

## **La farmacovigilancia en España: organización, metodología y generación de señales**

Desde su creación hasta la actualidad el Sistema Español de Farmacovigilancia de Medicamentos de Uso Humano ha mantenido una productividad científica constante, que se ha plasmado en múltiples publicaciones en revistas médicas nacionales e internacionales. Para la edición de este libro los coordinadores hemos seleccionado un total de 35 artículos, quizás los más relevantes, como reflejo de esa actividad científica. Se han dividido en dos apartados: metodológicos y asociados a la generación de señales. Junto a las referencias hemos incluido, cuando estaban disponibles, sus resúmenes. Esperamos que esta iniciativa sirva para difundir la labor científica realizada y para orientar a las personas que inician su formación en farmacovigilancia.

### **1. Organización y metodología**

- Laporte JR, Porta M, Capellà D, Frati ME. Voluntary reporting of adverse reactions to drugs. *Med Clin (Barc)* 1982;79:287-91.
- Sanz E, Artiles R, Boada J. Comparison of 6 decision algorithms used in the diagnosis of causality in adverse drug reactions. *Therapie* 1987;42:51-5.

- de Abajo FJ, Frías J, Lopo CR, Garijo B, Castro MA, Carcas A, et al. Adverse reactions to drugs as a reason for consulting the emergency services of a general hospital. *Med Clin (Barc)* 1989; 92:530-5.  
*The reports from the emergency service of La Paz General Hospital were daily reviewed for 4 months to investigate the number of consultations which, on the judgement of the physician on care, were due to adverse reactions to drugs. An overall number of 11,326 patients consulted. In 438 (3.9%) it was considered that the consultation was due to one or more definite, likely or possible adverse drug reactions. In 69 patients (15.8%), the reactions were considered to be severe, and 54 (12.3%) required admission; 59 reactions (13.4%) were moderate, and 310 (70.8%) were mild. The most common localizations were the skin and its appendages (37.7%) and gastrointestinal tract (25.3%). The most commonly implicated pharmacologic groups were analgesic and non-steroidal anti-inflammatory drugs (33.6%) and antimicrobials (22.1%). The incidence of adverse reactions was significantly higher in women (4.4% vs 3.3% in males,  $p$  less than 0.01). Depending on the age groups (14-29, 30-59, greater than or equal to 60 years) the incidence of nonallergic adverse reactions was significantly higher in patients aged 60 years or more (1.5%, 2%, 2.9%;  $\chi^2 = 15.2$ ,  $gl = 2$ ,  $p$  less than 0.001). In presumably allergic adverse reactions, the incidence was significantly higher among those under 30 years (2.9%, 2.2%, 0.5%;  $\chi^2 = 50.2$ ;  $gl = 2$ ,  $p$  less than 0.0001). The incidence of severe adverse reactions was significantly higher in patients over age 60 years (0.2%, 0.6%, 1.2%,  $\chi^2 = 29.2$ ,  $gl = 2$ ,  $p$  less than 0.001). In 32% of cases the adverse reactions might have been prevented.*
- Laporte JR, Capellà D. The Spanish drug surveillance system. *Med Clin (Barc)* 1994;103:335-6.
- Aguirre C, Haramburu F. Official systems of Pharmacovigilance in France and in Spain. Comparisons of spontaneous reporting in two regional centers: Pays Basque and Bordeaux. *Therapie* 1995;50:563-9.  
*This report compares the drug surveillance systems in France and Spain. The Spanish causality assessment method is explained. The*

*Spanish and French drug surveillance systems are rather similar, but with some variations in the data analysis and differences between causality algorithms used. Spontaneous reporting in two drug surveillance centres, Aquitaine (Bordeaux, France) and in the Spanish Basque Country (SBC) (type of reports, reporting form) is compared. Reports received by the two centres during the year 1992 are presented. The SBC Centre has received more reports and differences in the source and type of effects were observed.*

- Montero D, Madurga M, Palop R, Martín-Serrano G, De Abajo FJ. Organisation of Spanish Pharmacovigilance in the multinational situation: an overview. *Drug Inform J* 1997; 31:889-93.
- Álvarez-Requejo A, Carvajal A, Bégau B, Moride Y, Vega T, Arias LH. Under-reporting of adverse reactions. Estimate based on a spontaneous scheme and a sentinel system. *Eur J Clin Pharmacol* 1998;54:483-8.

*Spontaneous reporting is the most common method used in pharmacovigilance and the best one to generate signals on new or rare adverse drug reactions (ADRs). Under-reporting is a major drawback of this system. The objective of this study was to quantify the extent of under-reporting in general practice and to assess the factors which influence it. Details of ADRs collected through a short intensive survey were compared with primary care spontaneous reports received by the Castilla y Leon Regional Pharmacovigilance Centre during a 12-month reference period. The survey was undertaken by a random sample of 146 general practitioners (GPs), providing care to 149,487 people. The pharmacovigilance centre received reports concerning the whole regional population (2.5 million) covered by primary health care. The under-reporting coefficient (U) was estimated as the ratio between the number of effects observed by physicians in the survey and those spontaneously reported to the pharmacovigilance centre. The overall under-reporting rate was 1144 [95% confidence interval (CI): 928-1409]. Under-reporting was greater for psychiatric (2119; 945-4752) and gastrointestinal (1946; 1424-2659) disorders. Severe effects were more reported (U = 605; 151-2431)*

*than moderate (863; 473-1575) and mild (1209; 973-1503) ones. The under-reporting rate was lower for drugs recently marketed (706; 406-1230) and slightly lower for unlabelled effects (1031; 641-1657). The under-reporting rate of ADRs is considerable, though not homogeneous for the different cases. This should be taken into account when comparing adverse effects (AEs) for different drugs. Under-reporting seems to be positively selective, as it involves mainly the less severe and better-known effects, preserving the value of spontaneous reporting for signal detection.*

- Morales-Olivas FJ, Martínez-Mir I, Ferrer JM, Rubio E, Palop V. Adverse drug reactions in children reported by means of the yellow card in Spain. *J Clin Epidemiol* 2000; 53:1076-80.  
*To analyze the case reports concerning children (14 years or younger) in the Spanish Pharmacovigilance System over a 10-year period (1982-1991). The study of 1419 reports of adverse drug reaction (9.8% of all those received) showed the most commonly involved organs and systems to be the skin, digestive tract, and nervous system (62.8%). The most commonly involved pharmacological groups were antibiotics, respiratory medications, and vaccines (69%). The absolute number of reports is higher in children between 1 and 4 years of age (37.9%). There were more reports among males than in females. Less than 5% of the reports notified directly life-threatening or fatal reactions. Adverse drug reactions are not common in pediatric patients, and most are mild. However, due to limitations of clinical trials in children, pharmacoepidemiological studies may be the only source of information on the benefit-risk profile of drugs received by these patients, and as such require special attention.*
- de Abajo FJ. Improving pharmacovigilance practice beyond spontaneous reporting. *Inter J Pharmaceutical Medicine* 2005;19:209-18.
- Vallano A, Cereza G, Pedrós C, Agustí A, Danés I, Aguilera C, et al. Obstacles and solutions for spontaneous reporting of adverse reactions in the hospital. *Br J Clin Pharmacol* 2005; 60:653-8.

*To describe the opinions of hospital physicians concerning problems regarding the spontaneous reporting of adverse drug reactions (ADRs) and ways to solve them. A qualitative study was carried out. Fifteen focus groups were conducted among physicians working in a tertiary teaching hospital. A total of 208 physicians from different medical specialities participated. The focus group discussions were recorded by three different observers and the transcripts of each session were analysed for issues and themes emerging from the text. Four types of obstacles to spontaneous reporting were considered particularly important: (i) problems with the ADR(S) diagnosis; (ii) problems with the usual workload and lack of time; (iii) problems related to the organization and activities of the pharmacovigilance system; (iv) and problems related to potential conflicts. The potential solutions suggested for improving spontaneous reporting were to define the kind of ADR(S) which should be reported, to facilitate an easy contact and quick access to the hospital pharmacovigilance system, to facilitate information and support for reporting and feedback of pharmacovigilance activities. The perception of the different obstacles by the hospital physicians is an important factor in determining the causes of the underreporting of ADRs and addressing these obstacles could lead to an improvement in spontaneous reporting. A closer relationship between the doctors and the pharmacovigilance centre is suggested as a means of solving these problems. More information is needed to improve the spontaneous reporting of ADR(S) in specialized healthcare.*

- Esteban Calvo C, Ibáñez Ruiz C, Salgueiro Vázquez E, Manso Rodríguez G. Impact of the spanish pharmacovigilance system recommendations on the publication of cases of adverse drug reaction. *Aten Primaria* 2008;40:555-8.

*To assess the impact of the recommendations that, the Technical Committee of the Spanish Pharmacovigilance System sent, in 2004, to the editors of Spanish medical journals on the minimum information required for publication of adverse drug reaction case reports. National suspected adverse drug reactions database (FEDRA). Published adverse drug reaction reports registered in FEDRA,*

*published in the years before (2003) and after (2005) the recommendations were issued. The following data elements were analysed: sex, age, dose, disease treated with the suspected drug, length of treatment and adverse drug reaction, temporal sequence, withdrawal effect, and alternative causes. The results of the 2 years were compared. The information in the case reports published between years 2003 and 2005 was not significantly different. The data elements more often incomplete were dose, length of treatment, as well as length of adverse reaction. Approximately one third of the published case reports included full information. There seems to be a need to improve the data elements content of published adverse drug reactions case reports, so that such documentation can contribute to improve the assessment of alert signals.*

- Pedrós C, Vallano A, Cereza G, Mendoza-Aran G, Agustí A, Aguilera C, et al. An intervention to improve spontaneous adverse drug reaction reporting by hospital physicians: a time series analysis in Spain. *Drug Saf* 2009;32:77-83.

*Spontaneous reporting of adverse drug reactions (ADRs) in hospitals is scarce and several obstacles to such reporting have been identified previously. To assess the effectiveness of a multifaceted intervention based on healthcare management agreements for improving spontaneous reporting of ADRs by physicians in a hospital setting. In 2003, the spontaneous reporting of ADRs was included as one of the objectives of hospital physicians at the Vall d'Hebron Hospital, Barcelona, Spain, within the context of management agreements between clinical services and hospital managers. A continuous intervention related to these management agreements, including periodic educational meetings and economic incentives, was then initiated. We carried out an ecological time series analysis and assessed the change in the total number of spontaneous reports of ADRs, and the number of serious ADRs, unexpected ADRs, and ADRs associated with new drugs between a period previous to the intervention (from 1998 to 2002) and the period during the intervention (from 2003 to 2005). A time series analysis with ARIMA (Auto-Regressive Integrated Moving Average) models was performed. The median number of reported ADRs per year increased from 40*

*(range 23-55) in the first period to 224 (range 98-248) in the second period. In the first period, the monthly number of reported ADRs was stable (3.47 per month; 95% CI 1.90, 5.03), but in the second period the number increased progressively (increase of 0.74 per month; 95% CI 0.62, 0.86). In the second period, the proportion of reported serious ADRs increased nearly 2-fold (63.1% vs 32.5% in the first period). The absolute number of previously unknown or poorly known ADRs increased 4-fold in the second period (54 vs 13 in the first period). There was also an increase in the absolute number of suspected pharmacological exposures to new drugs (97 vs 28) and in the number of different new drugs suspected of causing ADRs (50 vs 19). A continuous intervention based on healthcare management agreements with economic incentives and educational activities is associated with a quantitative and qualitative improvement of spontaneous reporting of ADRs by hospital physicians.*

## **2. De la generación de señales a la toma de decisiones**

- Capellà D, Laporte JR, Castel JM, Tristán C, Cos A, Morales-Oliva FJ. Parkinsonism, tremor, and depression induced by cinnarizine and flunarizine. *Br Med J* 1988;297:722-3.
- Capellà D, Torres F, Avila P, Moreno V, Laporte JR. Cough caused by angiotensin-converting enzyme inhibitors. A series of cases collected by spontaneous notification of adverse reactions. *Med Clin (Barc)*1991;96:126-8.

*Cough is one of the possible untoward adverse drug effects of angiotensin converting enzyme inhibitors. We describe the available information on 50 cough episodes attributable to captopril and 18 episodes attributable to enalapril reported to the Spanish Drug Surveillance System. Cough represented 37% and 39% of the reports of side effects of captopril and enalapril, respectively. There was a remarkable female predominance among the patients with cough. Cough developed at very low doses (15 mg of captopril and 5 mg of*

*enalapril daily), although the patients on captopril who developed cough were receiving higher doses than those who presented other side effects. A high proportion of patients (29%) continued with the drug for more than six months after cough had developed, suggesting the need for a wider knowledge of this side effect.*

- Bakke O, Manocchia M, de Abajo FJ, Kaitin K, Lasagna L. Drug safety discontinuations in the United Kingdom, the United States and Spain from 1974 through 1993: a regulatory perspective. *Clin Pharmacol Ther* 1995;58:108-17.

*The objective of the present study was to compare the number of new chemical entities (NCEs) and new biologicals entities (NBEs) approved for marketing during the period 1974 through 1993 in the United Kingdom, the United States, and Spain that were subsequently discontinued (removed from the market, withdrawn, or whose license was allowed to lapse) while a question of safety existed. Of the products approved during the two decades of the study period, a total of 29 drugs were subsequently discontinued for safety reasons in at least one of the three countries (United Kingdom: 20 safety discontinuations; United States: 10; and Spain: 16). These represent 3% to 4% of all drugs introduced in these countries, an increase compared to the period from 1964 through 1983, when approximately 2% of all NCEs were discontinued for safety reasons. The therapeutic classes most commonly associated with safety discontinuations were the nonsteroidal anti-inflammatory drugs (nine drugs), vasodilators (four drugs), and antidepressants (three drugs). U.S. companies or their foreign subsidiaries were involved as originators (patent-holders and/or developers) of approximately 40% of the drugs discontinued for safety reasons.*

- de Abajo FJ, Rodríguez LA, Montero D. Association between selective serotonin reuptake inhibitors and upper gastrointestinal bleeding: population based case-control study. *Br Med J* 1999;319:1106-9.  
*To examine the association between selective serotonin reuptake inhibitors and risk of upper gastrointestinal bleeding. DESIGN: Population based case-control study. General practices included in the UK*

*general practice research database. Subjects: 1651 incident cases of upper gastrointestinal bleeding and 248 cases of ulcer perforation among patients aged 40 to 79 years between April 1993 and September 1997, and 10 000 controls matched for age, sex, and year that the case was identified. Review of computer profiles for all potential cases, and an internal validation study to confirm the accuracy of the diagnosis on the basis of the computerised information. Current use of selective serotonin reuptake inhibitors or other antidepressants within 30 days before the index date. Current exposure to selective serotonin reuptake inhibitors was identified in 3.1% (52 of 1651) of patients with upper gastrointestinal bleeding but only 1.0% (95 of 10 000) of controls, giving an adjusted rate ratio of 3.0 (95% confidence interval 2.1 to 4.4). This effect measure was not modified by sex, age, dose, or treatment duration. A crude incidence of 1 case per 8000 prescriptions was estimated. A small association was found with non-selective serotonin reuptake inhibitors (relative risk 1.4, 1.1 to 1.9) but not with antidepressants lacking this inhibitory effect. None of the groups of antidepressants was associated with ulcer perforation. The concurrent use of selective serotonin reuptake inhibitors with non-steroidal anti-inflammatory drugs increased the risk of upper gastrointestinal bleeding beyond the sum of their independent effects (15.6, 6.6 to 36.6). A smaller interaction was also found between selective serotonin reuptake inhibitors and low dose aspirin (7.2, 3.1 to 17.1). Selective serotonin reuptake inhibitors increase the risk of upper gastrointestinal bleeding. The absolute effect is, however, moderate and about equivalent to low dose ibuprofen. The concurrent use of non-steroidal anti-inflammatory drugs or aspirin with selective serotonin reuptake inhibitors greatly increases the risk of upper gastrointestinal bleeding.*

- de Abajo, Alvarez-Requejo A, Ayani I, Carrillo JA, Carvajal A, Castillo JR, et al. Safety of meningococcal A and C vaccine. Data from the Spanish drug surveillance system. Meningococcal Vaccine Research Group of the Spanish System of Drug Surveillance. *Gac Sanit* 1999;13:462-7.

*Data on meningococcal vaccines safety are scanty. In 1997 several vaccination campaigns took place in Spain. Thus, this situation was*

*used to improve our knowledge about the safety profile of this vaccine. An inquiry was carried out to the Regional Centers of the Spanish Pharmacovigilance System to know the number of vaccinated people and the type and number of suspected cases of adverse reactions. There were 133 identified cases of suspected adverse reactions associated with meningococcal A and C vaccine until June 1st, 1998. Most of them affected the skin (25,3%) or nervous system (similar proportion). Those of allergic reactions accounted for 35,2%. Two cases were considered as severe, although they were resolved without sequelae. Serious risks were not detected. The Spanish Pharmacosurveillance System as an epidemiological surveillance resource has been useful to know the safety problems associated with anti-meningococcal vaccine in the community.*

- Ibañez L, Ballarín E, Perez E, Vidal X, Capella D, Laporte JR. Agranulocytosis induced by pyrithyldione, a sedative hypnotic drug. *Eur J Clin Pharmacol* 2000;55:761-4.

*Pyrithyldione, a sedative-hypnotic drug with a poor clinical pharmacological development, was associated with anecdotal cases of agranulocytosis in the 1940s in the USA, in the 1960s and 1970s in the ex-Democratic Republic of Germany and in the 1980s in Japan. We describe the estimation of the risk of agranulocytosis associated with its use in Spain, which led to its withdrawal from the market. In collaboration with the haematology units of all the hospitals in a defined area ( $3.3\text{-}3.9 \times 10^6$  inhabitants), all cases of agranulocytosis meeting strict diagnostic criteria were identified. Each case - defined as an episode of agranulocytosis - was reviewed by a haematologist without knowledge of previous drug exposures. Cases and age-, gender- and hospital-matched controls were interviewed with a structured questionnaire about previous drug exposures. In addition, in order to estimate the risk of pyrithyldione-associated agranulocytosis through a case-population approach, its consumption among the cases was compared with its consumption among the general population. After a follow-up of  $66.5 \times 10^6$  person-years, 330 cases of agranulocytosis (230 community cases) were assembled. Reliable information on previous exposures was obtained for*

204 cases. They were compared with 1314 controls. Eleven patients (14 cases, 6.9%) and zero controls had been exposed to pyrithyldione. The adjusted OR was 200.11 (CI 95% 22. 62-infinity). All patients were female; none had a fatal outcome; three exhibited positive rechallenge; and all had concomitantly taken other drugs. Although pyrithyldione was a prescription-only medicine, only 8% had been dispensed with medical prescriptions. Assuming the worst case, i.e. that all the exposed cases could be attributed to pyrithyldione, the incidence was 35.6 cases per 100,000 patient-years (95% CI, 18.9-60.9), which gives a risk ratio estimate of 109.6 (57.5-191.5) if compared with the incidence of agranulocytosis among the non-exposed population [3.26 cases (CI 95% 2.83-3.71) per 10(6) inhabitants and per year]. Pyrithyldione was viewed by pharmacists as a mild hypnotic, and apparently this had conferred to this drug an unjustified image of safety. The National Commission of Pharmacovigilance recommended to the Ministry of Health its withdrawal from the market when eight cases of agranulocytosis had been identified. However, it took more than 2 years to withdraw it, and six additional cases occurred in the study area. This illustrates the need for quick regulatory action when pharmacoepidemiological data suggest an unfavourable benefit/risk ratio.

- Castillo JR, Torelló J, Hernandez A. Liver injury caused by ebrotidione: a new example of the utility of the postmarketing surveillance. *Eur J Clin Pharmacol* 2000;56:187-9.
- Carvajal García-Pando A, García del Pozo J, Sánchez AS, Velasco MA, Rueda de Castro AM, Lucena MI. Hepatotoxicity associated with the new antidepressants. *J Clin Psychiatry* 2002;63:135-7. *Safety profiles of classical and new antidepressants are well established. Hepatotoxicity is known to occur. Recently, several cases of severe hepatic injury associated with the new antidepressants have been reported, prompting us to quantify this risk. To estimate the cumulative incidence of hepatic adverse reactions associated with antidepressants, we used cases of hepatic damage collected via spontaneous reporting and included in the Spanish Pharmacovigi-*

*lance System database; for exposure, we have used data from drug sales to the Spanish National Health System. The estimated reported incidence did not show major differences for the antidepressants studied, ranging from 1.28 cases per 100,000 patient-years for sertraline to 4.00 for clomipramine, except for nefazodone, which was the agent that had the highest incidence with 28.96 cases per 100,000 patient-years. The reported incidence of hepatic adverse reactions to nefazodone seems to be higher than that estimated so far. Given the high prevalence of depression and the widespread use of antidepressants, physicians should be alert to the possibility that these medications cause hepatitis and consider early discontinuation of an antidepressant if the condition is suspected.*

- Macià MA, Carvajal A, del Pozo JG, Vera E, del Pino A. Hepatotoxicity associated with nimesulide: data from the Spanish Pharmacovigilance System. *Clin Pharmacol Ther* 2002;72:596-7.
- Gómez-Reino JJ, Carmona L, Valverde VR, Mola EM, Montero MD. Treatment of rheumatoid arthritis with tumor necrosis factor inhibitors may predispose to significant increase in tuberculosis risk: a multicenter active-surveillance report. *Arthritis Rheum* 2003; 48:2122-7.

*The long-term safety of therapeutic agents that neutralize tumor necrosis factor (TNF) is uncertain. Recent evidence based on spontaneous reporting shows an association with active tuberculosis (TB). We undertook this study to determine and describe the long-term safety of 2 of these agents, infliximab and etanercept, in rheumatic diseases based on a national active-surveillance system following the commercialization of the drugs. We analyzed the safety data actively collected in the BIOBADASER (Base de Datos de Productos Biológicos de la Sociedad Española de Reumatología) database, which was launched in February 2000 by the Spanish Society of Rheumatology. For the estimation of TB risk, the annual incidence rate in patients treated with these agents was compared with the background rate and with the rate in a cohort of patients with rheumatoid arthritis (RA) assembled before the era of anti-TNF treat-*

*ment. Seventy-one participating centers sent data on 1,578 treatments with infliximab (86%) or etanercept (14%) in 1,540 patients. Drug survival rates (reported as the cumulative percentage of patients still receiving medication) for infliximab and etanercept pooled together were 85% and 81% at 1 year and 2 years, respectively. Instances of discontinuation were essentially due to adverse events. Seventeen cases of TB were found in patients treated with infliximab. The estimated incidence of TB associated with infliximab in RA patients was 1,893 per 100,000 in the year 2000 and 1,113 per 100,000 in the year 2001. These findings represent a significant increased risk compared with background rates. In the first 5 months of 2002, after official guidelines were established for TB prevention in patients treated with biologics, only 1 new TB case was registered (in January). Therapy with infliximab is associated with an increased risk of active TB. Proper measures are needed to prevent and manage this adverse event.*

- Pedrós C, Cereza G, García N, Laporte JR. Liver toxicity of *Cameilia sinensis* dried etanolic extract. *Med Clin (Barc)* 2003;121:598-9.
- de Abajo FJ, Mesenguer CM, Antiñolo G, García Rodríguez LA, Montero D, Castillo JR, et al. Labor induction with dinoprostone or oxytocine and postpartum disseminated intravascular coagulation: a hospital-based case-control study. *Am J Obstet Gynecol* 2004 191:1637-43.

*This study was undertaken to test the hypothesis of an association between pharmacologic agents used for labor induction, in particular dinoprostone, and postpartum disseminated intravascular coagulation (DIC). A retrospective hospital-based case-control study. Adjusted odds ratios (AOR) were calculated by a conditional logistic regression. Forty valid cases of postpartum DIC were compared against 197 matched controls. Labor was induced in 17% of controls, and 56% of cases (AOR = 7.2; 95% CI: 2.1-24.6). The association was observed for both dinoprostone (AOR = 6.7; 95% CI: 1.7-26.5) and oxytocin (AOR = 8.4; 95% CI: 1.4-50.9). Other risk factors identified were as follows: a maternal age older than 34*

years (AOR = 9.5; 95% CI: 2.4-37.7), complications during pregnancy (AOR = 5.5; 95% CI: 1.3-22.8), and a gestational age of over 40 weeks (AOR = 3.5; 95% CI: 1.1-11.1). Such factors were shown to also have an interaction with the induction of labor. Oxytocin augmentation showed a negative association (AOR = 0.1; 95% CI: 0.02-0.4). The absolute risk attributable to induction was estimated in 5 per 10,000 deliveries. The pharmacologic induction of labor is associated with an increased risk of postpartum DIC, regardless the substance used. Although the absolute risk seems to be quite low, the obstetricians should not neglect it, in particular for the special risk groups identified.

- Laporte JR, Ibáñez L, Vidal X, Vendrell L, Leone R. Upper gastrointestinal bleeding associated with the use of NSAIDs: newer versus older agents. *Drug Saf* 2004;27:411-20.  
*The relative gastrointestinal toxicity of NSAIDs in normal clinical practice is unknown. The aim of this study was to estimate the risk of upper gastrointestinal bleeding associated with NSAIDs and analgesics, with special emphasis on those agents that have been introduced in recent years. Multicentre case-control study. All incident community cases of upper gastrointestinal bleeding from a gastric or duodenal lesion in patients aged >18 years of age (4309 cases). After secondary exclusions, 2813 cases and 7193 matched controls were included in the analysis. Eighteen hospitals in Spain and Italy with a total study experience of 10,734,897 person-years. Odds ratios of upper gastrointestinal bleeding for each drug, with adjustment for potential confounders. For each individual drug the reference category was defined as those not exposed to the drug. The incidence of upper gastrointestinal bleeding was 401.4 per million inhabitants aged >18 years. Thirty-eight percent of cases were attributable to NSAIDs. Individual risks for each NSAID were dose dependent. Ketorolac was associated with the highest risk estimate (24.7; 95% CI 8.0, 77.0). For newer NSAIDs, the risks were as follows: aceclofenac 1.4 (95% CI 0.6, 3.3), celecoxib 0.3 (95% CI 0.03, 4.1), dexketoprofen 4.9 (95% CI 1.7, 13.9), meloxicam 5.7 (95% CI 2.2, 15.0), nimesulide 3.2 (95% CI 1.9, 5.6) and rofecoxib*

7.2 (95% CI 2.3, 23.0). The risk was significantly increased in patients with a history of peptic ulcer and/or upper gastrointestinal bleeding, and in those taking antiplatelet drugs. NSAID-induced upper gastrointestinal bleeding is a common cause of hospital admission. Apart from the patient's history of peptic ulcer, its risk depends on the particular drug and its dose, and on concomitant treatments. Our results do not confirm that greater selectivity for COX-2 confers less risk of upper gastrointestinal bleeding.

- Ibáñez L, Vidal X, Ballarín E, Laporte JR. Agranulocytosis associated with dipyrrone (metamizol). *Eur J Clin Pharmacol* 2005;60:821-9. *Reported estimates of the risk of agranulocytosis associated with metamizol have varied by several orders of magnitude. We assessed this association in a large database for the surveillance of blood dyscrasias. Since 1980, all laboratory units of haematology in a defined area (3.3-4.1x10<sup>6</sup> inhabitants) contribute to the ascertainment of all cases of agranulocytosis meeting strict diagnostic criteria. These cases of patients with agranulocytosis and sex-, age-, hospital- and date-matched controls were interviewed using a structured questionnaire about previous drug exposures, and relative risks were calculated for several categories of exposure to metamizol. After a total follow-up of 78.73x10<sup>6</sup> person-years, 273 community cases of agranulocytosis had been found—of which 96 were excluded for various reasons and 177 were included in the case-control analysis—and were compared with 586 matched controls. Thirty cases of agranulocytosis (16.9%) and nine controls (1.5%) had been exposed to metamizol during the week before the index day. The adjusted relative risk was 25.8 [95% confidence interval (CI), 8.4-79.1], and the attributable incidence was 0.56 (0.4-0.8) cases per million inhabitants and per year. The risk disappeared after more than 10 days since the last dose of metamizol, and it increased with duration of use. Those with agranulocytosis exposed to metamizol had taken the drug for longer periods than the exposed controls. Compared with the cases recently reported from Sweden, the duration of use of metamizol by our exposed cases was substantially shorter, and the use of concomitant medications potentially causing*

*agranulocytosis was lower. In our milieu, agranulocytosis attributable to metazolol is rare. Geographical disparities in its risk estimate can be partly explained by differences in its patterns of use, in terms of dose, duration and concomitant medications.*

- Andrade RJ, Lucena MI, Fernández C, Pelaez G, Pachkoria K, García-Ruiz, E, et al., on behalf of the Spanish group for the Study of Drug-Induced Liver Disease. Drug-induced liver injury: an analysis of 461 incidences submitted to the Spanish registry over a 10-year period. *Gastroenterology* 2005;129:512-21.  
*Progress in the understanding of susceptibility factors to drug-induced liver injury (DILI) and outcome predictability are hampered by the lack of systematic programs to detect bona fide cases. A cooperative network was created in 1994 in Spain to identify all suspicions of DILI following a prospective structured report form. The liver damage was characterized according to hepatocellular, cholestatic, and mixed laboratory criteria and to histologic criteria when available. Further evaluation of causality assessment was centrally performed. Since April 1994 to August 2004, 461 out of 570 submitted cases, involving 505 drugs, were deemed to be related to DILI. The antiinfective group of drugs was the more frequently incriminated, amoxicillin-clavulanate accounting for the 12.8% of the whole series. The hepatocellular pattern of damage was the most common (58%), was inversely correlated with age ( $P < .0001$ ), and had the worst outcome (Cox regression,  $P < .034$ ). Indeed, the incidence of liver transplantation and death in this group was 11.7% if patients had jaundice at presentation, whereas the corresponding figure was 3.8% in nonjaundiced patients ( $P < .04$ ). Factors associated with the development of fulminant hepatic failure were female sex (OR = 25; 95% CI: 4.1-151;  $P < .0001$ ), hepatocellular damage (OR = 7.9; 95% CI: 1.6-37;  $P < .009$ ), and higher baseline plasma bilirubin value (OR = 1.15; 95% CI: 1.09-1.22;  $P < .0001$ ). Patients with drug-induced hepatocellular jaundice have 11.7% chance of progressing to death or transplantation. Amoxicillin-clavulanate stands out as the most common drug related to DILI.*

- Ibáñez L, Vidal X, Ballarín E, Laporte JR. Population-based drug-induced agranulocytosis. *Arch Intern Med* 2005;165: 869-74.  
*Since the publication of a major international case-control study on the risk of agranulocytosis associated with the use of medicines in the 1980s, many new drugs have been introduced in therapeutics. Seventeen units of hematology contribute to the case-control surveillance of agranulocytosis and aplastic anemia in Barcelona, Spain. After a follow-up of 78.73 million person-years, 177 community cases of agranulocytosis were compared with 586 sex-, age, and hospital-matched control subjects with regard to previous use of medicines. The annual incidence of community-acquired agranulocytosis was 3.46:1 million, and it increased with age. The fatality rate was 7.0%, and the mortality rate was 0.24:1 million. The drug most strongly associated with a risk of agranulocytosis was ticlopidine hydrochloride with an odds ratio (OR) of 103.23 (95% confidence interval [CI], 12.73-837.44), followed by calcium dobesilate (OR, 77.84 [95% CI, 4.50-1346.20]), antithyroid drugs (OR, 52.75 [95% CI, 5.82-478.03]), dipyrrone (metamizole sodium and metamizole magnesium) (OR, 25.76 [95% CI, 8.39-179.12]), and spironolactone (OR, 19.97 [95% CI, 2.27-175.89]). Other drugs associated with a significant risk were pyrithyldione, cinepazide, aprindine hydrochloride, carbamazepine, sulfonamides, phenytoin and phenytoin sodium, beta-lactam antibiotics, erythromycin stearate and erythromycin ethylsuccinate, and diclofenac sodium. Individual attributable incidences for all these drugs, which collectively accounted for 68.6% of cases, were less than 1:1 million per year. Agranulocytosis is rare but serious. A few drugs account for two thirds of the cases. Our results also provide reassurance regarding the risk associated with a number of newly marketed drugs.*
- Díaz RL, Gardeazabal J, Manrique P, Ratón JA, Urrutia I, Rodríguez-Sasian JM, et al. Greater allergenicity of topical ketoprofen in contact dermatitis confirmed by use. *Contact Dermatitis* 2006;54:239-43.  
*The use of topical non-steroidal anti-inflammatory drugs (NSAIDs) is very popular in spite of their doubtful efficacy and high number of*

*generally not serious, but preventable, adverse effects, especially photoallergy. The allergenic potential of different topical NSAIDs was determined by performing a retrospective observational study of the period 1996-2001 and comparing the cases of allergy and photoallergy with the use of each topical NSAID. The diagnoses were obtained from a review of the clinical records of patch/photo-patch testing carried out in the dermatology departments of 2 public hospitals in Bizkaia (Spain). The use of the different topical NSAIDs was obtained from invoices sent to the National Health System and the Reporting odds ratio (ROR) and Proportional reporting ratio (PRR) disproportionality estimates of the FEDRA database of the Spanish Pharmacovigilance System. A total of 139 contact reactions to topical NSAIDs were found with ketoprofen being responsible for 28% of the allergies and 82% of the contact photoallergies in spite of not being the most used topical NSAID (third in the ranking, diclofenac was the first). The ROR for ketoprofen was 3.9 (2.4-6.4) and the PRR 3.4 (2.1-5.5), thus confirming the possibility of a warning signal. The results support the need for regulatory action on topical ketoprofen.*

- Manso G, Thole Z, Salgueiro E, Revuelta P, Hidalgo A. Spontaneous reporting of hepatotoxicity associated with antiandrogens: data from the Spanish pharmacovigilance system. *Pharmacoepidemiol Drug Saf* 2006;15:253-9.

*To analyse the type and main features of the hepatotoxicity induced by steroidal and non-steroidal antiandrogens spontaneously reported by physicians, pharmacists and nurses. This analysis could increase the information related to these adverse reactions mainly available from the published isolated cases. Using the Spanish Pharmacovigilance database we searched for spontaneous reports recorded since the date of approval of each antiandrogen up to the present time. We analysed the frequency of liver disorders, the preferred terms coded, the presence of other hepatotoxic drugs, and the characteristics of cases of hepatitis. Liver disorders were the most common adverse reactions associated with flutamide and bicalutamide, but not with cyproterone acetate. 'Hepatitis' and 'cholestatic hepati-*

*tis' were the most frequent terms coded. In 38% of the reports related to cyproterone acetate, 18% of those related to flutamide and 33% of those related to bicalutamide the patient had simultaneously received other hepatotoxic drugs. The disproportionality analysis of hepatitis showed a strong association with flutamide and a weak association with bicalutamide and cyproterone acetate. Mean doses of flutamide and bicalutamide were very close to their defined daily dose (DDD) to treat prostate cancer, although in the case of cyproterone acetate it was slightly higher. The latency period of hepatitis was between 3 and 10 months for the three antiandrogens, and the recovery period was shorter (0.5-3 months). The majority of the reported cases of hepatitis evolved favourably. Our results highlight the hepatotoxic potential of flutamide compared to cyproterone acetate. The data related to bicalutamide should be cautiously considered due to the smaller number of reports.*

- Duque JM, Ferreiro J, Salgueiro E, Manso G. Hepatotoxicity associated with the consumption of herbal slimming products. *Med Clin (Barc)* 2007;128:238-9.
- Carvajal A, Macias D, Gutierrez A, Ortega S, Sainz M, Martín Arias LH, et al. Gynaecomastia associated with proton pump inhibitors: a case series from the Spanish Pharmacovigilance System. *Drug Saf* 2007;30:527-31.

*Proton pump inhibitors (PPIs) are widely used in the management of peptic ulcer and related symptoms. They have been linked to certain endocrine adverse reactions, including gynaecomastia. The aim of the present study is to investigate the association between the use of PPIs and the development of gynaecomastia. Reports of cases of gynaecomastia that had putatively been induced by PPIs and that had been collected by the Spanish Pharmacovigilance System via the 'yellow card' scheme were analysed. Reporting odds ratios (RORs) were calculated as a measure of disproportionality. Twenty-four cases of gynaecomastia associated with PPIs were identified in the database of the Spanish Pharmacovigilance System. Overall, there was a clear temporal sequence of events in all cases and the adverse*

*effect disappeared after drug withdrawal in most of the cases; 14 patients were also receiving other drugs at the time of the adverse effect. The ROR for omeprazole exposure versus no exposure, but not that for other PPIs, showed a statistically significant elevation (ROR adjusted for age 5.23; 95% CI 3.32, 8.26). Considering the widespread use of PPIs, gynaecomastia may affect a large number of patients. In most cases, the condition seems to be reversible with drug withdrawal. Doctors should be aware of this potential adverse reaction when prescribing PPIs to their patients over long periods of time.*

- Boada JN, Boada C, García-Sáiz M, García M, Fernández E, Gómez E. Net efficacy adjusted for risk (NEAR): a simple procedure for measuring risk: benefit balance. *Plos One* 2008;3:3580-6.  
*Although several mathematical models have been proposed to assess the risk:benefit of drugs in one measure, their use in practice has been rather limited. Our objective was to design a simple, easily applicable model. In this respect, measuring the proportion of patients who respond favourably to treatment without being affected by adverse drug reactions (ADR) could be a suitable endpoint. However, remarkably few published clinical trials report the data required to calculate this proportion. As an approach to the problem, we calculated the expected proportion of this type of patients. Theoretically, responders without ADR may be obtained by multiplying the total number of responders by the total number of subjects that did not suffer ADR, and dividing the product by the total number of subjects studied. When two drugs are studied, the same calculation may be repeated for the second drug. Then, by constructing a 2 x 2 table with the expected frequencies of responders with and without ADR, and non-responders with and without ADR, the odds ratio and relative risk with their confidence intervals may be easily calculated and graphically represented on a logarithmic scale. Such measures represent “net efficacy adjusted for risk” (NEAR). We assayed the model with results extracted from several published clinical trials or meta-analyses. On comparing our results with those originally reported by the authors, marked differences were found in some cases, with ADR arising as a relevant factor to balance the clinical*

*benefit obtained. The particular features of the adverse reaction that must be weighed against benefit is discussed in the paper. NEAR representing overall risk-benefit may contribute to improving knowledge of drug clinical usefulness. As most published clinical trials tend to overestimate benefits and underestimate toxicity, our measure represents an effort to change this trend.*

- Manso G, López-Rivas L, Duque JM, Salgueiro E. Spanish reports of hepatotoxicity associated with Herbalife products. *J Hepatol* 2008; 49:289-90.
- Sainz M, del Pozo JG, Arias LH, Carvajal A. Strontium ranelate may cause alopecia. *Br Med J* 2009; 338:1210.

