

Beyond the black box: drug- and device-associated hypersensitivity events

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Background: Drug- and device-associated hypersensitivity reactions are serious toxicities that can result in respiratory failure or acute cardiac ischemic events, or even severe hypersensitivity syndromes such as Stevens–Johnson syndrome. These toxicities are usually poorly described in the “black box” warnings section of the product labels.

Methods: Adverse event reports contained in databases maintained by the Project on Medical Research on Adverse Drug Events and Reports (Med-RADAR), product labels, safety advisories disseminated by pharmaceutical manufacturers, the Food and Drug Administration (FDA), and the Centers for Disease Control and Prevention (CDC) were reviewed.

Results: Adverse event reports identified three health care workers who developed nevirapine-associated Stevens–Johnson syndrome following occupational exposure to HIV-infected blood or blood products; four persons with localized hypersensitivity and fatal cardiac events associated with rapamycin- or paclitaxel-coated coronary artery stent placements; and six persons with breast cancer who developed severe or fatal anaphylaxis after receiving adjuvant chemotherapy with Cremophor-EL containing paclitaxel. Safety advisories from the FDA, CDC, and the relevant pharmaceutical manufacturers were ambiguous in their description in “black box” warning sections of package inserts describing these serious and potentially fatal toxicities.

Conclusion: Improvements are needed in pharmacovigilance and subsequent dissemination of safety advisories for drug/device-associated hypersensitivity reactions.

Keywords: adverse events, hypersensitivity, toxicity, drug

Introduction

Hypersensitivity reactions range in severity from mild pruritus to systemic anaphylaxis, and can result in potentially severe clinical outcomes, including respiratory arrest, cardiac collapse, and death.¹ There are four basic types of hypersensitivity reactions.² Type I (immediate) hypersensitivity involves cell-fixed antibody, mainly immunoglobulin E (IgE) attached to mast cells or basophils. Antigen binding causes the cell to release vasoactive factors. Type II (antigen-dependent cellular cytotoxicity) hypersensitivity causes cytotoxicity by interactions of immunoglobulins with complement or cytotoxic cells. Type III (immune-complex or subacute) hypersensitivity causes tissue damage and inflammation by deposition of antigen-antibody complexes that activate complement and attract polymorphonuclear cells. Type IV (delayed hypersensitivity) involves sensitized T lymphocytes that interact with cell bound or associated antigen and release lymphokines, causing mononuclear cell accumulation, tissue damage and inflammation. This hypersensitivity typically occurs at least 24 hours after exposure to the antigen.

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For several reasons, hypersensitivity-associated adverse drug events are particularly difficult to identify as part of routine pharmacovigilance initiatives conducted by the Food and Drug Administration (FDA) or pharmaceutical manufacturers. Spontaneous case descriptions are poorly described in the FDA's Adverse Event Reporting System (AERS) database or the Manufacturer and User Facility Device Experience (MAUDE) database, the primary pharmaceutical and device safety databases, respectively, used by the FDA.^{3,4} Unless the adverse event incidence rate is very high or the clinical outcome severe or fatal, registration clinical trial safety databases often will not contain many reports of these events. In other clinical trials, similar underreporting is likely to occur. In contrast, active pharmacovigilance initiatives can provide valuable information on drug-associated hypersensitivity events characterized by very comprehensive and low quantity case reports. Over the past decade, databases maintained by the Medical Research on Adverse Drug Events and Reports (Med-RADAR) project have focused in part on this toxicity.^{5,6} Herein, we describe these database findings and associated safety-related dissemination media, and outline the implications of these findings.

Methods

Med-RADAR databases were created by National Institutes of Health-funded R01 and American Cancer Society research grants.^{5,6} These databases contain detailed information on severe or potentially fatal adverse drug reactions. In most instances, the incidence rates of these events are low, but the clinical outcomes are severe. It is staffed by 25 co-investigators worldwide with background and expertise in clinical medicine, epidemiology, pharmacology, infectious diseases, oncology, hematology, pharmacy, and public policy. Databases evaluated in Med-RADAR investigations include MAUDE, MedWatch, spontaneous reports from physicians, active surveillance efforts, clinical trial reports, and case series reviews. To date, 43 distinct serious adverse drug reactions, including: thienopyridine-associated thrombotic thrombocytopenic purpura; epoetin-associated pure red cell aplasia, venous thromboembolism, and mortality; and rituximab-associated progressive multifocal leukoencephalopathy, have been identified and described in reports based on evaluations of Med-RADAR databases.^{5,6} Causal association grades were assigned according to World Health Organization (WHO) criteria.⁷ These criteria classify causal associations as certain, probable, possible, or unlikely based on timing, pathophysiology, de-challenge (agent withdrawal),

re-challenge (agent re-exposure), and competing explanations. Additional data sources included product labels, primarily "black box" label sections, and safety advisories disseminated by the FDA and pharmaceutical manufacturers.

Results

Med-RADAR databases were used to identify and report information on four distinct drug-associated hypersensitivity reactions: nevirapine-associated Stevens–Johnson syndrome, Cremophor-EL containing paclitaxel-associated anaphylaxis among breast cancer patients receiving adjuvant chemotherapy, and paclitaxel- and sirolimus-eluting coronary artery stent associated hypersensitivity^{7–9} (Table 1). These four events are characterized by their severity and by the difficulty associated with identifying relevant comprehensive clinical reports in traditional safety data sources maintained by the FDA or the pharmaceutical supplier.

Detailed information in the Med-RADAR databases is available for 13 individuals with these hypersensitivity reactions (Table 2). The clinical richness of these safety reports is evident as shown in information on patient sociodemographics, time to onset, administration of prophylaxis, presenting clinical findings, and outcome. For the drug-eluting stents coated with paclitaxel or rapamycin, autopsy materials supported the clinical diagnosis of localized hypersensitivity. Time to onset ranged from minutes (Cremophor-EL-containing paclitaxel), to within two weeks (nevirapine-administration to non-HIV-infected individuals following HIV exposure), to several weeks (coronary artery drug-eluting stents). Severe nonfatal anaphylaxis occurred in seven individuals (three non-HIV-infected health care workers who received nevirapine and four women with breast cancer who received adjuvant chemotherapy with Cremophor-EL-containing paclitaxel), while death occurred in six individuals (four persons with coronary artery disease who received coronary artery drug-eluting stents and two women with breast cancer who received Cremophor-EL-containing paclitaxel-based adjuvant chemotherapy). Of note, symptoms manifested primarily as Stevens–Johnson syndrome with dermatologic findings (nevirapine), severe respiratory failure (Cremophor EL-containing paclitaxel), or acute coronary events (paclitaxel- and sirolimus-eluting coronary artery stents).

Causality assessment is particularly difficult when evaluating serious hypersensitivity-like clinical events that occur following administration of a drug. The validated WHO classification system characterizes the Cremophor EL-containing paclitaxel events as probable based on timing,

Table 1 Med-RADAR

Drug	Adverse event (rate)	Outcome (symptom or syndrome)	Data source (# of patients)	Prophylaxis useful	Alternative strategy	Identification of high-risk individual	Publication
Nevirapine (to HIV-exposed health care workers)	Stevens-Johnson syndrome (40% in high-risk individuals)	Stevens-Johnson syndrome	Reports to the Centers for Disease Control (n = 3)	Not known	Avoid nevirapine administration to these persons	Persons with high CD4-lymphocyte counts	<i>Journal of the Acquired Immune Deficiency</i> 2002
Cremophor-EL containing paclitaxel administered as part of adjuvant chemotherapy regimens to women with breast cancer	Anaphylaxis (2%–4%)	Severe respiratory arrest, death in the setting of adjuvant breast cancer treatment	Reports to the FDA's MedWatch Program (n = 6)	Not always	Consider administering nab-paclitaxel as an alternative	None identified	<i>Community Oncology</i> 2009
Paclitaxel-based drug eluting stents	Local hypersensitivity (rare)	Cardiac arrest, death	Reports to the FDA's MAUDE database (n = 1)	Not known	Consider bare metal coronary stent	None identified	<i>Journal of the American College of Cardiology</i> 2006
Sirolimus-based drug eluting stents	Local hypersensitivity (rare)	Cardiac arrest, death	Reports to the FDA's MAUDE database (n = 3)	Not known	Consider bare metal coronary artery stent	None identified	<i>Journal of the American College of Cardiology</i> 2006

Abbreviations: FDA, US Food and Drug Administration; MAUDE, Manufacturer and User Facility Device Experience.

pathophysiology and absence of competing explanations, the paclitaxel- and sirolimus-containing cardiac stent events as probable based on pathophysiology and autopsy findings, and the nevirapine-associated Stevens-Johnson syndrome as probable based on timing, pathophysiology, and absence of competing explanations. “Black box” warnings were disseminated by the pharmaceutical manufacturers for three of the four products (the exception being hypersensitivity associated with paclitaxel-coated cardiac stents), although clinical information on effective strategies to prevent, diagnose, and treat these reactions as well as epidemiologic rate estimates was lacking (Table 3). Public health advisories from the manufacturer and the FDA have been disseminated for hypersensitivity associated with nevirapine- and sirolimus-eluting coronary artery stents, although the warning for the drug stents was retracted by the FDA one month after issuance.

Discussion

Hypersensitivity is a serious and occasionally fatal adverse drug reaction. Med-RADAR databases include detailed clinical information on 13 individuals who developed severe drug-associated hypersensitivity associated with four drugs/devices. Despite the small number of clinical reports contained in these databases, peer-reviewed publications containing detailed clinical information have been disseminated for each of these adverse drug reactions. In contrast, “black box” warnings for these adverse reactions contain incomplete and often inconsistent clinical and epidemiologic findings. In interpreting our findings, several factors should be considered.

Causality assessment for hypersensitivity reactions is challenging. With the paclitaxel- and sirolimus-coated coronary artery stents, the associated FDA and manufacturer warnings have been ambiguous.^{10,11} However, the Med-RADAR-related publication with autopsy findings identifying local inflammatory infiltrates for four patients provides support for causality. For the Cremophor-EL-containing paclitaxel, nonimmune-mediated activation of the complement system is one possible mechanism. However, Cremophor-EL can cause histamine release from mast cells (this is most likely an IgE-mediated event), and result in acute pulmonary toxicity.^{12–14} Similar hypersensitivity reactions have not been reported with a Cremophor-free formulation of paclitaxel that received FDA approval in 2005.¹⁵ For the nevirapine-associated hepatotoxicity among non-HIV-infected health care workers, a contemporaneous report from England identified five similar cases among 41

Table 2 Detailed case history of Med-RADAR reports for serious drug-associated hypersensitivity reactions classified as certain or probable according to the WHO classification system

Drug	Clinical finding	Outcome	Age	Gender	Time to onset	Prophylaxis administered	Publication reference
Cremophor-EL-containing Paclitaxel	Anaphylaxis	Death	37	Female	<10 minutes	Yes	<i>Community Oncology</i> 2009
Cremophor-EL-containing Paclitaxel	Anaphylaxis	Death	38	Female	NA	Yes	<i>Community Oncology</i> 2009
Cremophor-EL-containing Paclitaxel	Anaphylaxis	Recovered	34	Female	<10 minutes	Yes	<i>Community Oncology</i> 2009
Cremophor-EL-containing Paclitaxel	Anaphylaxis	Recovered	39	Female	<10 minutes	Yes	<i>Community Oncology</i> 2009
Cremophor-EL-containing Paclitaxel	Anaphylaxis	Recovered	48	Female	<10 minutes	Yes	<i>Community Oncology</i> 2009
Cremophor-EL-containing Paclitaxel	Anaphylaxis	Recovered	54	Female	20 minutes	Yes	<i>Community Oncology</i> 2009
Paclitaxel-coated cardiac stent	Localized hypersensitivity	Death	NA	NA	30 days	No	<i>Journal of the American College of Cardiology</i> 2006
Rapamycin-coated cardiac stent	Localized hypersensitivity	Death	NA	NA	78 days	No	<i>Journal of the American College of Cardiology</i> 2006
Rapamycin-coated cardiac stent	Localized hypersensitivity	Death	NA	NA	150 days	No	<i>Journal of the American College of Cardiology</i> 2006
Rapamycin-coated cardiac stent	Localized hypersensitivity	Death	58	Male	21 days	No	<i>Journal of the American College of Cardiology</i> 2006
Nevirapine	Stevens–Johnson	Recovered	27	Female	7 days	No	<i>Annals of Internal Medicine</i> 2002
Nevirapine	Stevens–Johnson	Recovered	38	Male	9 days	No	<i>Annals of Internal Medicine</i> 2002
Nevirapine	Stevens–Johnson	Recovered	41	Male	11 days	No	<i>Annals of Internal Medicine</i> 2002

Abbreviation: NA, not available.

non-HIV-infected individuals after occupational or sexual exposure to HIV.¹⁶

Improved dissemination of safety information to clinicians and patients is essential.¹⁷ As noted above, “black box warnings” were disseminated for three of the adverse reactions and pharmaceutical manufacturers disseminated safety advisories for two of the adverse drug reactions. However, the FDA retracted their safety advisory for the sirolimus-coated coronary artery stent-associated hypersensitivity one month

after issuance. The manufacturer of nevirapine disseminated safety alerts for nevirapine-associated hypersensitivity to clinicians in 2003, two years after the Centers for Disease Control disseminated a safety advisory describing associated clinical findings in the *Morbidity and Mortality Weekly Report*.¹⁸ While recent FDA initiatives include improved mechanisms for disseminating comprehensive and timely safety information, empirical evidence that these mechanisms are effective is lacking.¹⁹ In particular, improvements

Table 3 Manufacturer- and FDA-disseminated warnings related to drug-related serious hypersensitivity adverse events based on reports included in Med-RADAR databases

Drug	Toxicity	Package insert warning	FDA-disseminated public health advisory	Manufacturer-disseminated public health advisory
Cremophor EL-containing paclitaxel	Anaphylaxis	Black box (2001)	None	None
Paclitaxel-containing cardiac stent	Localized hypersensitivity	Black box (2003)	None	None
Rapamycin-containing cardiac stent	Localized hypersensitivity and subacute coronary artery thrombosis	None	2003 (retracted one month later)	Dear Colleague (2003)
Nevirapine	Stevens–Johnson Syndrome	Black box (2002)	2003	2003

Abbreviation: FDA, US Food and Drug Administration.

in approaches to disseminating important information that is briefly outlined as “black box” warnings are needed. Woolshin and colleagues recently described an improved “facts box” to facilitate comprehensive, yet concise information on both risks and benefits of drugs.²⁰

Strategies to prevent hypersensitivity reactions from occurring also deserve consideration (Table 1). For post-exposure prophylaxis following occupational exposure to HIV-infected blood or blood products, the United States Public Health Services has identified six antiretroviral agents (abacavir, delavirdine, zalcitabine, didanosine with stavudine, and nevirapine) that should not be administered because of toxicity considerations. For women with breast cancer, the cremophor-EL-free formulation of paclitaxel has a high efficacy and no evidence of hypersensitivity. For drug-eluting coronary artery stents, concern over late thrombotic events has resulted in increased usage of bare metal stents.

In summary, Med-RADAR database efforts focusing on drug/device-associated hypersensitivity reactions resulted in dissemination of safety information for two drugs and two devices through peer-reviewed publications in medical journals, although detailed descriptions of these toxicities were not disseminated by the manufacturers or the FDA.

Disclosures

Dr Bennett has previously served as a consultant to Boehringer-Ingelheim, Johnson and Johnson, and Abraxis Pharmaceuticals. Dr Calhoun has served as a consultant to Abraxis Pharmaceuticals. Dr Raisch has received grant support from Abraxis Pharmaceuticals.

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