

# PHARMACOEPIDEMIOLOGY AND DRUG UTILIZATION

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## Use of a spontaneous adverse drug events database for identification of unanticipated drug benefits

We describe an examination of a spontaneous adverse events database in an effort to identify agents with possible hitherto unknown antiangiogenic properties. The surrogate end point was abnormal wound healing. This analysis represents use of this database for identification of a possibly useful *in vivo* side effect. Through thoughtful choice of end points, we believe spontaneous adverse events databases have the capacity for hypothesis generation in a search for unanticipated beneficial drug properties. (*Clin Pharmacol Ther* 2002;71:99-102.)

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By definition, pharmacoepidemiology is the study of the use and effects of drug products in large numbers of persons. Anticipated beneficial and harmful effects are usually quantified from randomized clinical trials designed and powered to show drug efficacy. These trials identify side effects that occur commonly. Spontaneous adverse drug event (ADE) systems provide for the rapid identification of rare and serious safety signals (unanticipated harmful effects).

Unanticipated beneficial effects of drugs may be identified in randomized controlled trials conducted for other reasons or through clinical application of drug pharmacology. Herein we describe an investigation based on spontaneous adverse drug reports of delayed wound healing. Wound healing, like many physiologic processes, relies on angiogenesis, the formation of new blood vessels. Folkman<sup>1,2</sup> and others have advanced tumor angiogenesis and tumor vasculature as targets for neoplastic chemotherapy. Our intent was to identify agents associated with poor wound healing as a surrogate for potential unexpected antiangiogenic properties.

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### BACKGROUND

*Collection of spontaneous reports of adverse drug events.* Spontaneous ADE reports may be sufficient to assign causality for an association between a drug and an event.<sup>3</sup> Reports from alert clinicians are the most important source of information on the adverse effects of a drug during the first few years of marketing.<sup>4</sup> Since 1969, the US Food and Drug Administration (FDA) has maintained a computerized database of postmarketing ADE reports. Drug manufacturers are legally required to report ADEs associated with their drug products to the FDA. The FDA also has systematically solicited spontaneous and voluntary ADE reports directly from health

care professionals. The current program, called MedWatch, was launched in May 1993.<sup>5</sup> This program consolidated a fragmented reporting process into a single form and a single reporting site to report adverse reactions or product quality concerns for drugs, biologic agents, or medical devices used by humans. MedWatch also provides important updates on product safety on its Web site ([www.fda.gov/medwatch/index.html](http://www.fda.gov/medwatch/index.html)).

ADE reports are collected into an electronic database by drug and event. From 1969 through October 1997, the database and associated software were referred to as the Spontaneous Reports System (SRS). The Adverse Events Reports System (AERS), which offered technologic and data quality improvements, replaced the SRS in November 1997. Aggregate (text) versions of the SRS database and AERS data (quarterly) in CD-ROM format are available for purchase from the National Technology Information System (NTIS) ([www.ntis.gov](http://www.ntis.gov)).

**Report review.** The AERS database currently contains more than 2.5 million ADE reports. Of the approximately 260,000 reports the FDA received in 2000, 63% were generated by health professionals, including physicians and pharmacists; 23% were generated by consumers; and the others came from foreign and literature reports. When they are received, ADE reports are imaged and abstracted into the AERS database with the international dictionary MedDRA (Medical Dictionary for Drug Regulatory Affairs). Selected serious reports are triaged for immediate review. Review of ADE reports results in the generation of possible safety hypotheses. The initial evaluation of a safety hypothesis is based on collection of a case series. This includes elimination of duplicate and confounded reports and facilitates examination of data in aggregate for the identification of risk factors. Additional information can be obtained through contact with the initial reporter by FDA staff. Clinical details needed to support a causal association between a drug and an adverse event include temporality, drug dechallenge, and drug rechallenge, among others.

**Epidemiologic aspects of spontaneous reports.** Quantitative epidemiologic studies of aggregate adverse event reports are difficult but not impossible. Only a fraction of ADEs are reported to the FDA (underreporting). The fraction of reports received by the FDA has been estimated to be 1% to 10%,<sup>6</sup> but the absolute percentage is unknown.<sup>7</sup> Notoriety of a drug-event combination, the reporting practices of different clinicians in disparate populations, the clinical severity of the event, different drug sponsors, and secular trends may affect reporting.

Several epidemiologic approaches can be used to analyze spontaneous ADE reports. Reporting rates (based on division of the number of case reports for an event by the number of prescriptions) can be used to compare one drug with another. However, these rates are subject to uncertainty in the numerator given underreporting and, to a lesser extent, uncertainty in the denominator. A large difference in reporting rates between similar drug products may support an association between the event and one of the drug products, especially when combined with other information such as biologic plausibility. Another method that has been used to assess a possible safety hypothesis involves comparison of the number of cases reported (or observed) for a drug product with the number expected based on a background incidence rate for the event of interest. In general, interpretation of quantitative studies of potential safety hypotheses based on spontaneous ADE reports requires a working knowledge of the strengths and limitations of these data.

## METHODS

The AERS database was used to enumerate and collect spontaneous domestic (US) ADE reports categorized under the broad coding term *impaired healing* through July 2000. Selected case reports were further reviewed to collect detailed information on reports of delayed traumatic or surgical wound healing and to delete duplicate reports, reports of poor quality, and reports of injection site reactions (included under the coding term *impaired healing*).

## RESULTS

The top 6 agents, in order of frequency, to appear under the term *impaired healing* were as follows: isotretinoin (n = 106), levonorgestrel (n = 69), etanercept (n = 30), interferon  $\beta$ -1b (n = 25), interferon  $\beta$ -1a (n = 17), and methotrexate (n = 13). Isotretinoin and levonorgestrel, have a priori reasons to lead such a list; methotrexate is an antineoplastic agent that has been studied for antiangiogenic effects, and delayed wound healing is mentioned in the drug's approved labeling. No additional analyses were conducted on these agents.

The appearance of etanercept, interferon  $\beta$ -1b, and interferon  $\beta$ -1a near the top of this list prompted hands-on review of the reports for these agents and collection into case series. We identified 20 unduplicated cases of surgical or traumatic delayed wound healing for etanercept, 4 for interferon  $\beta$ -1b, and 9 for interferon  $\beta$ -1a. Included among these were 10 cases of delayed surgical wound healing for etanercept, 1 for interferon  $\beta$ -1b, and 4 for interferon  $\beta$ -1a. Eight (40%) of the 20

reviewed cases for etanercept noted discontinuation of the drug in response to delayed healing versus one (11%) of the 9 interferon  $\beta$ -1a cases and 0 of 4 interferon  $\beta$ -1b cases.

## DISCUSSION

Novel beneficial effects of drugs have been identified for numerous drug products during clinical trials or through clinical application of drug pharmacology. For example, hypertrichosis with minoxidil was identified as an unanticipated side effect during early clinical trials for its use in the management of hypertension.<sup>8</sup> An increase in erectile function was reported in early clinical trials of sildenafil (Viagra; Pfizer Inc, New York, NY) for use in the management of angina.<sup>9</sup> Ketoconazole was already marketed as an oral antifungal agent when its effects on serum level of testosterone were studied for the management of advanced prostate cancer.<sup>10</sup> The immunomodulating properties of thalidomide were outlined by Sheskin<sup>11</sup> in the management of leprosy decades after the drug was used (with catastrophic results) for symptoms of pregnancy. Most recently, *in vitro* data support the use of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) as agonists of bone formation and therefore possibly useful in the prevention of osteoporotic fractures.<sup>12</sup> (Conflicting observational data warrant further study before this hypothesis is confirmed.<sup>13</sup>) By inspection, we were intrigued by the appearance of etanercept near the top of the simple frequency distribution and case counts generated for this study (ie, no adjustment for use). In a search of the National Institutes of Health PubMed literature database, we found no previous reports of delayed wound healing in association with the use of etanercept or reports of ongoing preclinical studies for use of this drug as an antiangiogenic or antineoplastic agent. The appearance of etanercept in this list is not altogether unexpected, however, because this drug is a tumor necrosis factor (TNF) receptor fusion protein that binds to TNF- $\alpha$  and lymphotoxin  $\alpha$  (TNF- $\beta$ ) and thus interferes with TNF interaction with cell-based TNF receptors. Results of recent studies suggest TNF- $\alpha$  is important in new-vessel formation.<sup>14</sup> To qualitatively estimate the likelihood that etanercept appeared near the top of this list by chance, we calculated reporting rates for etanercept against another recently introduced disease modifying antirheumatic agent and the interferon products. In these analyses etanercept did appear to stand out. This information must be interpreted as limited support, given the substantial limitations to reporting rate comparisons as cited earlier.

Although this analysis has been based on the surrogate end point of impaired wound healing, two interferons used in the management of multiple sclerosis surfaced near the top of the frequency distribution. Interferons are currently in use as antineoplastic therapy and as antiangiogenic therapy in the management of life-threatening hemangioma.<sup>15</sup> We believe this supports the methods used in this analysis to identify agents with the potential to interfere with angiogenesis.

We found no published report of a beneficial drug property first identified through a spontaneous ADE database. We strongly believe in the merits of spontaneous systems and want to expand their utility. As in the analyses of spontaneous ADE data for potential safety concerns, we place no a priori value on any findings and consider analyses to be hypothesis generating. Although the study was subject to the same risk of false-positive results as is the study of safety signals, we believe the clinical effect of type I error to be minimized in the setting of oncology, in which there is substantial room for therapeutic improvement.

This analysis could be described as a form of data mining and represents a departure from our general approach to the surveillance of ADE reports. Pharmacoepidemiologic studies with health care databases, such as the General Practice Research Database in the United Kingdom, historically have been directed at quantification of safety signals.<sup>16</sup> This analysis represents use of this database for identification of a possibly useful *in vivo* side effect. In absolute terms no causal association can be drawn from these findings because of the small number of reports, concurrent therapies (including prednisone), and the clinical setting. However, these data can be used as a hypothesis for further preclinical study of inhibition of angiogenesis with etanercept (of particular interest), interferon  $\beta$ -1a, and interferon  $\beta$ -1b. We hope this article inspires further discussion of the use of spontaneous ADE report databases for unanticipated beneficial effects of drug products, including the use of surrogate end points.

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