for publication May 18, 2005.

Introduction

The publication of suspected adverse drug reactions (ADRs) in medical journals continues to have a prominent role as a method of pharmacovigilance (PV), despite the criticisms produced over the low level of evidence in the communication of isolated cases and due to the delay between the detection of the ADR and its publication.¹ PV is considered to have begun in 1961, when McBride published several cases of phocomelia due to thalidomide in the letters to the editor section (LE) of *The Lancet*. Recently, Arnaiz et al, in 2001, demonstrated that the publication of isolated cases continues to be of great importance, by confirming that of the 22 drugs withdrawn from the Spanish market for safety reasons in the 1990's, the decision was based on the publication of cases in medical journals in 59% of them.² However, to prevent causing false alarms the communication of cases of ADRs need to comply with some minimum criteria which can guarantee their quality.³⁻⁵ In 1982, Venulet showed that the information considered minimal featured in only 21% of the publications of ADRs,⁶ a situation which has since improved substantially from the beginning of the 1990's.⁷

In Spain, studies carried out on the publication of cases of ADRs have been limited and have focussed mainly on aspects such as causal relationship or the inclusion of a group of minimum criteria.^{8,9} However, there are no studies which analyse other aspects of ADR publications, such as patient characteristics or the importance of the publication.

The objectives of the present study have been to assess the characteristics, the causal relationship, quality of documentation (or the appearance of a group of minimum criteria) and relevance of the publication of suspected ADRs in the Letters to the Editor section of four Spanish internal and general medicine journals.

Patients and methods

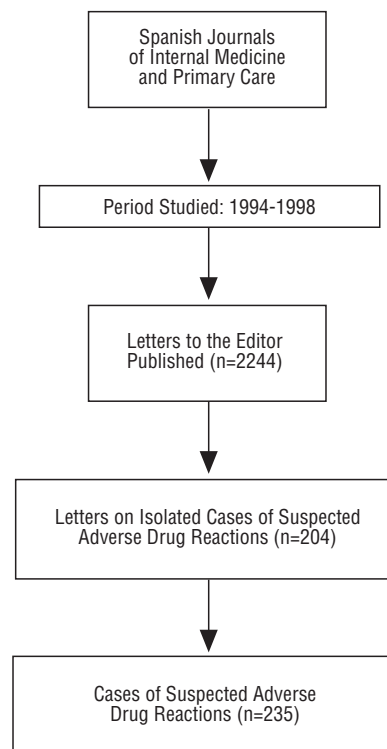
Design

It is a descriptive study of isolated cases of ADRs published in the LE section of four internal medicine (IM) or general medicine (GM) Spanish journals between 1994 and 1998.

Study Population

The first four journals from the "Citation Index and Bibliometric Indicators of Journals of Internal Medicine and its Specialties 1990-1991", according to the number of citations: *Medicina Clínica*, *Revista Clínica Española*, *ATENCIÓN PRIMARIA*, and *Anales de Medicina Interna*.¹⁰ A researcher reviewed, selected and documented the LE which were reporting ADRs, and a group of

Material and methods



General Scheme of the Study

Descriptive study on the quality and relevance of suspected adverse drug reactions published in the Letters to the Editor section of 4 Spanish journals of internal medicine and general medicine. Period 1994-1998.

doctors with experience in PV evaluated them and reached a consensus.

Measurements

Variables studied. a) From the journals: LE published; b) origin and notification of the ADR: year of publication, health care source (primary care, hospital, pharmacy service, clinical pharmacology service, PV service, emergency service, or other), and notification to the PV service; c) on the patients: age, sex, weight, and disease history; d) on the drugs administered: total and type of drugs (recent or non-recent), active ingredient, dose, indication administration route, and period of treatment; e) the adverse reaction and its latency period; f) the causality algorithm; g) the severity of the reaction; h) the quality of the documentation; i) the scientific or educational value, and j) the relevance of the publication.

The definition of ADR is that used by the Spanish PV System.¹¹ The causal relationship was established using the Spanish PV System algorithm, which classifies 5 categories of causality (attributability): improbable (≤ 0 points), conditional (1-3

points), possible (4-5 points), probable (6-7 points) and definitive (≥ 8 points).¹²

The coding of the drugs was carried out using the European Pharmaceutical Market Research Association Anatomical Classification of Pharmaceutical Products. The reasons for prescribing were coded using International Classification of Diseases. It was considered a recent drug if its marketing in Spain had been carried out in the 5 years preceding the publication. The WHO terminology was used for coding the ADR.

The severity was determined by applying the scale used by the Spanish PV System: mild, moderate, severe, lethal, or unable to code.¹³ The quality of the documentation was defined by the appearance of a series of criteria considered as minimum³⁻⁵:

- Associated with the patient:
 1. Age.
 2. Gender.
 3. Weight.
 4. Disease history.
- Associated with the drug involved:
 5. Indication.
 6. Dose.
 7. Administration route.
 8. Period of administration.
- Others:
 9. Dosing regimen of the drugs not implicated (indication, dose, route, and period of administering).
- Associated with the ADR:
 10. Latency period.
 11. Start and end.
 12. Performing pertinent complementary examinations.

Each criterion is awarded one point; thus, the quality of documentation varied between 0 and 12, the scientific or educational value was obtained by calculating the mean of the subjective scores of the members of the evaluation group, and its range varied between 1 and 10, with a maximum of 5 for scientific value and another 5 for educational value. For the scientific value, consideration was given if the publication contributed any new aspect on the ADR, if it was well documented, or if it postulated any new mechanism of a previously known ADR. For educational value, consideration was given if the publication could lead to changes in prescribing the drug involved.

The relevance of the publication of ADRs was defined, from a proposal by Meyboom et al,¹⁴ by 4 variables: severity, previous knowledge, scientific or educational value, and type of drug involved (recent or not). Its value fluctuated between 0 and 10 (Table 1).

Statistical Analysis

The results are presented as percentages for the qualitative variables and as arithmetic mean $\pm$ standard deviation (SD) for the quantitative ones. A bivariate comparison was performed. A 95% was taken as the limit of statistical significance. The results are shown in the Tables and Figures. The software programs SPSS 1996 and Office 97 were used.

Results

Of the 2244 LE published, 204 (9.1%) related to ADR, which corresponded to 235 cases. The percentage of LE

on ADRs was similar for each journal (Table 2). The origins were: hospital in 192 cases (81.7%), 44 (18.7%) in primary care, pharmacy services, 21 (8.9%), 17 (7.2%) pharmacological services, 15 (6.4%) from pharmacovigilance centres and 12 (5.1%) from emergency services. Thirty-three cases (14.0%) were notified to PV centres.

The mean age was 53.2 ± 20.3 years, with no difference between sexes and with 53.7% males. There were 85 cases (36.2%) > 64 years, 143 (60.9%) adults and 6 (2.6%) < 15 years.

Of the 554 drugs (2.4 ± 1.6 per case) administered, 267 (1.1 ± 0.4 per case) of them were implicated. In 24 cases (10.2%) it was due to an interaction between drugs.

More than 60% of the drugs implicated were concentrated in 5 therapeutic groups: systemic infection therapy (19.9%), nervous system (15%), cardiovascular system (11.2%), blood and haematopoietic organs (9.4%), and digestive system and metabolism (9%). The most frequent subgroups and indications are shown in Tables 3 and 4.

In 48 cases (20.4%) the reaction was due to recent drugs, which in 6 cases were unknown (Table 2).

Five groups were involved in more than half of the reactions: the nervous system (13.6%), liver, (10.2%), skin and appendages

(9.8%), general (9.8%), and digestive system (8.1%). There was a wide dispersion in the particular ADRs and hepatitis stood out, with 24 cases (9.5%) (Table 5).

TABLE 1
Calculation of the Relevance* of the Publication of Adverse Reactions. Variables Included, With Their Values, Scores and Relative Weight

	Values	Score†	Weight‡
a) Knowledge of the reaction		(25%)	
Unknown	0	2.50	25.0%
Anecdotal	1	1.25	12.5%
Well known	2	0	0.0%
b) Severity of the reaction		(25%)	
Fatal	4	2.50	25.0%
Severe	3	1.66	16.6%
Moderate	2	0.83	8.3%
Mild	1	0	0.0%
c) Recent drug		(25%)	
Recent	1	2.50	25.0%
Not recent	2	0	0.0%
d) Scientific or educational value(SEV)		(25%)	
Range§	0-10	0-2.50	0%-25.0%

*Range of relevance scores: 0-10.

†Score: range of possible values (0 to 2.5) according to the weight awarded to each value of the variable.

‡Relative weight of each variable, or value of the variable over relevance.

§SEV is a continuous quantitative variable. The value is obtained by dividing the score by 0.25.

TABLE 2 Variables Determining the Relevance, Algorithm of Causality and Documentation Quality by Journal. Cases of Adverse Drug Reactions in Spanish Journals, Period 1994-1998*

	<i>Medicina Clínica</i> (n=136)		<i>Revista Clínica Española</i> (n=23)		<i>ATENCIÓN PRIMARIA</i> (n=40)		<i>Anales de Medicina Interna</i> (n=36)		Total (n=235)		
	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	P
Recent drugs	35	(25.7)	3	(13.0)	6	(15.0)	4	(11.1)	48	(20.4)	NS
Unknown reactions	14	(10.3)	2	(8.7)	6	(15.0)	2	(5.6)	24	(10.2)	NS
Severe or fatal reactions	44	(32.4)	12	(52.2)	4	(10.0)	20	(55.6)	80	(34.0)	<.001†
	Mean±SD		Mean±SD		Mean±SD		Mean±SD		Mean±SD		P
Causality algorithm	6.0±2.1		5.1±2.0		6.0±2.9		5.7±1.9		5.9±2.2		NS
Documentation quality‡	9.5±1.2		9.6±1.3		9.6±1.4		9.5±1.2		9.5±1.2		NS
Scientific and educational value§	5.2±1.8		4.3±1.6		3.8±2.0		3.7±1.7		4.6±1.9		<.0001¶
Relevance	3.5±1.5		3.1±1.6		2.4±1.7		2.8±1.2		3.2±1.6		<.0001¶

*NS indicates not significant; SD, standard deviation.

†Significant differences in favour of *Revista Clínica Española* and *Anales de Medicina Interna*.

‡Documentation quality or number of minimum criteria of publication (score: 0 to 12).

§Scientific and educational value (score: 0 to 10).

||Relevance (score: 0 to 10).

¶Significant differences of *Medicina Clínica* with *ATENCIÓN PRIMARIA* and *Anales de Medicina Interna*.**TABLE 3** The 10 Therapeutic Subgroups Most Frequently Implicated (140 Drugs Out of a Total 267 Drugs Involved). Adverse Drug Reactions in Spanish Journals, Period 1994-1998

Therapeutic Subgroups	N	(%)
B01 Anticoagulants and antiplatelets	17	(6.4)
J01 Antibiotics	17	(6.4)
L01 Antineoplastics	17	(6.4)
M01 Antiinflammatories and antirheumatics	15	(5.6)
J05 Antivirals (excluding vaccinations)	14	(5.2)
C01 Cardiotherapy	13	(4.9)
J03 Systemic chemotherapy	13	(4.9)
N05 Psycholeptics	13	(4.9)
P01 Antiparasitics	11	(4.1)
C02 Hypotensives	10	(3.7)
Subtotal	140	(52.4)

TABLE 4 The 10 Most Frequent Indications of the Drugs Implicated (80 Drugs Out of a Total of 267). Adverse Drug Reactions in Spanish Journals, Period 1994-1998*

Indication	N	(%)
High blood pressure	16	(6.0)
AIDS	13	(4.9)
AMI	9	(3.4)
Depression	8	(3.0)
Unknown	6	(2.2)
Self-medication	6	(2.2)
Conjunctivitis	6	(2.2)
Epilepsy	6	(2.2)
Schizophrenia	5	(1.9)
Cardiac failure	5	(1.9)
Subtotal	80	(29.9)

*AIDS indicates acquired immunodeficiency syndrome; AMI, acute myocardial infarction.

As regards causal relationship of the reactions, 3 (1.3%) were improbable, 23 (9.8%) conditional, 64 (27.2%) possible, 117 (49.8%) probable, and 28 (11.9%) definitive. In 168 cases (75%) the ADR was well known beforehand, in 24 (10.2%) unknown and in 43 (18.3%), anecdotal. In 6 cases the drug had to be withdrawn. Thirty two cases (13.6%) were re-exposed to the drug and were positive in 31.

In 118 cases (50.2%) the ADR was moderate, in 67 (28.5%) severe, 37 (15.7%) mild and in 13 cases (5.5%), fatal (Table 2). The severity was similar between sexes and did not increase with age or with the number active ingredients administered.

Of the minimum criteria, 9.5±1.2 were recorded (quality of documentation) per case, with no differences between journals (Table 2). Four criteria were recorded in 100% of the cases, 9 or more in 80%, and 4 (1.7%) had the 12 criteria (Table 6). Significant differences were detected in the scientific or educational value and in the relevance of the publication, in favour of *Medicina Clínica* (Table 2).

Discussion

The importance of publishing suspected ADRs in medical journals is endorsed by the high percentage of previously

TABLE 5 The 10 Most Frequent Adverse Reactions According to WHO* Terminology (79 Reactions Out a Total of 235). Cases of Adverse Drug Reactions in Spanish Journals, Period 1994-1998

Reaction†	N	(%)
Hepatitis (including cholestatic)	24	(9.5)
Malignant neuroleptic syndrome	9	(3.8)
Anaphylactic reaction	8	(3.4)
Arthritis	6	(2.6)
Diabetes mellitus, worsening	6	(2.6)
Metrorrhagia	6	(2.6)
Acute renal failure	5	(2.1)
Vasculitis	5	(2.1)
Thrombocytopenia	5	(2.1)
Pancreatitis	5	(2.1)
Subtotal	79	(32.9)

*WHO indicates WHO Collaborating Centre for International Drug

†Monitoring of Adverse Reaction Terminology codes.

unknown reactions which are published before being notified to the pharmacovigilance centres.^{2,15} This explains why Spanish journals dedicated 9.1% of the published LE to the communication of ADR cases during the period studied (1994-1998). This interest in pharmacovigilance has experienced a notable increase in Spanish literature since the period 1972-1974, when articles on any problem on this subject were only 2.1% of the total.⁹

The majority of published ADRs in Spanish journals come from specialised care (81.7%), with a limited contribution from primary care. However, the family doctor is the

TABLE 6 Minimum Publication Criteria (Documentation Quality). Percentage of Cases of Adverse Drug Reactions Published in 4 Spanish Journals in Which Each Criteria is Described, Period 1994-1999

Criteria	N	(%)
Age	234	(99.6)
Sex	232	(98.7)
Indication	231	(98.3)
Start and end of the reaction	218	(92.8)
Disease history	212	(90.2)
Latency period	208	(88.5)
Administration period	204	(86.8)
Relevant examinations	202	(86.0)
Dose*	181	(77.0)
Administration route*	174	(74.0)
Dosing regimen of other drugs†	128	(54.5)
Weight	15	(6.4)

*Criteria mentioned on the drugs implicated in adverse drug reactions.

†Drugs not involved in adverse drug reactions.

Discussion
Key points



What Is Known About the Subject

- The publication of suspected drug reactions has been and continues to be one of the basic pillars of pharmacovigilance.
- There are doubts on the quality of these publications, with the subsequent danger of causing false alarms.
- Little is known on the causal relationship and relevance of these publications.

What This Study Contributes

- The publication of suspected adverse drug reactions is an important part of the Letters to the Editor section.
- The causal relationship is acceptable, with a high documentation quality, but they are generally of limited relevance, with few recent or previously unknown reactions published.

professional who traditionally contributes more to notifying, at least in Spain, by yellow card. Also, it is estimated that they see a mean of 2 ADRs per day.¹⁶ The simultaneous notification to the PV services (12%) of the cases published is deficient, and could be improved if the journals recommended that they are first communicated to the PV centres.

The predominance of the middle aged group shown in this study agrees with the majority of descriptive studies and PV centres, but not with those from hospital settings, where the elderly predominate.¹⁷⁻²¹ Likewise, the ratio detected in males and females also contrasts with the majority of PV studies, where females predominate.²²

The groups of drugs most frequently involved coincide with data from PV centres.^{20,23}

The percentage of ADR to recent drugs (25.7%), is low and should be improved by the journals which aspire to be the vehicle of authentic new reports which can provide alerts.²⁴ In this sense, a tendency for *Medicina Clínica* to stand out over the rest of the journals is detected.

The distribution of the reactions by systems generally agrees with data from the PV centres,^{20,25} although with a higher percentage of hepatic reactions (10.2%); this contrasts with hospital studies, where the most frequent ADRs are normally gastrointestinal due to non-steroidal anti-inflammatories.^{26,27}

The high causal relationship detected, with 77% possible or probable ADRs and 11.9% definitive, was as expected in the scientific journals, since anything else would cause false alarms or scepticism on the part of the readers. A low percentage (10.2%) of previously unknown ADRs were published during the study, broadly coinciding with the cases notified to the PV centres²⁸ and higher than Spanish studies in hospital settings.²⁹ This suggests that, as regards PV, the role of Spanish journals is more one of education or the transfer of new data already reported in higher impact journals to the Spanish scientific community.

If one takes into account that it is hardly ethical to re-expose the patient to the suspect drug, the 13.2% cases which were positive on re-exposure can be considered acceptable and near the 19.2% obtained by Haramburu et al.⁷

The severity of the ADRs published is an indicator of their importance, therefore it should be desirable for a high percentage of severe reactions to appear in the journals. In the period studied, 34% of ADRs published were severe or fatal, a much higher percentage than that recorded in the Spanish PV centres²⁰ and in other Spanish studies.³⁰

Overall, it can be considered, that in the four journals studied, they have high documentation quality, since they included the majority of the minimum criteria for the publication of an ADR.^{3-5,8}

The results are similar to those shown by Gil et al⁹ for the period 1992-1994. However, some criteria, such as weight or the dosing regimen of non-involved drugs, are still lacking; this deficiency would be easy to correct if the journals proposed a list of minimum criteria for the publication of ADRs.

The scientific or educational value, as well as the relevance, is a new concept introduced by Meyboom et al¹⁴ which, despite a certain subjectivity, gives added value to the seriousness and documentation quality of the ADRs. In this study, the only journal which was higher than the mean value was *Medicina Clínica* (5.2 out of 10).

The relevance of the publication was low and *Medicina Clínica*, although it does not reach the mean value, again stands out against *ATENCIÓN PRIMARIA* and *Anales de Medicina Interna*. This concept of relevance has not been used until now, therefore it has not been possible to make comparisons.¹⁴ With its use, it has attempted to go beyond the description of ADRs with the classic categories of attributability by algorithms of causality, an insufficient method in any case to determine the importance of a publication. In conclusion, it can be stated that the Spanish internal medicine and general medicine journals have a high quality as regards the inclusion of the minimum publication criteria and the causality, although overall their relevance is limited, with none of them reaching a pass mark, although *Medicina Clínica* stands out slightly. The cause is

mainly due to the fact that the majority of publications refer to well known reactions, not particularly severe, and reactions to older drugs.

Acknowledgements

The authors would like to thank F.J. Morales-Olivas for his comments and support of this work.

References

1. Aronson J K. Anecdotes as evidence. We need guidelines for reporting anecdotes of suspected adverse drug reactions. *BMJ*. 2003;326:1346.
2. Arnaiz JA, Carné X, Riba N, Codina C, Ribas J, Trilla A. The use of evidence in pharmacovigilance. Case reports as the reference for use of drug withdrawals. *Eur J Clin Pharmacol*. 2001;57:89-91.
3. Jones JK. Criteria for journal reports of suspected drug reactions. *Clin Pharm*. 1982;1:554-5.
4. Edwards IR, Lindquist M, Wiholm BE, Napke E. Quality criteria for early signals of possible adverse drug reactions. *Lancet*. 1990;336:156-8.
5. Laporte JR, Lience E. Información mínima que deben contener las publicaciones sobre sospechas de reacciones adversas a medicamentos. *Med Clin (Barc)*. 1991;97:56-7.
6. Venulet J, Blattne R, von Büow J, Berneker CG. How good are articles on adverse drug reactions? *BMJ*. 1982;284:252-4.
7. Haramburu F, Bégaud B, Péré JC. Comparison of 500 spontaneous and 500 published reports of adverse drug reactions. *Eur J Clin Pharmacol*. 1990;39:287-8.
8. Bravo R, Campos C. Comunicación de reacciones adversas a medicamentos por médicos de atención primaria. *Aten Primaria*. 1995;15:155-61.
9. Gil A, Vargas E, García M, García M, Terleira A, Moreno A. Reacciones adversas a medicamentos en la bibliografía médica española: comparación de tres períodos. *Med Clin (Barc)*. 1999; 112:55-6.
10. Terrada ML, López JM, Aleixandre R, Zorrilla V, Mota A, Giménez JV. Índice de citas e indicadores bibliométricos de revistas. Españolas de medicina interna y sus especialidades 1991. Barcelona: Instituto de Estudios Documentales e Históricos sobre la Ciencia-Doyma; 1993.
11. Karch FE, Lasagna L. Toward the operational identification of adverse drug reactions. *Clin Pharmacol Ther*. 1977;21:247-54.
12. Meyboom RHB, Rover RJ. Causality classification at Pharmacovigilance Centres in the European Community. *Pharmacoepidemiol Drug Safety*. 1992;1:87-9.
13. Capellà D, Laporte JR. La notificación espontánea de reacciones adversas a medicamentos. In: Laporte JR, Tognoni G, editors. *Principios de epidemiología del medicamento*. Barcelona: Masson-Salvat; 1993. p. 147-70.
14. Meyboom RHB, Kekster YA, Egbert CG, Gribnau FWJ, Edwards IR. Causal or casual. The role of causality assessment in Pharmacovigilance. *Drug Saf*. 1997;17:374-89.
15. Rossi AC, Knapp DE. Discovery of new adverse drug reactions. *JAMA*. 1984;252:1030-3.
16. Moride Y, Haramburu F, Requejo A, Bégaud B. Under-reporting of adverse drug reactions in general practice. *Br J Clin Pharmacol*. 1997;43:177-81.

17. Planells H, Rodríguez JM, Jiménez NV. Reacciones adversas a medicamentos que motivan la admisión hospitalaria detectadas mediante el diagnóstico de ingreso. *Farm Hosp*. 1993;17:133-43.
18. san Miguel MT, Vila MN, Azorín MD, Sanz JA, Díaz MS, de la Rubia A, et al. Atenciones en puerta de urgencias por reacciones adversas a medicamentos. *Farm Clin*. 1992;9:24-9.
19. Hallas J, Gram LF, Grodum E, Damsbo N, Brosen K, Haghfelt T, et al. Drug related hospital admissions to medical wards: a population based survey. *Br J Clin Pharmacol*. 1992;33:61-8.
20. Notificaciones recibidas durante el año 2001. *Boletín de Farmacovigilancia Comunidad Valenciana*. 2001;57:869-78.
21. Martin RM, Biswas PN, Freemantle SN, Pearce GL, Mann RD. Age and sex distribution of suspected adverse drug reactions to newly marketed drug in general practice in England: analysis of 48 cohorts studies. *Br J Pharmacol*. 1998;46:505-11.
22. Stephens MDB. Introduction. In: Stephens MDB, Talbot JCC, Routledge PA, editors. *Detection of new adverse drug reactions*. 4th ed. London: Macmillan Reference; 2000. p. 1-58.
23. Laporte JR, Capellà D. El Sistema Español de Farmacovigilancia. *Med Clin (Barc)*. 1994;103:335-6.
24. Morales-Olivas FJ, Palop V, Ferrer JM. Experiencia de un centro regional del sistema español de Farmacovigilancia. 1: Centro de la Comunidad Valenciana. In: Debajo de FJ, Madurga M, Olalla JF, Palop R, editors. *La farmacovigilancia en España*. Madrid: Instituto de Salud Carlos III; 1992. p. 45-55.
25. Carvajal A, Martín-Arias LH, Álvarez A. Experiencia de un centro regional del sistema español de Farmacovigilancia. In: Abajo de FJ, Madurga M, Olalla FJ, Palop R, editors. *La farmacovigilancia en España*. Madrid: Instituto de Salud Carlos III; 1992. p. 57-70.
26. Smith CC, Bennett PM, Pearce HM, Harrison PI, Reynolds JM, Aronson JK, 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.
27. Martín MT, Codina C, Tuset M, Carné X, Nogué S, Ribas J. Problemas relacionados con la medicación como causa de ingreso hospitalario. *Med Clin (Barc)*. 2002;118:205-10.
28. Notificaciones recibidas durante el año 1997. *Boletín de Farmacovigilancia Comunidad Valenciana*. 1997;41:606-17.
29. Muñoz MJ, Ayani I, Rodríguez-Sasiain, Gutiérrez G, Aguirre C. Monitorización en un servicio de urgencias de reacciones adversas causadas por medicamentos en niños y adultos. *Med Clin (Barc)*. 1998;111:92-8.
30. Hidalgo A, García J, Carvajal A. Mortalidad y morbilidad producidas por fármacos. Aproximación a su magnitud en nuestro medio. *Pharm Care Esp*. 1999;1:179-83.

COMMENTARY

The Publication Quality of Adverse Reactions

J. Gené-Badia

Deputy Editor of the journal ATENCIÓN PRIMARIA.

The comparative analysis of adverse drug reactions published in the Letters to the Editor section of 4 Spanish internal medicine and general medicine journals by Sempere et al has prompted the editorial committee of the journal ATENCIÓN PRIMARIA to reconsider its policy on this subject. The study shows that the letters published in different journals have similar characteristics.

The cases are normally well described, since they give sufficient information on the patient, the disease, the medication taken and the adverse reaction. They also enable a causal relationship¹ to be established but, overall, their relevance is low. The authors did not pass any of them and only those of the journal *Medicina Clínica* stood out slightly. As pointed out by the authors, Spanish journals publish reactions which are well known, of low severity and on older drugs.

This is almost certainly due to Spanish clinicians sending letters on the more interesting adverse reactions to higher impact journals.

Key Points

- The medical literature is, overall, probably the most effective system for the initial detection of adverse reactions to marketed drugs.
- Letters to the Editor on adverse effects must be complementary to, and not a substitute for, the pharmacovigilance systems.
- The journal ATENCIÓN PRIMARIA is interested in publishing letters on adverse reactions of drugs prescribed in primary care when these are really new or when they concern drugs recently placed on the market.
- The clinical case, the prescription of the drug and the adverse reaction has to be perfectly described, and the causal relationship also must be well explained.

The slight advantage of the journal *Medicina Clínica*, although it can be attributed to its higher impact index, is probably also due to the fact it has published its policy on this subject. In 1991, the General Secretary of *Medicina Clínica* clearly set out the information that had to be included in publications on suspect adverse drug reactions.² It particularly pointed out that only adverse reactions which had editorial interest would be published.

Up until now, the journal ATENCIÓN PRIMARIA has followed the policy of publishing practically all the adverse drug reactions which it received as letters to the editor. It probably does not make any sense to continue along this line as the pharmacovigilance programmes, using the yellow card system, are well established.

The publication of isolated cases of known adverse reactions only serves to refresh the memory of the medical practitioner. This type of information is probably better placed in the context of a review article in the sections of journals set aside for Continuing Education than in the Letters to the Editor section.

The editorial committee understands that a journal, whose function is to publish studies on primary care, has to make a more significant contribution towards the safety of drugs prescribed after they are placed on the market.

The experts point out that the biomedical literature is probably, overall, the most effective system for the initial detection, since the case descriptions are detailed, the reviewers have checked their quality, there are no commercial incentives and they are open to all interested parties. Evidently, not all cases published are true adverse reactions and there is a risk that they might be false positives, but they do serve as an alert on new reactions, to warn on uncommon events and allow population groups at risk to be identified.³

The journal, ATENCIÓN PRIMARIA, wants to move forward along this line. The editorial committee is interested in publishing letters of isolated cases of adverse reactions to prescribed drugs in primary care when these are really new or when they concern drugs recently placed on the market. These types of articles can encourage original studies which would have an experimental design and serve to check the hypothesis generated by clinical observations.

These articles can appear in the Originals section of the journal ATENCIÓN PRIMARIA if they pass the review process.

Despite the clinical information which appears in the letters on adverse reactions normally being of sufficient quality, we want to pay special attention in that all the aspects considered essential are included.^{1,2} They must provide information on the sex, age, clinical characteristics of the patient, the suspected drug and other concomitant medication, with information on dates taken, the doses and administration routes, the indication for its use, the time sequence between the appearance of the event and the administration of the drug, the clinical course, other diseases and relevant environmental factors, such as their corresponding dates, previous experience of the patient with the suspected drug or history of reactions to other analogous drugs, previous publications of the same case, if there were any, and other factors which may be relevant to check other specific reactions (e.g., blood levels, histology and ethnic origin). If available, it would be very interesting to notify how the adverse effect has progressed after stopping the drug and what happened when subjected to re-exposure of the drug.

The journal ATENCIÓN PRIMARIA is interested in publishing letters on adverse reactions of drugs prescribed in primary care when these are really new or when they concern drugs recently placed on the market, which are well described clinically and where the causal relationship can be established. Notifying the pharmacovigilance systems of the effect by yellow card must be done before sending the article to the publisher.

References

1. Edwards IR, Lindquist M, Wiholm BE, Naike E. Quality criteria for early signals of possible adverse drug reactions. *Lancet*. 1990;336:156-58.
2. Laporte JR, Lience E. Información mínima que deben contener las publicaciones sobre sospechas de reacciones adversas a medicamentos. *Med Clin (Barc)*. 1991;97:56-7.
3. Stricker B, Psaty BM. Detection, verification, and quantification of adverse drug reactions. *BMJ*. 2004;329:44-7.