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Underreporting of Hemorrhagic and Thrombotic Complications of Pharmaceuticals to the U.S. Food and Drug Administration: Empirical Findings for Warfarin, Clopidogrel, Ticlopidine, and Thalidomide from the Southern Network on Adverse Reactions (SONAR)

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Abstract

The U.S. Food and Drug Administration's (FDA) Adverse Event Reporting System (AERS), familiarly known as “MedWatch,” is the nation's primary tool for postmarket pharmaceutical safety surveillance. This system relies on adverse events voluntarily reported by health care providers and consumers either directly to the FDA or to drug manufacturers, which are required to prepare and forward the information to the agency. Little is known about how frequently adverse events are reported. Previous estimates range from 1 to 31% depending on the event, drug, and time period. We used published incidence studies to calculate reporting rates for hemorrhage, emergency hospitalization, and venous thromboembolism (VTE) associated with four drugs. We estimated annual reporting rates of 1.07% for 33,171 emergency hospitalizations of patients older than 65 years associated with warfarin, 0.9% for 13,363 hospitalizations of clopidogrel and ticlopidine, and 1.02% for an estimated 67,200 hemorrhage cases associated with warfarin. We also estimated a 9-year reporting rate of 2.3% for VTE associated with thalidomide. The incidence of these hematologic adverse drug events is high and reporting rates are low, and near the lower boundary of the 1 to 15% range seen for other events.

Keywords

U.S. Food and Drug Administration; adverse drug events; hemorrhage; venous thromboembolism; warfarin; thalidomide; clopidogrel; ticlopidine

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The primary source of information for postmarket pharmaceutical safety surveillance is the U.S. Food and Drug Administration's Adverse Event Reporting System (AERS), better known to clinicians as “MedWatch,” the name that appears on case report forms.[1] Health professionals and consumers may voluntarily submit a report of an adverse drug event directly to the FDA or to a drug manufacturer, which is required to complete and submit a report of any adverse drug event of which it is informed.[2] In 2010, the FDA received 142,000 reports of domestic, serious adverse drug events[3] and 760,000 reports of all kinds, including revisions, non-serious events, and foreign events.[4]

Although the annual total of reported death, disability, hospitalization, and other serious injury associated with prescription drug therapy appears large, little is known about what fraction of events that occur are actually reported. A frequently cited estimate of a 1 to 10% adverse drug event reporting rate can be traced to an FDA journal commentary that did not provide underlying data.[5] At one extreme,a study in 1994 calculated that 544/202,011 (0.3%) of hospitalizations for digoxin toxicity were reported from 1985 to 1991.[6] However, a more recent FDA study of statin-associated rhabdomyolysis concluded that 5 to 15% of these cases had been reported and, in one special instance, 31% of cases.[7] One study based on hospital admissions estimates that pharmaceuticals account for 100,000 deaths in the United States annually.[8] An additional feature of the system is a sustained long-term growth in reports, primarily foreign and domestic manufacturer reports of serious events for which adequate warnings are not included in the prescribing information. These reports have grown fourfold, from 95,000 in 2000 to 410,000 in 2010.[4]

Although hematologic adverse effects are among the most prominent undesirable properties of prescription medication, the numbers events that occur and reporting rates of these events are unknown. In this study, we used published incidence data to estimate reporting rates for hemorrhagic and thrombotic complications of four drugs: warfarin, clopidogrel, ticlopidine, and thalidomide.

Methods

Hemorrhagic Adverse Events

Incidence estimates for hemorrhagic and hospitalization events were developed from two published studies. Emergency hospitalizations in the elderly were estimated for 2007 to 2009 using nationally representative samples of hospital emergency departments.[9] The incidence of hemorrhage associated with warfarin was estimated from the control arm of a Phase III clinical trial comparing warfarin with dabigatran for the prevention of stroke in patients with atrial fibrillation (termed the RE-LY trial).[10] In the 2-year RE-LY trial of 18,113 patients, the rate of major bleeding for warfarin was 3.36% per year. The patient population for warfarin was estimated at 2 million patients based on FDA risk management evaluation documents, and published prescription volume information.[11] The AERS case reports for warfarin, clopidogrel, and ticlopidine were extracted from the Institute for Safe Medication Practices QuarterWatch database of all adverse drug events reported to the FDA since 1998.[11] This study focused on domestic, serious adverse events for the three years, 2008 to 2010. The MedWatch reporting form permits respondents to identify one or more specific health outcomes, including hospitalization, death, disability, life-threatening, and required intervention to prevent harm. For the hospitalization comparison, cases were selected with the specific hospitalization outcome, even if other outcomes (including death) were also reported, and limited to a reported age of 65 years or older for comparability with the hospitalization study. For the hemorrhage comparison, we selected cases with one or more preferred terms in the *Hemorrhage* Standardized Med-DRA Query (SMQ) broad scope in MedDRA version 14.1.[12] An SMQ is a tool developed to identify possible cases of

various specific drug adverse effects. The report total was the 3-year mean for cases initially received by the FDA during the 2008 to 2010 calendar years.

Venous Thromboembolism Adverse Events

A published systematic review of VTE associated with thalidomide evaluated VTE incidence in Phase II and Phase III clinical trials published between 1998 and 2006.[13] Cases were identified using the terms *deep vein thrombosis*, *thromboembolism*, and *pulmonary embolism*. Patient exposure for thalidomide was estimated from participants in the thalidomide registry program Systems for Thalidomide Education on Prescriber Safety (n = 400,000).[14]

Results

The overall reports are summarized in ▸Table 1.

Hemorrhage Events

For emergency hospitalizations in patients aged 65 years or older, the published study estimated 33,171 hospital admissions annually from the emergency room associated with warfarin, and 13,263 cases for oral antiplatelet agents. In the 2008 to 2010 period, we identified an annual average of 381 cases reported to the FDA for warfarin, yielding a reporting rate of 1.15%. For the two antiplatelet agents, clopidogrel and ticlopidine, we identified a combined annual average of 130cases in 2008 to 2010 for a reporting rate of 0.98%.

For hemorrhages associated with warfarin, we estimated an annual total of 67,200 cases based on serious bleeding rates reported in the RE-LY trial and a patient population of 2 million. In 2008 to 2010, we identified an annual average of 685 cases falling in the hemorrhage SMQ, yielding a reporting rate of 1.02%.

Venous Thromboembolic Events

The incidence VTE in clinical and observational studies of thalidomide for cancer treatment from 1998 to 2006 was reported as 585/4,682 (12%), yielding an estimate of 48,000 cases over the 9-year period. For the same period, the FDA received 1,118 reports of VTE for an estimated reporting rate of 2.3%.

Discussion

These studies identified similar reporting rates for hematologic adverse effects of around 1 to 2% despite great diversity in the agents under study, the time period, and the methods used to estimate the rates. Warfarin is a generic drug four decades old; clopidogrel was largely sold as a brand name drug in the study period, and thalidomide is a special restricted distribution drug with additional reporting requirements. We used three different sources to estimate the number of exposed patients, and one method, hospitalizations, did not require a patient exposure estimate. The estimates spanned a 13-year period, with thalidomide capturing 1998 to 2006 reports and the other three drugs 2008 to 2010. The adverse events studied are clearly defined and associated with the study drugs.

The study has limitations. The estimate of hospitalizations for warfarin and the antiplatelet agents could be an underestimate because the reference study only examined hospitalizations that originated in the emergency rooms and would not have captured patients admitted through other mechanisms. The definitions of serious bleeding in the RE-LY clinical trial and in the query of the FDA's MedWatch data to capture adverse events

were similar but not identical. We studied only the two most widely used antiplatelet agents. The patient exposure estimates for thalidomide and warfarin are approximations derived from available data, and the thalidomide-associated VTE rate assumes that the rates reported in Phase III clinical trials would be similar to those in clinical practice and would involve multiple agents. Because of lack of data for estimation, we did not evaluate hemorrhage reporting rates for recently launched brand name drugs such as the anticoagulant dabigatran. Newer and aggressively marketed drugs may have a higher reporting rate because of extensive manufacturer contact with physicians through sales representatives and with patients through Web sites, consumer hot lines, and other direct contact programs. Unusual and very serious events such as rhabdomyolysis or Stevens-Johnson syndrome also may have higher reporting rates. In conclusion, these reporting rates for hematologic adverse drug events are low, and at the lower boundary of the 1 to 15% range seen for other events.

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Table 1

Estimates of adverse event reporting rates to the FDA

Event	Agent	Source	Events[a]	Reported	Rate (%)
Hospitalization	Warfarin	Budnitz et al	33,171	381	1.15
Hospitalization	Antiplatelet agents	Budnitz et al	13,263	130	0.98
Hemorrhage	Warfarin	Connolly et al	67,200	685	1.02
VTE	Thalidomide	Bennett et al	48,000	1,118	2.33

Abbreviations: FDA, U.S. Food and Drug Administration; VTE, venous thromboembolism.

[a]Annual estimates except VTE, which is 1998–2006 inclusive.