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Effect of an intervention on the features of adverse drug reactions spontaneously reported in a hospital

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EFFECT OF AN INTERVENTION ON THE FEATURES OF ADVERSE DRUG REACTIONS SPONTANEOUSLY REPORTED IN A HOSPITAL

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For Peer Review

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3 **EFFECT OF AN INTERVENTION ON THE FEATURES OF ADVERSE DRUG**
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5 **REACTIONS SPONTANEOUSLY REPORTED IN A HOSPITAL**
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ABSTRACT

Background.- A continuous intervention based on healthcare management agreements was associated in our hospital with an increase in the absolute number of spontaneous reporting of adverse drug reactions (ADRs), and also with an increase in the number of reports of serious or unexpected ADRs and ADRs associated with new drugs.

Objective.- To analyze the effect of this intervention on the features of ADRs spontaneously reported in a hospital, the drugs involved and the number of signals identified.

Methods.- A longitudinal study with two periods, the 1st period without intervention from 1998 to 2002 and the 2nd period with intervention from 2003 to 2005, was carried out in a teaching tertiary Hospital. Changes between the two periods in the following variables were analysed: (a) the patients' characteristics, such as gender and age; (b) the reported ADRs, and their medical assistance required; (c) the suspected drugs involved in the ADRs and (d) the main signals identified.

Results.- Gender and age distribution of patients described in the spontaneous reports were no different in the two periods. During the second period, spontaneously reported cases requiring hospital admission and those occurring in-hospital increased (236 from 2 in the first period and 277 from 99 in the first period, respectively) and cases from outpatient hospital consultations began to be reported (13.9% of reports). The spontaneous reporting on all kinds of ADRs and drugs increased during the second period. Cutaneous reactions were the most frequently spontaneous reported ADRs in both periods followed by cardiovascular and neurological reactions in the first period, and haematological and gastrointestinal reactions in the second one. However, during the second period the higher increase was for endocrinological, urinary and hepatic reactions. Systemic antibiotics, antithrombotics and cardiac therapy drugs were the most commonly therapeutic subgroups reported as suspected drugs in both periods, but in the second period the proportion of immunostimulants, beta blocking agents, immunosuppressants and psychoanaleptics increased. No

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3 signals were recognized during the first period, however two signals and one
4 additional safety concern were identified during the second.
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7 **Conclusion.-** An intervention based on healthcare management agreements,
8 was associated with an important increase in spontaneous reporting of ADRs by
9 hospital physicians and also with a change in terms of type of ADRs identified
10 affecting different organs or systems, and the therapeutic groups of drugs
11 involved. Future studies should analyze the effect of different types of
12 intervention on spontaneous reporting of ADRs in hospitals.
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20 Words account: 399

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22 Keywords: Pharmacovigilance; Adverse Drug Reactions Reporting Systems;
23 Drug Toxicity; Intervention Studies; Hospital
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INTRODUCTION

The spontaneous reporting system is currently the cornerstone of post-marketing signal detection in pharmacovigilance.^[1-2] Detection of adverse drug reactions (ADRs) in hospitals is important because serious events may be identified, novel drugs are commonly used, new and unexpected ADRs may be detected early on and cases are usually well-documented with high quality information. Nevertheless, spontaneous reporting has been scarcely used as a method of ADRs detection in hospitals and underreporting is a major flaw,^[3-5] as it is in the primary health care setting.^[6]

Several interventions (educational or others) aimed at solving this major drawback have been proposed and the effectiveness of some of them has been evaluated in a number of studies.^[5,7-12] In this sense we have reported that an intervention based on healthcare management agreements with economic incentives and educational activities was associated with a quantitative and qualitative improvement of spontaneous reporting of ADRs by hospital physicians.^[13] Not only did the absolute number of spontaneous reports increase but so did the number of reports of serious or unexpected ADRs and ADRs associated with new drugs.

The pattern of adverse drug reactions notified by spontaneous reporting in hospitals has been described in a few studies.^[14-19] Furthermore, there are no studies assessing if the improvement in reporting in the hospital setting allows a more efficient detection of new drug safety issues or if it facilitates signal identification. The usefulness of an increase in spontaneous reporting depends on the increase in the number of meaningful reports that help in raising concerns. Therefore, the aim of this study was to analyze the effect of the spontaneous reporting increase after an intervention in the hospital on the features of the ADRs reported, the drugs involved and the signals identified.

METHODS

A time series analysis was carried out at Vall d'Hebron University Hospital (Barcelona, Spain) from 1998 to 2005 in order to assess the effectiveness of a continuous multifaceted intervention for improving spontaneous reporting of ADRs by hospital physicians to the Pharmacovigilance Programme (PhVP) of the hospital. The intervention was based on health care management agreements between hospital managers and clinical services, and was initiated in 2003. A framework agreement between hospital managers and physicians included different commitments linked to economic incentives. One of the objectives for physicians was to increase their participation in the PhVP increasing the number of spontaneous ADR reports. This objective was integrated into other clinical objectives at three levels: a) institution or whole hospital, b) clinical department or clinical team, and c) physician. The financial incentive obtained was variable according to the objectives achieved, and was approximately 5-7% of the physician's salary. The size of the financial payment for ADR reporting accounted for less than 10% of the total of agreed incentives and was, on average, less than 1% of the physician's salary. In each clinical service, an initial meeting between physicians and the hospital pharmacovigilance team was held. In this first meeting, the hospital's pharmacovigilance activities, the aim of spontaneous ADR reporting and how to report ADRs, were presented. In addition to reinforcement, twice-yearly educational meetings were held in each clinical service, offering information about pharmacovigilance and emphasizing the priorities for spontaneous reporting ADRs (serious ADRs, unexpected ADRs, and those ADRs associated with new drugs). These meetings lasted 45-60 minutes, and consisted of a brief explanation of the number and main characteristics of ADRs detected in the whole hospital and in the specific clinical service. Signals identified by the PhVP and news about ADRs released by regulatory agencies were also commented on. Finally, reminder cards with the telephone number of the pharmacovigilance team and a list of the most important ADRs to be reported on (serious, unexpected and those associated with new drugs) were distributed to the hospital wards.

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3 Changes between the two periods of study (the 1st period without intervention
4 from 1998 to 2002 and the 2nd period with intervention from 2003 to 2005) in
5 the total number of spontaneous reports of ADRs, and in the number of serious
6 reports, reports of unexpected ADRs and reports of ADRs related to recently
7 marketed drugs were therein presented.^[13]
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14 In this paper, changes between the two periods in the following variables of the
15 longitudinal study have been analyzed: (a) The patients' characteristics, such as
16 gender and age; (b) the reported ADRs, with their seriousness, outcome,
17 medical assistance required, and previous knowledge; (c) the suspected drugs
18 involved in the ADRs, including those recently marketed; and (d) the most
19 frequent drug-ADR associations and the main signals identified.
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27 The ADRs were classified in organ-system categories according to the World
28 Health Organization terminology (WHOART - WHO Adverse Reaction
29 Terminology). The suspected drugs were grouped in therapeutic classes
30 according to the Anatomical Therapeutic Chemical classification system. The
31 seriousness of the cases was classified according to the European Union's
32 criteria and cases were considered serious (ADRs that result in death, are life-
33 threatening, require hospitalisation or prolongation of existing hospitalisation,
34 result in persistent or significant disability or incapacity, are congenital anomaly
35 or birth defect, or are important medical events) or non-serious (the remaining
36 cases).^[21] Its outcome was classified into recovery, permanent sequelae, death
37 or unknown. According to the medical attention required, the cases were
38 classified into those requiring hospital admission, in-hospital cases, cases
39 requiring attention at the emergency room, and cases from the outpatient
40 department. Previous knowledge of the ADRs was classified according to the
41 Spanish Pharmacovigilance System's (SPhVS) causality algorithm in well-known
42 ADRs, known from anecdotal reports, or unknown.^[22] New-drugs were defined
43 as those marketed for less than five years at the time when the ADRs began.
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3 Statistical analysis. The spontaneous reports of ADRs during the two studied
4 periods were analyzed separately. Descriptive analysis of continuous variables
5 was performed by means of median and range; and statistical differences were
6 assessed by means of the Mann-Whitney test. Categorical variables were
7 described using percentages; statistical differences were assessed by means of
8 the χ^2 test. Significance was set at a level of 0.05, two tailed. The statistical
9 analysis was performed using the SPSS version 15.0 statistical package (SPSS
10 Inc. Chicago-Illinois).

20 RESULTS

23 Number of spontaneous reports of adverse drug reactions

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27 Of the total number of cases of ADRs identified by the PhVP, the proportion of
28 spontaneous ADR reports increased from 29.5% (n=200) during the first period
29 to 71.5% (n= 631) during the second period. More details about this increase
30 were presented in the previous paper.

36 Patients' characteristics

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40 Gender and age distribution of patients described in the spontaneous reports
41 were no different between the two periods. The ratio female-to-male in the
42 spontaneous reports from the first period was 1.08 (104 females and 96
43 males); it was 0.96 in the second one (310 females and 321 males; p=0.516).
44 Median age (minimum-maximum) was 64 (14-94) for patients described in both
45 periods (p=0.150).

52 Medical attention required

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57 Most cases reported during the first period either required medical attention at
58 the emergency room without hospital admission (99; 49.5%) or were in-

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3 hospital cases (99; 49.5%). The two remaining cases (1%) required hospital
4 admission.
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9 The number of cases requiring only medical attention at emergency room
10 decreased during the second period (30; 4.8%). In-hospital cases slightly
11 decreased in relative terms although the absolute number of reports increased
12 (277; 43.9%). Conversely, cases requiring hospital admission increased both in
13 relative and in absolute terms (236; 37.4%). On the other hand, cases from
14 outpatient department not requiring attention at the emergency room or
15 hospital admission began to be reported during the second period, accounting
16 for 13.9% (88) of the overall reports received at the end of this period ($p <$
17 0.001).
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26 27 Seriousness and outcome 28

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31 In the second period, the proportion of serious cases almost doubled (63.1% vs
32 32.5%) and the number of serious cases increased by more than 6-fold (398 vs
33 65; $p < 0.001$).
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39 The most frequently reported outcome in both periods was recovery (70% in
40 the first one and 74.2% in the second one). The number of cases that
41 recovered with sequelae was 2 in the first period and 16 in the second one.
42 There were 9 fatal cases during the first period and 15 in the second one. The
43 adverse reactions and drugs involved in these fatal cases are presented below
44 in the drug-reaction associations section. Finally, the outcome was unknown in
45 49 cases in the first period and 132 in the second one ($p=0.153$).
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53 Adverse reactions 54

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57 Overall, 220 adverse reactions were described in the 200 first-period
58 spontaneous reports. Cutaneous reactions were the most frequent, followed by
59 cardiovascular and neurological reactions. In the 631 second-period
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3 spontaneous reports, 694 adverse reactions were described. Cutaneous
4 reactions were the most frequent as well, followed in this case by
5 haematological and gastrointestinal reactions (table 1). However, during the
6 second period the frequency of endocrinological, urinary and hepatic reactions
7 increased (3.7% vs. 0.5%, 4.6% vs. 1.8% and 9.2% vs. 5.5%, respectively).
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14 The most commonly reported individual adverse reactions (with a frequency \geq
15 3% of reports) during the first period were urticaria, angioedema,
16 bronchospasm, hypotension, and haematoma. In the second period, individual
17 reactions described in \geq 3% of reports were rash and erythematous rash (table
18 2). During the second period the frequency of hyperthyroidism,
19 thrombocytopenia and gastrointestinal haemorrhage increased by 4.3 and more
20 than 2-fold, respectively.
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29 Suspected drugs

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33 Two hundred and eighty-five and 877 suspected pharmacological exposures
34 were contained in the reports in the first and the second period respectively. In
35 both periods, the most common therapeutic subgroups were systemic
36 antibiotics, antithrombotics, and cardiac therapy. These three groups accounted
37 for 38.2% and 30.3% of the total suspected pharmacological exposures in each
38 period respectively (table 3). Regarding the remaining therapeutic subgroups,
39 the greatest changes between periods were the increase in the proportion of
40 immunostimulants, beta blocking agents, immunosuppressants and
41 psychoanaleptics, and the decrease in the proportion of systemic antihistamines
42 during the second period.
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53 The drugs with the highest number of suspected exposures were amiodarone,
54 amoxicillin-clavulanic acid, metamizole, and enoxaparin in both periods (table
55 4). Some drugs with no suspected exposures during the first period appeared
56 during the second one (i.e., ceftriaxone, methotrexate, and tacrolimus).
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3 Additionally, a 9-fold increase was seen in the number of suspected exposures
4 to ibuprofen, azithromycin and fluoxetine during the second period.
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9 In both study periods, around 10% of suspected pharmacological exposures
10 concerned recently marketed drugs. Nevertheless, both the overall number of
11 suspected pharmacological exposures and the number of different drugs
12 increased in the second period (97 vs. 28, and 50 vs. 19, respectively). The
13 new drugs with the highest number of suspected exposures were clopidogrel,
14 levoﬂoxacin, and nevirapine (three exposures each) in the first period, and
15 linezolid (eight exposures), tiotropium bromide, glatiramer acetate,
16 oxcabazepine, tenofovir, and voriconazole (five exposures each) in the second
17 one.
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27 Drug-reaction associations

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31 In the first period, the most frequently reported drug-reaction associations were
32 haemoperitoneum, retroperitoneal haemorrhage or muscular haematoma due
33 to enoxaparin (11 cases, 5.5% of reports). In the second period, they were
34 hepatotoxicity induced by amoxicillin-clavulanic acid and hyperthyroidism due to
35 amiodarone (14 cases and 2.2% of reports each) (table 5).
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43 Three out of nine fatal reports from the first period were cases of haemorrhagic
44 reactions in patients treated with enoxaparin (two retroperitoneal
45 haemorrhages and a gastrointestinal bleeding), three were cases of
46 cardiovascular reactions (myocardial infarction after terbutaline treatment,
47 salbutamol and levofloxacin-induced *torsade de pointes*, and cardiac arrest in a
48 patient treated with levomepromazine and carbamazepine) and the remaining
49 three reports described adverse reactions related to other systems. The most
50 frequent reactions in the fifteen fatal cases reported during the second period
51 were also haemorrhagic events (seven cases). There were four cases of
52 intracranial haemorrhage (three of them with tenecteplase, enoxaparin and
53 acetylsalicylic acid, and one with drotrecogin alpha and enoxaparin), one case
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3 of enoxaparin-induced retroperitoneal haemorrhage, one case of intraabdominal
4 haemorrhage due to enoxaparin, acenocoumarol and acetylsalicylic acid, and
5 one case of acetylsalicylic acid-induced gastrointestinal haemorrhage. Of the
6 eight remaining cases, three were toxic epidermal necrolysis and the other
7 described reactions related to other systems.
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10 11 Previous knowledge/Signals identified 12

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18 The absolute number of previously unknown or poorly known drug-reaction
19 associations had a fourfold increase in the second period (54 vs. 13 in the first
20 period). Most of them were serious cases (5 out of 13 in the first period and 40
21 out of 54 in the second one; $p=0.047$).
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28 No signals were identified during the first period. In the second one, two
29 serious and previously unknown or poorly known drug-reaction associations
30 were considered signals that required the adoption of regulatory measures by
31 the Spanish Agency for Medicines and Medical Devices (AEMPS). The first signal
32 was *pseudoproteinuria* induced by gelatine succinate infusion. A warning
33 regarding this problem was added in the summary of product characteristics [23]
34 and a "Dear Dr letter" was sent to Spanish nephrologists and to the National
35 Transplant Organization. The second signal was veralipride withdrawal
36 syndrome; it required a risk-benefit assessment of the use of this orthopramide
37 in the treatment of menopausal hot flushes and, as a result, the AEMPS
38 withdrew this drug from the market. [24] Afterwards, the EMEA also
39 recommended the withdrawal of this drug from the European market. [25]
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52 Additionally, the fatal case of cerebral haemorrhage due to drotrecogin alfa
53 activated, which occurred in a patient who had recently undergone surgery, led
54 to a review of safety data of this drug in the surgical population. As a result, the
55 AEMPS proposed changes in the authorized conditions of use of drotrecogin alfa
56 activated at the EMEA level. Those proposals contributed to updating the
57 authorized conditions of use and contraindications of this drug. [26]
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DISCUSSION

Our study has been the first one to assess the effect of a specific intervention on the features of ADRs spontaneously reported in a hospital setting, the drugs involved and the number of signals identified. It has shown that the improvement in spontaneous reporting of ADRs achieved following an intervention based on educational activities and economic incentives allowed us to detect some safety problems and to identify several signals. It is noteworthy that the reporting of all kind of adverse reactions and drugs increased.

The traditional methods and systems to detect ADRs in hospitals have been spontaneous reporting, intensive surveillance of hospital admissions and, more recently, computer-assisted approaches using routine data from hospital information systems.^[3] Different methods identify different types of ADRs and drugs. Moreover, the type of suspect drugs, their rank order and the types of ADRs identified vary widely among studies. In studies that only or predominantly included ADR-related hospitalisations, nonsteroidal anti-inflammatory drugs causing gastrointestinal bleeding play a major role, followed by cardiovascular drugs and drugs acting on the central nervous system. In contrast, antibacterials/antiinfectives very often cause ADRs in hospitalised patients (mainly allergic reactions), as do opioids, cardiovascular drugs and anticoagulants.^[3]

In our study the most frequently reported ADRs were similar in both periods, although some types of ADRs that were hardly reported on the first period increased in the second one. Cutaneous reactions were the most frequently reported ADRs in both periods: other ADRs commonly reported during both periods were cardiovascular, haematological, neurological and gastrointestinal reactions. Nevertheless, a high increase in endocrinological, urinary and hepatic

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3 reactions was observed in the second period. There are no other published
4 studies comparing the effect of an intervention on the organ-system categories
5 of reactions spontaneously reported in a hospital. A few studies have reported
6 the pattern of spontaneously reported ADRs in hospitals.^[16-19, 27,28] As in ours, in
7 the majority of these studies dermatological reactions were the most frequently
8 identified ^[17-19, 27] and skin rash was the most commonly reported reaction.^[17,18]
9 Other ADRs such as neurological, gastrointestinal, and haematological reactions
10 were also frequently reported. However, it is interesting to note that, in
11 contrast with our study, endocrinological and urinary reactions were rarely
12 reported in others. In our opinion, the intervention could be responsible for the
13 increase in the reporting of these ADRs in the second period. Further studies
14 should be carried out to analyze the effect of different interventions on the
15 features of the spontaneously reported ADRs.
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29 The majority of therapeutic subgroups of suspected drugs increased during the
30 intervention. Systemic antibiotics, antithrombotics, and cardiac therapy drugs
31 were the most commonly involved therapeutic subgroups in the spontaneous
32 reports in both periods. These therapeutic subgroups were also frequently
33 reported in other studies that assessed the drugs involved in spontaneously
34 reported ADRs in hospitals.^[18,19,27] In our study, the greatest changes between
35 periods were the increase in the proportion of immunostimulants,
36 immunosuppressants and psychoanaleptics. In addition, antineoplastics, a
37 therapeutic subgroup highly reported in other studies,^[17,19,27] also increased
38 during the intervention. The therapeutic subgroups most commonly involved in
39 the spontaneously reported ADRs were drugs frequently used in the hospital
40 setting. Nevertheless, taking into account the differences in the pattern of
41 suspect drugs in the two periods, it is likely that the intervention allowed us to
42 identify during the second period some suspect drugs involved in ADRs
43 infrequently reported in the first one. It would be interesting to investigate the
44 effect of other interventions on the type of suspected drugs in spontaneously
45 reported ADRs.
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3 Furthermore, the absolute number of spontaneous reports from any origin
4 increased during the second period, except for those from emergencies. It is
5 worth noting that spontaneous reports from the outpatient hospital
6 consultations began to be reported during the second period. The effect of the
7 intervention was evident, since the physicians had been informed in the
8 educational meetings that they could report ADRs from every assistance
9 setting. Unexpectedly, spontaneous reporting of ADRs requiring only medical
10 attention at emergency room did not increase in spite of the intervention. The
11 reason for that is unknown, although high attendance-pressure, specially in this
12 area, lack of time, and other clinical priorities have been argued as potential
13 obstacles to the spontaneous reporting of ADRs by the doctors at our
14 hospital.^[5] Therefore, in the emergency area some other specific strategies
15 aimed at increasing spontaneous reporting should be planned.
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29 One of the main objectives of spontaneous reporting of ADRs is to detect drug
30 safety concerns related to new drugs. Surprisingly, the novelty of suspect drugs
31 has not been analyzed in published studies on spontaneous reporting in
32 hospitals. In our study we observed that during the intervention the number of
33 suspected pharmacological exposures to recently marketed drugs and the
34 number of serious cases, including those with a fatal outcome, increased. It is
35 noteworthy that one of the signals identified referred to a serious reaction to a
36 recently marketed drug and arose through the reporting of a fatal case (i.e.
37 intracranial haemorrhage associated to drotecogin alfa activated).
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48 The majority of drug-reaction associations spontaneously reported in both
49 periods of the study were well-known reactions related to old drugs (i.e.,
50 haemorrhage due to enoxaparin, hepatotoxicity due to amoxicillin-clavulanic
51 acid, and hyperthyroidism due to amiodarone). However, the reporting of
52 known ADRs can help to identify local problems related to the use of specific
53 drugs. For example, in our hospital haemorrhages related to low-weight
54 molecular heparins led to an analysis of the severe cases in order to identify
55 possible risk factors. On the other hand, two previously unknown reactions
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3 associated with old drugs that were reported in the second period led to the
4 withdrawal of the market of one drug and an update of the summary of product
5 characteristics in the other one. This point is interesting because it shows that
6 even old drugs must be kept under surveillance through their entire life-span to
7 detect some possible previously unknown reactions.
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14 Obviously our study has some limitations. First of all, it was carried out in only
15 one hospital with specific characteristics (a teaching tertiary hospital; the
16 biggest one in our geographical area). Additionally, the Catalan Centre of the
17 Spanish Pharmacovigilance System is located in the hospital. Therefore, our
18 findings could not be generalized to other hospitals. Secondly, since our study
19 was a time series study without a control group, we can not rule out the
20 influence of other factors in the observed results. Nevertheless, the number of
21 the spontaneous ADRs reported by the other Catalan hospital to the
22 Pharmacovigilance regional Centre during the two study's periods did not
23 increase. Thirdly, the number of signals identified was low and we can not
24 confirm the effect of intervention on its detection. Fourthly, we did not collect
25 information on the category of physicians, medical speciality and other
26 characteristics of the reporters that might have influenced the results. In spite
27 of all these limitations, our study generates new information on the effect of a
28 specific intervention on the features of the spontaneously reported ADRs, the
29 drugs involved and the signals identified. On the one hand, that confirms the
30 usefulness of the implementation of these types of strategies to improve
31 reporting of ADRs in hospitals. On the other hand, these results can be and
32 even should be used as an argument when stimulating the spontaneous
33 reporting by health care professionals by means of supporting evidence of the
34 usefulness of pharmacovigilance activities.
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55 As a conclusion, an intervention based on educational activities and economic
56 incentives led not only to a quantitative improvement in spontaneous reporting
57 of ADRs by hospital physicians but also to a qualitative improvement in terms of
58 seriousness of reactions identified affecting different organs or systems, and
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3 type of drugs involved, including those most recently marketed. Moreover, a
4 number of signals were generated during the intervention and they contributed
5 to the adoption of decisions by the regulatory authorities on either the
6 withdrawal of drugs from the market or changes in the information contained in
7 the summary of product characteristics of some drugs. Future studies should
8 analyse the effect of other types of intervention on spontaneous reporting of
9 ADRs in hospitals, the number of identified signals and quickness of their
10 recognition.
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Table 1. Adverse drug reactions classified by organ or system affected

| Organ or system | First period | | Second period | |
|-------------------------------------|--------------|--------|---------------|--------|
| | N | (%) | N | (%) |
| Cutaneous reactions | 44 | (20.0) | 128 | (18.4) |
| Haematological reactions | 23 | (10.5) | 68 | (9.8) |
| Gastrointestinal reactions | 19 | (8.6) | 68 | (9.8) |
| Cardiovascular reactions | 27 | (12.3) | 67 | (9.7) |
| Hepatic reactions | 12 | (5.5) | 64 | (9.2) |
| Neurological reactions | 26 | (11.8) | 58 | (8.4) |
| Metabolic and nutritional reactions | 10 | (4.5) | 43 | (6.2) |
| Respiratory reactions | 19 | (8.6) | 39 | (5.6) |
| General disorders | 9 | (4.1) | 37 | (5.3) |
| Urinary reactions | 4 | (1.8) | 32 | (4.6) |
| Endocrinological reactions | 1 | (0.5) | 26 | (3.7) |
| Psychiatric reactions | 12 | (5.5) | 24 | (3.5) |
| Others | 14 | (6.3) | 40 | (5.8) |
| Total | 220 | (100) | 694 | (100) |

Table 2. Most frequent adverse reactions

| Adverse reaction | First period (N=220) | | Second period (N=694) | |
|------------------------------|-------------------------|-------|--------------------------|-------|
| | N | (%) | N | (%) |
| Erythematous rash | 5 | (2.3) | 31 | (4.5) |
| Rash | 6 | (2.7) | 25 | (3.6) |
| Hepatitis | 3 | (1.4) | 20 | (2.9) |
| Thrombocytopenia | 2 | (0.9) | 19 | (2.7) |
| Hepatic enzymes increased | 6 | (2.7) | 18 | (2.6) |
| Acute renal failure | 4 | (1.8) | 18 | (2.6) |
| Hepatitis cholestatic | 3 | (1.4) | 17 | (2.4) |
| Gastrointestinal haemorrhage | 2 | (0.9) | 17 | (2.4) |
| Diarrhoea | 3 | (1.4) | 16 | (2.3) |
| Anaphylactic shock | 4 | (1.8) | 15 | (2.2) |
| Heart failure | 2 | (0.9) | 14 | (2.0) |
| Hyperthyroidism | 1 | (0.5) | 14 | (2.0) |
| Urticaria | 10 | (4.5) | 12 | (1.7) |
| Angioedema | 9 | (4.1) | 11 | (1.6) |
| Bronchospasm | 9 | (4.1) | 10 | (1.4) |
| Haematoma | 8 | (3.6) | 9 | (1.3) |
| Atrioventricular block | 4 | (1.8) | 8 | (1.2) |
| Encephalopathy | 4 | (1.8) | 8 | (1.2) |
| Extrapyramidal disorder | 5 | (2.3) | 4 | (0.6) |
| Retroperitoneal haemorrhage | 6 | (2.7) | 3 | (0.4) |
| Distonia | 5 | (2.3) | 3 | (0.4) |
| Hypotension | 9 | (4.1) | 2 | (0.3) |

Only adverse reactions present in at least five reports of any period are displayed.

Table 3. Suspect drugs by therapeutic subgroup

| Therapeutic subgroup | First period | | Second period | |
|--|--------------|--------|---------------|--------|
| | N | (%) | N | % |
| Systemic antibiotics (J01) | 62 | (21.8) | 149 | (17.0) |
| Antithrombotics (B01) | 30 | (10.5) | 69 | (7.9) |
| Cardiac therapy (C01) | 17 | (6.0) | 47 | (5.4) |
| Antiinflammatories and antirheumatics (M01) | 12 | (4.2) | 46 | (5.2) |
| Psychoanaleptics (N06) | 8 | (2.8) | 44 | (5.0) |
| Analgesics (N02) | 17 | (6.0) | 35 | (4.0) |
| Drugs acting on the renin-angiotensin system (C09) | 10 | (3.5) | 35 | (4.0) |
| Antiepileptics (N03) | 9 | (3.1) | 35 | (4.0) |
| Antineoplastics (L01) | 8 | (2.8) | 34 | (3.9) |
| Antimycobacterials (J04) | 14 | (4.9) | 32 | (3.6) |
| Systemic antivirals (J05) | 7 | (2.5) | 31 | (3.5) |
| Immunosuppressive drugs (L04) | 4 | (1.4) | 29 | (3.3) |
| Diuretics (C03) | 9 | (3.1) | 27 | (3.1) |
| Psycholeptics (N05) | 9 | (3.1) | 24 | (2.7) |
| Drugs for obstructive airway diseases (R03) | 6 | (2.1) | 22 | (2.5) |
| Beta blocking drugs (C07) | 3 | (1.1) | 22 | (2.5) |
| Immunostimulants (L03) | 0 | (-) | 18 | (2.1) |
| Systemic corticosteroids (H02) | 4 | (1.4) | 16 | (1.8) |
| Lipid modifying drugs (C10) | 6 | (2.1) | 15 | (1.7) |
| Systemic antihistamines (R06) | 11 | (3.9) | 4 | (0.5) |
| Others | 39 | (13.7) | 143 | (16.3) |
| Total | 285 | (100) | 877 | (100) |

Table 4. Most frequent suspect drugs

| Drug | First period | | | Second period | | |
|-----------------------------|------------------------------|-------|--------------------|------------------------------|-------|--------------------|
| | Suspect exposures (N=285) | | Reports (N=200) | Suspect exposures (N=877) | | Reports (N=631) |
| | N | (%) | % | N | (%) | % |
| Amiodarone | 11 | (3.9) | 5.5 | 36 | (4.1) | 5.7 |
| Amoxicillin-clavulanic acid | 16 | (5.6) | 8.0 | 35 | (3.9) | 5.5 |
| Metamizole | 12 | (4.2) | 6.0 | 23 | (2.6) | 3.6 |
| Enoxaparin | 16 | (5.6) | 8.0 | 21 | (2.4) | 3.3 |
| Enalapril | 4 | (1.4) | 2.0 | 21 | (2.4) | 3.3 |
| Ibuprofen | 2 | (0.7) | 1.0 | 18 | (2.1) | 2.9 |
| Acenocoumarol | 2 | (0.7) | 1.0 | 15 | (1.7) | 2.4 |
| Acetylsalicylic acid | 6 | (2.1) | 3.0 | 14 | (1.6) | 2.2 |
| Prednisone | 2 | (0.7) | 1.0 | 13 | (1.5) | 2.1 |
| Phenytoin | 3 | (1.1) | 1.5 | 10 | (1.1) | 1.6 |
| Levofloxacin | 3 | (1.1) | 1.5 | 10 | (1.1) | 1.6 |
| Pyrazinamide | 3 | (1.1) | 1.5 | 10 | (1.1) | 1.6 |
| Furosemide | 3 | (1.1) | 1.5 | 9 | (1.0) | 1.4 |
| Azithromycin | 1 | (0.4) | 0.5 | 9 | (1.0) | 1.4 |
| Fluoxetine | 1 | (0.4) | 0.5 | 9 | (1.0) | 1.4 |
| Ciprofloxacin | 6 | (2.1) | 3.0 | 8 | (0.9) | 1.3 |
| Spirolactone | 1 | (0.4) | 0.5 | 8 | (0.9) | 1.3 |
| Linezolid | 0 | (-) | - | 8 | (0.9) | 1.3 |
| Diclofenac | 6 | (2.1) | 3.0 | 7 | (0.8) | 1.1 |
| Hydrochlorothiazide | 3 | (1.1) | 1.5 | 7 | (0.8) | 1.1 |
| Cefepime | 2 | (0.7) | 1.0 | 7 | (0.8) | 1.1 |
| Rifampicin-isoniazid | 1 | (0.4) | 0.5 | 7 | (0.8) | 1.1 |
| Clarithromycin | 5 | (1.8) | 2.5 | 6 | (0.7) | 1.0 |
| Carbamazepine | 3 | (1.1) | 1.5 | 6 | (0.7) | 1.0 |
| Digoxin | 3 | (1.1) | 1.5 | 6 | (0.7) | 1.0 |
| Moxifloxacin | 2 | (0.7) | 1.0 | 6 | (0.7) | 1.0 |
| Azathioprine | 1 | (0.4) | 0.5 | 6 | (0.7) | 1.0 |
| Vancomycin | 1 | (0.4) | 0.5 | 6 | (0.7) | 1.0 |
| Ceftriaxone | 0 | (-) | - | 6 | (0.7) | 1.0 |
| Methotrexate | 0 | (-) | - | 6 | (0.7) | 1.0 |
| Tacrolimus | 0 | (-) | - | 6 | (0.7) | 1.0 |
| Thiethylperazine | 8 | (2.8) | 4.0 | 3 | (0.3) | 0.5 |

Only drugs with at least six suspect exposures in any period are displayed.

Table 5. Most frequent drug-reaction associations

| Drug | Reaction | First period (N=200 reports) | | Second period (N=631 reports) | |
|-----------------------------|--|---------------------------------|-------|----------------------------------|-------|
| | | N | (%) | N | (%) |
| Amoxicillin-clavulanic acid | Hepatic enzymes increased, hepatitis or cholestatic hepatitis | 2 | (1.0) | 14 | (2.2) |
| Amiodarone | Hyperthyroidism | 1 | (0.5) | 14 | (2.2) |
| Enoxaparin | Haemoperitoneum, retroperitoneal haemorrhage or haematoma | 11 | (5.5) | 8 ^a | (1.3) |
| Acenocoumarol | Haemoperitoneum, retroperitoneal haemorrhage or haematoma | 1 | (0.5) | 7 ^a | (1.1) |
| Amiodarone | QT interval prolonged, <i>torsade de pointes</i> or ventricular fibrillation | 0 | (-) | 7 | (1.1) |
| Phenytoin | Erythematous, maculopapular or unspecified rash | 1 | (0.5) | 7 | (1.1) |
| Metamizole | Erythematous, maculopapular or unspecified rash | 1 | (0.5) | 7 | (1.1) |
| Enalapril | Acute renal failure | 0 | (-) | 6 | (1.0) |
| Prednisone | Hyperglycaemia, diabetes mellitus or diabetes mellitus aggravated | 0 | (-) | 6 | (1.0) |
| Acetylsalicylic acid | Gastrointestinal haemorrhage | 1 ^b | (0.5) | 5 ^c | (0.8) |
| Enalapril | Cough | 0 | (-) | 5 | (0.8) |
| Enoxaparin | Cerebral haemorrhage | 0 | (-) | 5 ^d | (0.8) |
| Thiethylperazine | Distonia and/or dyskinesia | 7 | (3.5) | 3 | (0.5) |
| Amoxicillin-clavulanic acid | Angioedema or laryngeal oedema | 5 | (2.5) | 0 | (-) |

Only associations present in at least five reports of any period are displayed.

^a Concomitant administration of enoxaparin and acenocoumarol in two cases. ^b Enoxaparin concomitantly administered. ^c Drugs concomitantly administered: clopidogrel (in one case); clopidogrel, enoxaparin and abciximab (in one case); enoxaparin and streptokinase (in one case). ^d Drugs concomitantly administered: tenecteplase and acetylsalicylic acid (in four cases); drotrecogin alfa activated (in one case).

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For Peer Review

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3 **EFFECT OF AN INTERVENTION ON THE FEATURES OF ADVERSE DRUG**
4
5 **REACTIONS SPONTANEOUSLY REPORTED IN A HOSPITAL**
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10 Cereza G^{1,2}, Agustí A^{1,3,4}, Pedrós C⁵, Vallano A^{5,6}, Aguilera C^{1,3}, Danés I^{1,3,4},
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ABSTRACT

Background.- A continuous intervention based on healthcare management agreements was associated in our hospital with an increase in the absolute number of spontaneous reporting of adverse drug reactions (ADRs), and also with an increase in the number of reports of serious or unexpected ADRs and ADRs associated with new drugs.

Objective.- To analyze the effect of this intervention on the features of ADRs spontaneously reported in a hospital, the drugs involved and the number of signals identified.

Methods.- A longitudinal study with two periods, the 1st period without intervention from 1998 to 2002 and the 2nd period with intervention from 2003 to 2005, was carried out in a teaching tertiary Hospital. Changes between the two periods in the following variables were analysed: (a) the patients' characteristics, such as gender and age; (b) the reported ADRs, and their medical assistance required; (c) the suspected drugs involved in the ADRs and (d) the main signals identified.

Results.- Gender and age distribution of patients described in the spontaneous reports were no different in the two periods. During the second period, spontaneously reported cases requiring hospital admission and those occurring in-hospital increased (236 from 2 in the first period and 277 from 99 in the first period, respectively) and cases from outpatient hospital consultations began to be reported (13.9% of reports). The spontaneous reporting on all kinds of ADRs and drugs increased during the second period. Cutaneous reactions were the most frequently spontaneous reported ADRs in both periods followed by cardiovascular and neurological reactions in the first period, and haematological and gastrointestinal reactions in the second one. However, during the second period the higher increase was for endocrinological, urinary and hepatic reactions. Systemic antibiotics, antithrombotics and cardiac therapy drugs were the most commonly therapeutic subgroups reported as suspected drugs in both periods, but in the second period the proportion of immunostimulants, beta blocking agents, immunosuppressants and psychoanaleptics increased. No

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3 signals were recognized during the first period, however two signals and one
4 additional safety concern were identified during the second.
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7 **Conclusion.-** An intervention based on healthcare management agreements,
8 was associated with an important increase in spontaneous reporting of ADRs by
9 hospital physicians and also with a change in terms of type of ADRs identified
10 affecting different organs or systems, and the therapeutic groups of drugs
11 involved. Future studies should analyze the effect of different types of
12 intervention on spontaneous reporting of ADRs in hospitals.
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20 Words account: 399

21
22 Keywords: Pharmacovigilance; Adverse Drug Reactions Reporting Systems;
23 Drug Toxicity; Intervention Studies; Hospital
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INTRODUCTION

The spontaneous reporting system is currently the cornerstone of post-marketing signal detection in pharmacovigilance.^[1-2] Detection of adverse drug reactions (ADRs) in hospitals is important because serious events may be identified, novel drugs are commonly used, new and unexpected ADRs may be detected early on and cases are usually well-documented with high quality information. Nevertheless, spontaneous reporting has been scarcely used as a method of ADRs detection in hospitals and underreporting is a major flaw,^[3-5] as it is in the primary health care setting.^[6]

Several interventions (educational or others) aimed at solving this major drawback have been proposed and the effectiveness of some of them has been evaluated in a number of studies.^[5,7-12] In this sense we have reported that an intervention based on healthcare management agreements with economic incentives and educational activities was associated with a quantitative and qualitative improvement of spontaneous reporting of ADRs by hospital physicians.^[13] Not only did the absolute number of spontaneous reports increase but so did the number of reports of serious or unexpected ADRs and ADRs associated with new drugs.

The pattern of adverse drug reactions notified by spontaneous reporting in hospitals has been described in a few studies.^[14-19] Furthermore, there are no studies assessing if the improvement in reporting in the hospital setting allows a more efficient detection of new drug safety issues or if it facilitates signal identification. The usefulness of an increase in spontaneous reporting depends on the increase in the number of meaningful reports that help in raising concerns. Therefore, the aim of this study was to analyze the effect of the spontaneous reporting increase after an intervention in the hospital on the features of the ADRs reported, the drugs involved and the signals identified.

METHODS

A time series analysis was carried out at Vall d'Hebron University Hospital (Barcelona, Spain) from 1998 to 2005 in order to assess the effectiveness of a continuous multifaceted intervention for improving spontaneous reporting of ADRs by hospital physicians to the Pharmacovigilance Programme (PhVP) of the hospital. The intervention was based on health care management agreements between hospital managers and clinical services, and was initiated in 2003. A framework agreement between hospital managers and physicians included different commitments linked to economic incentives. One of the objectives for physicians was to increase their participation in the PhVP increasing the number of spontaneous ADR reports. This objective was integrated into other clinical objectives at three levels: a) institution or whole hospital, b) clinical department or clinical team, and c) physician. The financial incentive obtained was variable according to the objectives achieved, and was approximately 5-7% of the physician's salary. The size of the financial payment for ADR reporting accounted for less than 10% of the total of agreed incentives and was, on average, less than 1% of the physician's salary. In each clinical service, an initial meeting between physicians and the hospital pharmacovigilance team was held. In this first meeting, the hospital's pharmacovigilance activities, the aim of spontaneous ADR reporting and how to report ADRs, were presented. In addition to reinforcement, twice-yearly educational meetings were held in each clinical service, offering information about pharmacovigilance and emphasizing the priorities for spontaneous reporting ADRs (serious ADRs, unexpected ADRs, and those ADRs associated with new drugs). These meetings lasted 45-60 minutes, and consisted of a brief explanation of the number and main characteristics of ADRs detected in the whole hospital and in the specific clinical service. Signals identified by the PhVP and news about ADRs released by regulatory agencies were also commented on. Finally, reminder cards with the telephone number of the pharmacovigilance team and a list of the most important ADRs to be reported on (serious, unexpected and those associated with new drugs) were distributed to the hospital wards.

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3 Changes between the two periods of study (the 1st period without intervention
4 from 1998 to 2002 and the 2nd period with intervention from 2003 to 2005) in
5 the total number of spontaneous reports of ADRs, and in the number of serious
6 reports, reports of unexpected ADRs and reports of ADRs related to recently
7 marketed drugs were therein presented.^[13]
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14 In this paper, changes between the two periods in the following variables of the
15 longitudinal study have been analyzed: (a) The patients' characteristics, such as
16 gender and age; (b) the reported ADRs, with their seriousness, outcome,
17 medical assistance required, and previous knowledge; (c) the suspected drugs
18 involved in the ADRs, including those recently marketed; and (d) the most
19 frequent drug-ADR associations and the main signals identified.
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28 The ADRs were classified in organ-system categories according to the World
29 Health Organization terminology (WHOART - WHO Adverse Reaction
30 Terminology). The suspected drugs were grouped in therapeutic classes
31 according to the Anatomical Therapeutic Chemical classification system. The
32 seriousness of the cases was classified according to the European Union's
33 criteria and cases were considered serious (ADRs that result in death, are life-
34 threatening, require hospitalisation or prolongation of existing hospitalisation,
35 result in persistent or significant disability or incapacity, are congenital anomaly
36 or birth defect, or are important medical events) or non-serious (the remaining
37 cases).^[21] Its outcome was classified into recovery, permanent sequelae, death
38 or unknown. According to the medical attention required, the cases were
39 classified into those requiring hospital admission, in-hospital cases, cases
40 requiring attention at the emergency room, and cases from the outpatient
41 department. Previous knowledge of the ADRs was classified according to the
42 Spanish Pharmacovigilance System's (SPhVS) causality algorithm in well-known
43 ADRs, known from anecdotal reports, or unknown.^[22] New-drugs were defined
44 as those marketed for less than five years at the time when the ADRs began.
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3 Statistical analysis. The spontaneous reports of ADRs during the two studied
4 periods were analyzed separately. Descriptive analysis of continuous variables
5 was performed by means of median and range; and statistical differences were
6 assessed by means of the Mann-Whitney test. Categorical variables were
7 described using percentages; statistical differences were assessed by means of
8 the χ^2 test. Significance was set at a level of 0.05, two tailed. The statistical
9 analysis was performed using the SPSS version 15.0 statistical package (SPSS
10 Inc. Chicago-Illinois).

20 RESULTS

23 Number of spontaneous reports of adverse drug reactions

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27 Of the total number of cases of ADRs identified by the PhVP, the proportion of
28 spontaneous ADR reports increased from 29.5% (n=200) during the first period
29 to 71.5% (n= 631) during the second period. More details about this increase
30 were presented in the previous paper.

36 Patients' characteristics

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40 Gender and age distribution of patients described in the spontaneous reports
41 were no different between the two periods. The ratio female-to-male in the
42 spontaneous reports from the first period was 1.08 (104 females and 96
43 males); it was 0.96 in the second one (310 females and 321 males; p=0.516).
44 Median age (minimum-maximum) was 64 (14-94) for patients described in both
45 periods (p=0.150).

52 Medical attention required

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57 Most cases reported during the first period either required medical attention at
58 the emergency room without hospital admission (99; 49.5%) or were in-

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3 hospital cases (99; 49.5%). The two remaining cases (1%) required hospital
4 admission.
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9 The number of cases requiring only medical attention at emergency room
10 decreased during the second period (30; 4.8%). In-hospital cases slightly
11 decreased in relative terms although the absolute number of reports increased
12 (277; 43.9%). Conversely, cases requiring hospital admission increased both in
13 relative and in absolute terms (236; 37.4%). On the other hand, cases from
14 outpatient department not requiring attention at the emergency room or
15 hospital admission began to be reported during the second period, accounting
16 for 13.9% (88) of the overall reports received at the end of this period ($p <$
17 0.001).
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26 27 Seriousness and outcome 28

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31 In the second period, the proportion of serious cases almost doubled (63.1% vs
32 32.5%) and the number of serious cases increased by more than 6-fold (398 vs
33 65; $p < 0.001$).
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39 The most frequently reported outcome in both periods was recovery (70% in
40 the first one and 74.2% in the second one). The number of cases that
41 recovered with sequelae was 2 in the first period and 16 in the second one.
42 There were 9 fatal cases during the first period and 15 in the second one. The
43 adverse reactions and drugs involved in these fatal cases are presented below
44 in the drug-reaction associations section. Finally, the outcome was unknown in
45 49 cases in the first period and 132 in the second one ($p=0.153$).
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53 Adverse reactions 54

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57 Overall, 220 adverse reactions were described in the 200 first-period
58 spontaneous reports. Cutaneous reactions were the most frequent, followed by
59 cardiovascular and neurological reactions. In the 631 second-period
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3 spontaneous reports, 694 adverse reactions were described. Cutaneous
4 reactions were the most frequent as well, followed in this case by
5 haematological and gastrointestinal reactions (table 1). However, during the
6 second period the frequency of endocrinological, urinary and hepatic reactions
7 increased (3.7% vs. 0.5%, 4.6% vs. 1.8% and 9.2% vs. 5.5%, respectively).
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14 The most commonly reported individual adverse reactions (with a frequency \geq
15 3% of reports) during the first period were urticaria, angioedema,
16 bronchospasm, hypotension, and haematoma. In the second period, individual
17 reactions described in \geq 3% of reports were rash and erythematous rash (table
18 2). During the second period the frequency of hyperthyroidism,
19 thrombocytopenia and gastrointestinal haemorrhage increased by 4.3 and more
20 than 2-fold, respectively.
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29 Suspected drugs

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33 Two hundred and eighty-five and 877 suspected pharmacological exposures
34 were contained in the reports in the first and the second period respectively. In
35 both periods, the most common therapeutic subgroups were systemic
36 antibiotics, antithrombotics, and cardiac therapy. These three groups accounted
37 for 38.2% and 30.3% of the total suspected pharmacological exposures in each
38 period respectively (table 3). Regarding the remaining therapeutic subgroups,
39 the greatest changes between periods were the increase in the proportion of
40 immunostimulants, beta blocking agents, immunosuppressants and
41 psychoanaleptics, and the decrease in the proportion of systemic antihistamines
42 during the second period.
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53 The drugs with the highest number of suspected exposures were amiodarone,
54 amoxicillin-clavulanic acid, metamizole, and enoxaparin in both periods (table
55 4). Some drugs with no suspected exposures during the first period appeared
56 during the second one (i.e., ceftriaxone, methotrexate, and tacrolimus).
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3 Additionally, a 9-fold increase was seen in the number of suspected exposures
4 to ibuprofen, azithromycin and fluoxetine during the second period.
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9 In both study periods, around 10% of suspected pharmacological exposures
10 concerned recently marketed drugs. Nevertheless, both the overall number of
11 suspected pharmacological exposures and the number of different drugs
12 increased in the second period (97 vs. 28, and 50 vs. 19, respectively). The
13 new drugs with the highest number of suspected exposures were clopidogrel,
14 levoﬂoxacin, and nevirapine (three exposures each) in the first period, and
15 linezolid (eight exposures), tiotropium bromide, glatiramer acetate,
16 oxcabazepine, tenofovir, and voriconazole (five exposures each) in the second
17 one.
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28 Drug-reaction associations

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31 In the first period, the most frequently reported drug-reaction associations were
32 haemoperitoneum, retroperitoneal haemorrhage or muscular haematoma due
33 to enoxaparin (11 cases, 5.5% of reports). In the second period, they were
34 hepatotoxicity induced by amoxicillin-clavulanic acid and hyperthyroidism due to
35 amiodarone (14 cases and 2.2% of reports each) (table 5).
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42 Three out of nine fatal reports from the first period were cases of haemorrhagic
43 reactions in patients treated with enoxaparin (two retroperitoneal
44 haemorrhages and a gastrointestinal bleeding), three were cases of
45 cardiovascular reactions (myocardial infarction after terbutaline treatment,
46 salbutamol and levofloxacin-induced *torsade de pointes*, and cardiac arrest in a
47 patient treated with levomepromazine and carbamazepine) and the remaining
48 three reports described adverse reactions related to other systems. The most
49 frequent reactions in the fifteen fatal cases reported during the second period
50 were also haemorrhagic events (seven cases). There were four cases of
51 intracranial haemorrhage (three of them with tenecteplase, enoxaparin and
52 acetylsalicylic acid, and one with drotrecogin alpha and enoxaparin), one case
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3 of enoxaparin-induced retroperitoneal haemorrhage, one case of intraabdominal
4 haemorrhage due to enoxaparin, acenocoumarol and acetylsalicylic acid, and
5 one case of acetylsalicylic acid-induced gastrointestinal haemorrhage. Of the
6 eight remaining cases, three were toxic epidermal necrolysis and the other
7 described reactions related to other systems.
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10 11 Previous knowledge/Signals identified 12

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15 The absolute number of previously unknown or poorly known drug-reaction
16 associations had a fourfold increase in the second period (54 vs. 13 in the first
17 period). Most of them were serious cases (5 out of 13 in the first period and 40
18 out of 54 in the second one; $p=0.047$).
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24 No signals were identified during the first period. In the second one, two
25 serious and previously unknown or poorly known drug-reaction associations
26 were considered signals that required the adoption of regulatory measures by
27 the Spanish Agency for Medicines and Medical Devices (AEMPS). The first signal
28 was *pseudoproteinuria* induced by gelatine succinate infusion. A warning
29 regarding this problem was added in the summary of product characteristics [23]
30 and a "Dear Dr letter" was sent to Spanish nephrologists and to the National
31 Transplant Organization. The second signal was veralipride withdrawal
32 syndrome; it required a risk-benefit assessment of the use of this orthopramide
33 in the treatment of menopausal hot flushes and, as a result, the AEMPS
34 withdrew this drug from the market. [24] Afterwards, the EMEA also
35 recommended the withdrawal of this drug from the European market. [25]
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52 Additionally, the fatal case of cerebral haemorrhage due to drotrecogin alfa
53 activated, which occurred in a patient who had recently undergone surgery, led
54 to a review of safety data of this drug in the surgical population. As a result, the
55 AEMPS proposed changes in the authorized conditions of use of drotrecogin alfa
56 activated at the EMEA level. Those proposals contributed to updating the
57 authorized conditions of use and contraindications of this drug. [26]
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DISCUSSION

Our study has been the first one to assess the effect of a specific intervention on the features of ADRs spontaneously reported in a hospital setting, the drugs involved and the number of signals identified. It has shown that the improvement in spontaneous reporting of ADRs achieved following an intervention based on educational activities and economic incentives allowed us to detect some safety problems and to identify several signals. It is noteworthy that the reporting of all kind of adverse reactions and drugs increased.

The traditional methods and systems to detect ADRs in hospitals have been spontaneous reporting, intensive surveillance of hospital admissions and, more recently, computer-assisted approaches using routine data from hospital information systems.^[3] Different methods identify different types of ADRs and drugs. Moreover, the type of suspect drugs, their rank order and the types of ADRs identified vary widely among studies. In studies that only or predominantly included ADR-related hospitalisations, nonsteroidal anti-inflammatory drugs causing gastrointestinal bleeding play a major role, followed by cardiovascular drugs and drugs acting on the central nervous system. In contrast, antibacterials/antiinfectives very often cause ADRs in hospitalised patients (mainly allergic reactions), as do opioids, cardiovascular drugs and anticoagulants.^[3]

In our study the most frequently reported ADRs were similar in both periods, although some types of ADRs that were hardly reported on the first period increased in the second one. Cutaneous reactions were the most frequently reported ADRs in both periods: other ADRs commonly reported during both periods were cardiovascular, haematological, neurological and gastrointestinal reactions. Nevertheless, a high increase in endocrinological, urinary and hepatic

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3 reactions was observed in the second period. There are no other published
4 studies comparing the effect of an intervention on the organ-system categories
5 of reactions spontaneously reported in a hospital. A few studies have reported
6 the pattern of spontaneously reported ADRs in hospitals.^[16-19, 27,28] As in ours, in
7 the majority of these studies dermatological reactions were the most frequently
8 identified ^[17-19, 27] and skin rash was the most commonly reported reaction.^[17,18]
9 Other ADRs such as neurological, gastrointestinal, and haematological reactions
10 were also frequently reported. However, it is interesting to note that, in
11 contrast with our study, endocrinological and urinary reactions were rarely
12 reported in others. In our opinion, the intervention could be responsible for the
13 increase in the reporting of these ADRs in the second period. Further studies
14 should be carried out to analyze the effect of different interventions on the
15 features of the spontaneously reported ADRs.
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29 The majority of therapeutic subgroups of suspected drugs increased during the
30 intervention. Systemic antibiotics, antithrombotics, and cardiac therapy drugs
31 were the most commonly involved therapeutic subgroups in the spontaneous
32 reports in both periods. These therapeutic subgroups were also frequently
33 reported in other studies that assessed the drugs involved in spontaneously
34 reported ADRs in hospitals.^[18,19,27] In our study, the greatest changes between
35 periods were the increase in the proportion of immunostimulants,
36 immunosuppressants and psychoanaleptics. In addition, antineoplastics, a
37 therapeutic subgroup highly reported in other studies,^[17,19,27] also increased
38 during the intervention. The therapeutic subgroups most commonly involved in
39 the spontaneously reported ADRs were drugs frequently used in the hospital
40 setting. Nevertheless, taking into account the differences in the pattern of
41 suspect drugs in the two periods, it is likely that the intervention allowed us to
42 identify during the second period some suspect drugs involved in ADRs
43 infrequently reported in the first one. It would be interesting to investigate the
44 effect of other interventions on the type of suspected drugs in spontaneously
45 reported ADRs.
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3 Furthermore, the absolute number of spontaneous reports from any origin
4 increased during the second period, except for those from emergencies. It is
5 worth noting that spontaneous reports from the outpatient hospital
6 consultations began to be reported during the second period. The effect of the
7 intervention was evident, since the physicians had been informed in the
8 educational meetings that they could report ADRs from every assistance
9 setting. Unexpectedly, spontaneous reporting of ADRs requiring only medical
10 attention at emergency room did not increase in spite of the intervention. The
11 reason for that is unknown, although high attendance-pressure, specially in this
12 area, lack of time, and other clinical priorities have been argued as potential
13 obstacles to the spontaneous reporting of ADRs by the doctors at our
14 hospital.^[5] Therefore, in the emergency area some other specific strategies
15 aimed at increasing spontaneous reporting should be planned.
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29 One of the main objectives of spontaneous reporting of ADRs is to detect drug
30 safety concerns related to new drugs. Surprisingly, the novelty of suspect drugs
31 has not been analyzed in published studies on spontaneous reporting in
32 hospitals. In our study we observed that during the intervention the number of
33 suspected pharmacological exposures to recently marketed drugs and the
34 number of serious cases, including those with a fatal outcome, increased. It is
35 noteworthy that one of the signals identified referred to a serious reaction to a
36 recently marketed drug and arose through the reporting of a fatal case (i.e.
37 intracranial haemorrhage associated to drotecogin alfa activated).
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48 The majority of drug-reaction associations spontaneously reported in both
49 periods of the study were well-known reactions related to old drugs (i.e.,
50 haemorrhage due to enoxaparin, hepatotoxicity due to amoxicillin-clavulanic
51 acid, and hyperthyroidism due to amiodarone). However, the reporting of
52 known ADRs can help to identify local problems related to the use of specific
53 drugs. For example, in our hospital haemorrhages related to low-weight
54 molecular heparins led to an analysis of the severe cases in order to identify
55 possible risk factors. On the other hand, two previously unknown reactions
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3 associated with old drugs that were reported in the second period led to the
4 withdrawal of the market of one drug and an update of the summary of product
5 characteristics in the other one. This point is interesting because it shows that
6 even old drugs must be kept under surveillance through their entire life-span to
7 detect some possible previously unknown reactions.
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14 Obviously our study has some limitations. First of all, it was carried out in only
15 one hospital with specific characteristics (a teaching tertiary hospital; the
16 biggest one in our geographical area). Additionally, the Catalan Centre of the
17 Spanish Pharmacovigilance System is located in the hospital. Therefore, our
18 findings could not be generalized to other hospitals. Secondly, since our study
19 was a time series study without a control group, we can not rule out the
20 influence of other factors in the observed results. Nevertheless, the number of
21 the spontaneous ADRs reported by the other Catalan hospital to the
22 Pharmacovigilance regional Centre during the two study's periods did not
23 increase. Thirdly, the number of signals identified was low and we can not
24 confirm the effect of intervention on its detection. Fourthly, we did not collect
25 information on the category of physicians, medical speciality and other
26 characteristics of the reporters that might have influenced the results. In spite
27 of all these limitations, our study generates new information on the effect of a
28 specific intervention on the features of the spontaneously reported ADRs, the
29 drugs involved and the signals identified. On the one hand, that confirms the
30 usefulness of the implementation of these types of strategies to improve
31 reporting of ADRs in hospitals. On the other hand, these results can be and
32 even should be used as an argument when stimulating the spontaneous
33 reporting by health care professionals by means of supporting evidence of the
34 usefulness of pharmacovigilance activities.
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55 As a conclusion, an intervention based on educational activities and economic
56 incentives led not only to a quantitative improvement in spontaneous reporting
57 of ADRs by hospital physicians but also to a qualitative improvement in terms of
58 seriousness of reactions identified affecting different organs or systems, and
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3 type of drugs involved, including those most recently marketed. Moreover, a
4 number of signals were generated during the intervention and they contributed
5 to the adoption of decisions by the regulatory authorities on either the
6 withdrawal of drugs from the market or changes in the information contained in
7 the summary of product characteristics of some drugs. Future studies should
8 analyse the effect of other types of intervention on spontaneous reporting of
9 ADRs in hospitals, the number of identified signals and quickness of their
10 recognition.
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26 directly relevant to the content of this study.
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Table 1. Adverse drug reactions classified by organ or system affected

| Organ or system | First period | | Second period | |
|-------------------------------------|--------------|--------|---------------|--------|
| | N | (%) | N | (%) |
| Cutaneous reactions | 44 | (20.0) | 128 | (18.4) |
| Haematological reactions | 23 | (10.5) | 68 | (9.8) |
| Gastrointestinal reactions | 19 | (8.6) | 68 | (9.8) |
| Cardiovascular reactions | 27 | (12.3) | 67 | (9.7) |
| Hepatic reactions | 12 | (5.5) | 64 | (9.2) |
| Neurological reactions | 26 | (11.8) | 58 | (8.4) |
| Metabolic and nutritional reactions | 10 | (4.5) | 43 | (6.2) |
| Respiratory reactions | 19 | (8.6) | 39 | (5.6) |
| General disorders | 9 | (4.1) | 37 | (5.3) |
| Urinary reactions | 4 | (1.8) | 32 | (4.6) |
| Endocrinological reactions | 1 | (0.5) | 26 | (3.7) |
| Psychiatric reactions | 12 | (5.5) | 24 | (3.5) |
| Others | 14 | (6.3) | 40 | (5.8) |
| Total | 220 | (100) | 694 | (100) |

Table 2. Most frequent adverse reactions

| Adverse reaction | First period (N=220) | | Second period (N=694) | |
|------------------------------|-------------------------|-------|--------------------------|-------|
| | N | (%) | N | (%) |
| Erythematous rash | 5 | (2.3) | 31 | (4.5) |
| Rash | 6 | (2.7) | 25 | (3.6) |
| Hepatitis | 3 | (1.4) | 20 | (2.9) |
| Thrombocytopenia | 2 | (0.9) | 19 | (2.7) |
| Hepatic enzymes increased | 6 | (2.7) | 18 | (2.6) |
| Acute renal failure | 4 | (1.8) | 18 | (2.6) |
| Hepatitis cholestatic | 3 | (1.4) | 17 | (2.4) |
| Gastrointestinal haemorrhage | 2 | (0.9) | 17 | (2.4) |
| Diarrhoea | 3 | (1.4) | 16 | (2.3) |
| Anaphylactic shock | 4 | (1.8) | 15 | (2.2) |
| Heart failure | 2 | (0.9) | 14 | (2.0) |
| Hyperthyroidism | 1 | (0.5) | 14 | (2.0) |
| Urticaria | 10 | (4.5) | 12 | (1.7) |
| Angioedema | 9 | (4.1) | 11 | (1.6) |
| Bronchospasm | 9 | (4.1) | 10 | (1.4) |
| Haematoma | 8 | (3.6) | 9 | (1.3) |
| Atrioventricular block | 4 | (1.8) | 8 | (1.2) |
| Encephalopathy | 4 | (1.8) | 8 | (1.2) |
| Extrapyramidal disorder | 5 | (2.3) | 4 | (0.6) |
| Retroperitoneal haemorrhage | 6 | (2.7) | 3 | (0.4) |
| Distonia | 5 | (2.3) | 3 | (0.4) |
| Hypotension | 9 | (4.1) | 2 | (0.3) |

Only adverse reactions present in at least five reports of any period are displayed.

Table 3. Suspect drugs by therapeutic subgroup

| Therapeutic subgroup | First period | | Second period | |
|--|--------------|--------|---------------|--------|
| | N | (%) | N | % |
| Systemic antibiotics (J01) | 62 | (21.8) | 149 | (17.0) |
| Antithrombotics (B01) | 30 | (10.5) | 69 | (7.9) |
| Cardiac therapy (C01) | 17 | (6.0) | 47 | (5.4) |
| Antiinflammatories and antirheumatics (M01) | 12 | (4.2) | 46 | (5.2) |
| Psychoanaleptics (N06) | 8 | (2.8) | 44 | (5.0) |
| Analgesics (N02) | 17 | (6.0) | 35 | (4.0) |
| Drugs acting on the renin-angiotensin system (C09) | 10 | (3.5) | 35 | (4.0) |
| Antiepileptics (N03) | 9 | (3.1) | 35 | (4.0) |
| Antineoplastics (L01) | 8 | (2.8) | 34 | (3.9) |
| Antimycobacterials (J04) | 14 | (4.9) | 32 | (3.6) |
| Systemic antivirals (J05) | 7 | (2.5) | 31 | (3.5) |
| Immunosuppressive drugs (L04) | 4 | (1.4) | 29 | (3.3) |
| Diuretics (C03) | 9 | (3.1) | 27 | (3.1) |
| Psycholeptics (N05) | 9 | (3.1) | 24 | (2.7) |
| Drugs for obstructive airway diseases (R03) | 6 | (2.1) | 22 | (2.5) |
| Beta blocking drugs (C07) | 3 | (1.1) | 22 | (2.5) |
| Immunostimulants (L03) | 0 | (-) | 18 | (2.1) |
| Systemic corticosteroids (H02) | 4 | (1.4) | 16 | (1.8) |
| Lipid modifying drugs (C10) | 6 | (2.1) | 15 | (1.7) |
| Systemic antihistamines (R06) | 11 | (3.9) | 4 | (0.5) |
| Others | 39 | (13.7) | 143 | (16.3) |
| Total | 285 | (100) | 877 | (100) |

Table 4. Most frequent suspect drugs

| Drug | First period | | | Second period | | |
|-----------------------------|------------------------------|-------|--------------------|------------------------------|-------|--------------------|
| | Suspect exposures (N=285) | | Reports (N=200) | Suspect exposures (N=877) | | Reports (N=631) |
| | N | (%) | % | N | (%) | % |
| Amiodarone | 11 | (3.9) | 5.5 | 36 | (4.1) | 5.7 |
| Amoxicillin-clavulanic acid | 16 | (5.6) | 8.0 | 35 | (3.9) | 5.5 |
| Metamizole | 12 | (4.2) | 6.0 | 23 | (2.6) | 3.6 |
| Enoxaparin | 16 | (5.6) | 8.0 | 21 | (2.4) | 3.3 |
| Enalapril | 4 | (1.4) | 2.0 | 21 | (2.4) | 3.3 |
| Ibuprofen | 2 | (0.7) | 1.0 | 18 | (2.1) | 2.9 |
| Acenocoumarol | 2 | (0.7) | 1.0 | 15 | (1.7) | 2.4 |
| Acetylsalicylic acid | 6 | (2.1) | 3.0 | 14 | (1.6) | 2.2 |
| Prednisone | 2 | (0.7) | 1.0 | 13 | (1.5) | 2.1 |
| Phenytoin | 3 | (1.1) | 1.5 | 10 | (1.1) | 1.6 |
| Levofloxacin | 3 | (1.1) | 1.5 | 10 | (1.1) | 1.6 |
| Pyrazinamide | 3 | (1.1) | 1.5 | 10 | (1.1) | 1.6 |
| Furosemide | 3 | (1.1) | 1.5 | 9 | (1.0) | 1.4 |
| Azithromycin | 1 | (0.4) | 0.5 | 9 | (1.0) | 1.4 |
| Fluoxetine | 1 | (0.4) | 0.5 | 9 | (1.0) | 1.4 |
| Ciprofloxacin | 6 | (2.1) | 3.0 | 8 | (0.9) | 1.3 |
| Spirolactone | 1 | (0.4) | 0.5 | 8 | (0.9) | 1.3 |
| Linezolid | 0 | (-) | - | 8 | (0.9) | 1.3 |
| Diclofenac | 6 | (2.1) | 3.0 | 7 | (0.8) | 1.1 |
| Hydrochlorothiazide | 3 | (1.1) | 1.5 | 7 | (0.8) | 1.1 |
| Cefepime | 2 | (0.7) | 1.0 | 7 | (0.8) | 1.1 |
| Rifampicin-isoniazid | 1 | (0.4) | 0.5 | 7 | (0.8) | 1.1 |
| Clarithromycin | 5 | (1.8) | 2.5 | 6 | (0.7) | 1.0 |
| Carbamazepine | 3 | (1.1) | 1.5 | 6 | (0.7) | 1.0 |
| Digoxin | 3 | (1.1) | 1.5 | 6 | (0.7) | 1.0 |
| Moxifloxacin | 2 | (0.7) | 1.0 | 6 | (0.7) | 1.0 |
| Azathioprine | 1 | (0.4) | 0.5 | 6 | (0.7) | 1.0 |
| Vancomycin | 1 | (0.4) | 0.5 | 6 | (0.7) | 1.0 |
| Ceftriaxone | 0 | (-) | - | 6 | (0.7) | 1.0 |
| Methotrexate | 0 | (-) | - | 6 | (0.7) | 1.0 |
| Tacrolimus | 0 | (-) | - | 6 | (0.7) | 1.0 |
| Thiethylperazine | 8 | (2.8) | 4.0 | 3 | (0.3) | 0.5 |

Only drugs with at least six suspect exposures in any period are displayed.

Table 5. Most frequent drug-reaction associations

| Drug | Reaction | First period (N=200 reports) | | Second period (N=631 reports) | |
|-----------------------------|--|---------------------------------|-------|----------------------------------|-------|
| | | N | (%) | N | (%) |
| Amoxicillin-clavulanic acid | Hepatic enzymes increased, hepatitis or cholestatic hepatitis | 2 | (1.0) | 14 | (2.2) |
| Amiodarone | Hyperthyroidism | 1 | (0.5) | 14 | (2.2) |
| Enoxaparin | Haemoperitoneum, retroperitoneal haemorrhage or haematoma | 11 | (5.5) | 8 ^a | (1.3) |
| Acenocoumarol | Haemoperitoneum, retroperitoneal haemorrhage or haematoma | 1 | (0.5) | 7 ^a | (1.1) |
| Amiodarone | QT interval prolonged, <i>torsade de pointes</i> or ventricular fibrillation | 0 | (-) | 7 | (1.1) |
| Phenytoin | Erythematous, maculopapular or unspecified rash | 1 | (0.5) | 7 | (1.1) |
| Metamizole | Erythematous, maculopapular or unspecified rash | 1 | (0.5) | 7 | (1.1) |
| Enalapril | Acute renal failure | 0 | (-) | 6 | (1.0) |
| Prednisone | Hyperglycaemia, diabetes mellitus or diabetes mellitus aggravated | 0 | (-) | 6 | (1.0) |
| Acetylsalicylic acid | Gastrointestinal haemorrhage | 1 ^b | (0.5) | 5 ^c | (0.8) |
| Enalapril | Cough | 0 | (-) | 5 | (0.8) |
| Enoxaparin | Cerebral haemorrhage | 0 | (-) | 5 ^d | (0.8) |
| Thiethylperazine | Distonia and/or dyskinesia | 7 | (3.5) | 3 | (0.5) |
| Amoxicillin-clavulanic acid | Angioedema or laryngeal oedema | 5 | (2.5) | 0 | (-) |

Only associations present in at least five reports of any period are displayed.

^a Concomitant administration of enoxaparin and acenocoumarol in two cases. ^b Enoxaparin concomitantly administered. ^c Drugs concomitantly administered: clopidogrel (in one case); clopidogrel, enoxaparin and abciximab (in one case); enoxaparin and streptokinase (in one case). ^d Drugs concomitantly administered: tenecteplase and acetylsalicylic acid (in four cases); drotrecogin alfa activated (in one case).

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