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A strategy to improve the detection of drug-induced hepatotoxicity

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ABSTRACT

Aims: to report a new strategy for the detection of hepatotoxic adverse drug reactions (ADRs) in hospitalized patients improving the results obtained with other methods.

Design: the model is based on the identification of a single alert signal in various target clinical departments over a 12-month period. Each patient was later interviewed following a set protocol. The main results analyzed were the drugs suspected of ADR; causal relationship between suspected drugs and ADRs; ADR severity, and incidence of hepatotoxic ADR/100,000 inhabitants.

Subjects: population served by a university-affiliated urban teaching hospital (519,381 inhabitants).

Results: The overall ratio of confirmed/suspected ADRs was high (35/80). The most commonly reported drug was amoxicillin-clavulanic acid (4 cases). With regard to causality, 2 suspected cases were classified as definite and 14 as probable. The distribution according to the severity of hepatotoxicity was 6 severe and 29 mild cases. The incidence of hepatotoxic ADRs/100,000 inhabitants as revealed by our method was much higher *versus* voluntary report (6.74 and 1.79, respectively).

Conclusions: our method has proven effective for improving the detection of hepatotoxic ADRs, and may be extended to other types of adverse reactions.

Key words: Drug-induced hepatotoxicity. Pharmacovigilance.

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INTRODUCTION

Hepatotoxicity is one of the most frequent and serious adverse drug reactions (ADRs) (1). Recent years have witnessed a growing interest in its detection and understanding (2-5). In hospitalized patients, detection is usually achieved through intensive record taking and in the general population by voluntary reports. Both methods have shortcomings leading to a deficient epidemiological understanding of drug-induced hepatotoxicity (6).

The aim of this work is to communicate a strategy that improves the results obtained with those methods in the detection of hepatotoxic ADRs.

METHODS

A pilot study was carried out, promoted, and coordinated by the Clinical Pharmacology Department of "Virgen Macarena" University Hospital (Seville, Spain) to test a model for the detection of hepatotoxic ADRs. The main demographic and clinico-therapeutic characteristics of the patients included are summarized in table I.

The model, applied between June 2002 and July 2003, is based on the identification of a *single alert signal* in various *target departments* within the hospital.

Alert signals raising suspicion of drug-induced liver toxicity may include the following (7): a) > 76 U/L of GPT; b) > 0.6 mg/dL of conjugated bilirubin; c) > 80 U/L of GOT, > 2 mg/dL of total bilirubin, and 516 U/L of alkaline phosphatase (simultaneously).

The presence of just one of them was sufficient to generate suspicion.

The choice of *target departments* was based on the number of consultations for suspected drug-induced hepatotoxicity received in the Hepatology Unit (Gastroenterology Department). They comprised the following: In-

Table I. Main demographic and clinico-pharmacologic characteristics of patients

Age[a]	*Sex*[b]	*Drug*	*Indication*	*Type of liver lesion*	*Severity*
35	F	Amox-clav[c]	Respiratory infection	Mixed	Severe
54	F	Amox-clav[c]	Urinary tract infection	Cholestatic	Severe
63	M	Amox-clav[c]	Pneumonia	Cholestatic	Mild
41	F	Amox-clav[c]	Dental phlegmon	Cholestatic	Mild
80	F	Atorvastatin	Hyperlipemia	Hepatocellular	Mild
55	F	Atorvastatin	Hyperlipemia	Hepatocellular	Mild
48	M	Atorvastatin	Hyperlipemia	Hepatocellular	Mild
64	M	Ticlopidine	Coronary stent	Cholestatic	Severe
72	F	Ticlopidine	Vasculocerebral accident	Cholestatic	Severe
63	F	Ticlopidine	Vasculocerebral accident	Cholestatic	Mild
64	M	Ranitidin	Epigastralgia	Mixed	Mild
37	F	Ranitidin	Epigastralgia	Cholestatic	Mild
62	M	Clopidogrel	Vasculocerebral accident	Cholestatic	Severe
67	F	Clopidogrel	Coronary stent	Cholestatic	Mild
60	F	Lorazepam	Anxiety	Hepatocellular	Mild
75	M	Lorazepam	Anxiety	Hepatocellular	Mild
52	F	Loratadin	Rhinoconjunctivitis	Hepatocellular	Mild
43	M	Loratadin	Rhinoconjunctivitis	Hepatocellular	Mild
37	M	Valproic Ac.	Epilepsy	Hepatocellular	Mild
24	F	Carbamazepine	Epilepsy	Cholestatic	Severe
39	M	Itraconazole	Genital mycosis	Hepatocellular	Mild
45	M	Captopril	Blood hypertension	Mixed	Mild
62	F	Levodopa	Parkinson	Mixed	Mild
73	F	Verapamil	Blood hypertension	Cholestatic	Mild
47	F	Methotrexate	Erythematous lupus	Hepatocellular	Mild
66	M	Diclofenac	Knee osteoarthritis	Hepatocellular	Mild
53	M	Pravastatin	Hyperlipemia	Hepatocellular	Mild
54	F	Paroxetine	Depression	Hepatocellular	Mild
26	F	Cypr-medrox[d]	Amenorrhea	Hepatocellular	Mild
52	M	Ciprofloxacin	Urinary tract infection	Hepatocellular	Mild
33	M	Diazepam	Muscle contracture	Hepatocellular	Mild
42	F	Tetrazepam	Anxiety	Hepatocellular	Mild
71	F	Ciprofloxacin	Gastroenteritis	Hepatocellular	Mild
41	M	Ciprofloxacin	Urinary tract infection	Hepatocellular	Mild
27	M	Hydroxizine	Urticaria	Cholestatic	Mild

a: In years; b: F: female; M: male; c: Amoxicillin-clavulanic; d: Cyproterone-medroxyprogesterone

ternal Medicine (Lipids Unit), Neurology, Dermatology, Oncology, and the Hepatology Unit itself.

When doctors in these departments detected one or several *alert signals*, they flagged the first page of the patient's clinical record with a pre-established mark. Trained staff (interns) at the Clinical Pharmacology Department paid weekly visits to *target departments*, gathered clinical record data, and called each patient to a subsequent interview under a set protocol for the analysis and evaluation of this type of ADR. When any *non-target department* spontaneously notified a suspected hepatotoxic ADR, it was done through the Hepatology Unit, and the case followed the course described above. Exceptionally, some suspected cases at these *non-target departments* were directly reported to the Clinical Pharmacology Department. The flow of information is diagrammatically shown in figure 1.

The overall information was analyzed to reveal:

—The drugs suspected of ADR (identification and number).

—The causal relationship between suspected drugs and ADRs using the María & Vitorino scale. Depending

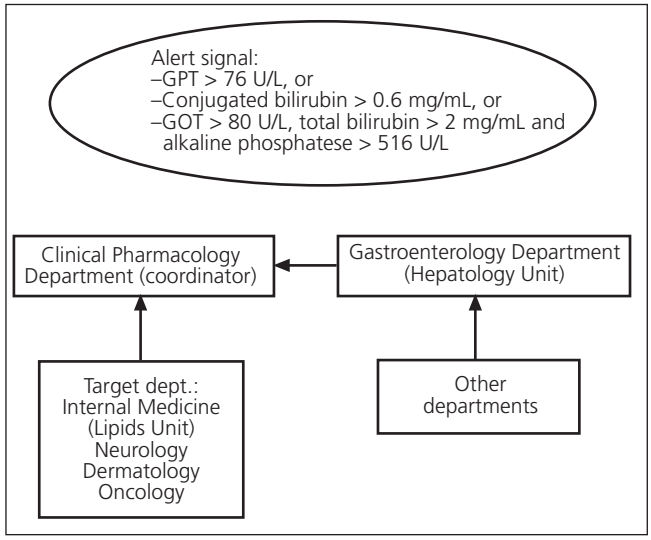

Fig. 1.- Warning sign and report pathways for suspected drug-related hepatotoxicity cases as followed in this study.
Señal de alerta y vías de notificación de las sospechas de hepatotoxicidad por medicamentos seguidas en el estudio.

on the result, the relationship was classified as definite, probable, possible, improbable, or ruled out (8).

—The seriousness of the ADR (severe, moderate, or slight) (9).

—The incidence of the hepatotoxic ADR/100,000 inhabitants.

—The number of suspected cases confirmed/number notified ratio for each department.

RESULTS

During the study period, 80 suspected hepatotoxic ADRs were collected, of which 45 were excluded when found to have a non-pharmacological etiology. Of the remaining 35, 57.1% were men, and the mean age for ADR development was 54.5 ± 17.8 years.

The drugs involved were amoxicillin-clavulanic acid (4 cases); ticlopidine, atorvastatin, and ciprofloxacin (3 cases each); ranitidine, clopidogrel, lorazepam, and loratadine (2 cases each); diazepam, tetrazepam, valproic acid, carbamazepine, hydroxyzine, itraconazole, captopril, levodopa, verapamil, methotrexate, diclofenac, pravastatin, paroxetine, and ciproterone-medroxyprogesterone (1 case each).

With regard to causality, 2 suspected cases were classified as definite, 14 as probable, and 19 as possible.

The distribution according to the severity of hepatotoxicity was 6 serious and 29 mild cases.

In this period, the incidence of hepatotoxic ADRs/100,000 inhabitants was 6.74 (35 in a population of 519,381 inhabitants) (10).

The distribution of the confirmed ADRs/notified ADRs ratio for the different departments was: Gastroenterology (20/30), Internal Medicine (9/21), Neurology (4/15), Dermatology (2/10), and Oncology (0/4).

DISCUSSION

The results confirm the correct choice of *target departments,* with the exception of Oncology, in which adverse effects from medication are very frequent; for this reason, only those with grade III and IV toxicity (according to the WHO classification of antineoplastic drugs) have been considered. Moreover, the overall proportion of confirmed ADRs/suspected ADRs was high (35/80), thus reinforcing the method's applicability.

The method of intensive record taking for drug-induced ADRs is easily organized and highly sensitive. Nevertheless, it does have a number of shortcomings: little representativeness of the general population, scant efficiency, low sensitivity for new or unexpected ADRs, and difficult permanent maintenance (6). The method used in this study, which may be categorized as selective intensive recording, overcomes some of these shortcomings: it enables this type of suspected ADRs to be reported, it may be maintained permanently, since it does not overload the daily work of doctors, and the number of hepatotoxic ADRs detected approaches the actual incidence.

The method of voluntary reporting has the advantage of simplicity. However, it has two drawbacks: under-notification of ADRs, and abundant biases resulting in low efficiency. The incidence of hepatotoxic ADRs/100,000 inhabitants was higher with our method than with voluntary reporting. Thus, over the same period of time, our method yielded a value of 6.74 (35 in a population of 519,381 inhabitants), whereas the system of voluntary notification yielded 1.79 (262 in a population of 40,202,160 inhabitants) (11,12). Nevertheless, if results are not to be interpreted incorrectly, it should be remembered that these two methods have different aims: that of the present study is to know the approximate real incidence of hepatotoxic ADRs in the area served by our hospital, whereas voluntary notification attempts to detect serious and infrequent ADRs in the general population.

The main shortcoming of our method is that it does not detect hepatic ADRs of low clinical significance in *non-target departments* and in outpatient care. In contrast, it does detect all serious-to-moderate hepatotoxic ADRs presented in the milieu where it is implemented, and all those of whatever seriousness generated in *target departments*.

In conclusion, our method demonstrated its validity for improving and increasing the detection of hepatotoxic ADRs, and may be extended to other types of ADRs.

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