

Adverse event profiles of solvent-based and nanoparticle albumin-bound paclitaxel formulations using the Food and Drug Administration Adverse Event Reporting System

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Abstract

Objectives: Paclitaxel is a highly effective antitumor agent with notable adverse events, including hypersensitivity reactions, peripheral neuropathy, arthralgia, myalgias, and neutropenia. Solvent-based paclitaxel causes severe allergic, hypersensitivity, and anaphylactic reactions. Nanoparticle albumin-bound paclitaxel was recently developed and provides an advantage over solvent-based paclitaxel in avoiding solvent/surfactant-related adverse events. The aim of this study was to assess the adverse event profiles of solvent-based paclitaxel and nanoparticle albumin-bound paclitaxel formulations using data from the spontaneous adverse event reporting system of the US Food and Drug Administration Adverse Event Reporting System database.

Methods: This study relied on Medical Dictionary for Regulatory Activities preferred terms and standardized queries, and calculated the reporting ratio and reporting odds ratios of paclitaxel formulations.

Results: Of 8,867,135 reports recorded in the US Food and Drug Administration Adverse Event Reporting System database from January 2004 to December 2016, 3469 and 4447 adverse events corresponded to solvent-based paclitaxel and nanoparticle albumin-bound paclitaxel, respectively. Reporting odds ratios (95% confidence interval) for *anaphylactic reaction* (standardized MedDRA query code: 20000021) associated with the use of solvent-based paclitaxel and nanoparticle albumin-bound paclitaxel were 1.69 (1.56–1.84) and 0.75 (0.68–0.83), respectively. Reporting odds ratio signal for *anaphylactic reaction* was not detected for nanoparticle albumin-bound paclitaxel. Reporting odds ratios (95% confidence interval) for *acute renal failure* (standardized MedDRA query code: 20000003) associated with the use of solvent-based paclitaxel and nanoparticle albumin-bound paclitaxel were 0.75 (0.58–0.98) and 1.60 (1.37–1.89), respectively.

Conclusion: This is the first study to evaluate the adverse event profile of nanoparticle albumin-bound paclitaxel using US Food and Drug Administration Adverse Event Reporting System data. Considering that the US Food and Drug Administration Adverse Event Reporting System database does not allow to infer causality or risk ranking, the different reporting frequencies of *anaphylactic reaction* and *acute renal failure* between solvent-based paclitaxel and nanoparticle albumin-bound paclitaxel must be further investigated via analytical observational research.

Keywords

Paclitaxel, Abraxane, Taxol, Food and Drug Administration Adverse Event Reporting System

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Introduction

Paclitaxel (PTX) is an antitumor agent used for the treatment of breast cancer, ovarian cancer, non-small-cell lung cancer, bladder cancer, prostate cancer, melanoma, and esophageal cancer.^{1,2} PTX received Food and Drug Administration (FDA) approval in 1992 and has been formulated and marketed as solvent-based (sb)-PTX (Taxol[®], Bristol-Myers Squibb, New York, NY, USA) since. Although highly effective, PTX is associated with several adverse events (AEs), including hypersensitivity reactions, peripheral neuropathy, arthralgia, myalgias, and neutropenia.^{3,4}

Albumin is an attractive drug delivery vehicle in oncology, allowing reversible, non-covalent binding of drugs,^{5,6} and it has offered a breakthrough in the treatment of numerous cancers.^{7,8} The solvent-free, human albumin-stabilized PTX formulation Abraxane[®] (nanoparticle albumin-bound PTX (nab-PTX), Celgene corporation, Summit, NJ, USA) is characterized by rapid as well as preferential delivery and accumulation of PTX at tumor sites, enhancing the therapeutic effects of PTX.^{9–11} nab-PTX was developed as a solvent-free PTX formulation because Cremophor EL (CrEL, a synthetic, nonionic surfactant used as a solubilizer for PTX) and ethanol (co-solvent) conventionally used to prepare sb-PTX were associated with high incidence of hypersensitivity reactions. nab-PTX displays a reasonable toxicity profile, avoiding solvent/surfactant-related AEs and the need for premedication.^{9,12} Use of nab-PTX resulted in a lower incidence of grade 4 neutropenia than that of sb-PTX.¹³ However, the detailed AE profile of PTX products in clinical setting is uncertain.

The US FDA Adverse Event Reporting System (FAERS) database is a spontaneous reporting system (SRS) covering several million case reports on AEs and is used for pharmacovigilance, reflecting the realities of clinical practice.^{14–16} The aim of this study was to assess the AE profiles of sb-PTX and nab-PTX formulations using the FAERS database. To the best of our knowledge, this is the first study to evaluate nab-PTX using the FAERS database.

Materials and methods

FAERS data from January 2004 to December 2016 are publicly available and can be downloaded from the FDA website (www.fda.gov). All data from the FAERS database were fully anonymized by the FDA before we used them. The FAERS database comprises seven data tables: patient demographic and administrative information (DEMO); drug/biologic information (DRUG); AEs (REAC); patient outcomes (OUTC); report sources (RPSR); drug therapy start and end dates (THER); and indications for use/diagnosis (INDI). FAERS database structure complies with the international safety reporting guidelines.¹⁷ Data obtained were integrated into a relational database using FileMaker Pro 13 software (FileMaker, Inc., Santa Clara, CA, USA).

Next, we followed the FDA recommendation for excluding duplicate reports for patients and used the most recent case numbers to identify and exclude such records from the analysis.¹⁸

For the extraction of cases from the FAERS database, we used two brand names—Taxol[®] for sb-PTX and Abraxane[®] for nab-PTX. MedWatch is the FDA Safety Information and AE Reporting Program. The MedWatch form is sent to the FDA for inclusion in FAERS. It is a two-page document that contains basic patient information, a description of the AE, suspected product (s), and concomitant product (s). If multiple products are reported on a MedWatch form, the reporter can identify a primary suspect (PS) drug that they feel is most responsible for the AE(s).¹⁹ Only reports with the drug code of PS were included in this analysis.

AEs in the REAC table are coded using preferred terms (PTs) in the Medical Dictionary for Regulatory Activities (MedDRA, www.meddra.org), which is the terminology dictionary.²⁰ MedDRA version 19.0 was used in this study. Standardized MedDRA queries (SMQs) are widely used to analyze SRS reports.^{21–23} SMQs, which are built by the Maintenance and Support Services Organization, are groupings of PTs according to the level that relates to a defined medical condition. The included terms may relate to signs, symptoms, diagnoses, syndromes, physical findings, and laboratory and other physiologic test data.²¹ The grouping of SMQs allows for useful data retrieval and presentation of relevant individual case safety reports. We used the following SMQs: *anaphylactic reaction* (SMQ code: 20000021, containing 86 related PTs), *peripheral neuropathy* (SMQ code: 20000034, containing 75 related PTs), *acute renal failure* (SMQ code: 20000003, containing 47 related PTs), *hematopoietic erythropenia* (SMQ code: 20000029, containing 27 related PTs), *hematopoietic leucopenia* (SMQ code: 20000030, containing 60 related PTs), *hematopoietic thrombocytopenia* (SMQ code: 20000031, containing 13 related PTs), *hematopoietic cytopenias affecting more than one type of blood cell* (SMQ code: 20000028, containing 27 related PTs), *interstitial lung disease* (SMQ code: 20000042, containing 60 related PTs), and *taste and smell disorders* (SMQ code: 20000046, containing 12 related PTs).

We calculated the reporting ratio and the reporting odds ratio (ROR) to study the influence of sb-PTX and nab-PTX on AEs. The strength of the association between drug of interest and reported AE compared with other drugs in the FAERS database is calculated as ROR.^{14–16,24,25} In our study, ROR provides an estimate for the extent to which AEs are reported in association with the use of sb-PTX or nab-PTX as suspected medication relative to the use of other drugs. To compare one of the index groups with the reference group, we calculated ROR values as $(a \times d)/(b \times c)$ and expressed the data as point estimates with a 95% confidence interval (CI). Safety signals were considered significant when ROR estimates and the lower limits of the

Table 1. Demographic information of sb-PTX and nab-PTX in the FAERS database.

	sb-PTX	Case (n)	nab-PTX	Case (n)
Age		57.6 ± 17.0*		58.0 ± 18.5*
Sex	Male	940	Male	1636
	Female	2153	Female	2334
Occupation	Physician	857	Physician	1491
	Pharmacist	212	Pharmacist	151
	Other health professional	1182	Other health-professional	2368
	Lawyer	3	Lawyer	–
	Consumer	839	Consumer	281
Reporter country	USA	1148	USA	1535
	Japan	543	Germany	311
	France	179	Japan	309
	Others	1599	Others	2292
Type of report	PS drug	3469	PS drug	4447
	SS drug	5379	SS drug	1478
	C	2801	C	527
	I	11	I	1
Outcome	Death	527	Death	1742
	Life-threatening	283	Life-threatening	310
	Hospitalization—initial or prolonged	1388	Hospitalization—initial or prolonged	1986
	Disability	147	Disability	114
	Congenital anomaly	–	Congenital anomaly	–
	Required invention to prevent permanent impairment/damage	79	Required invention to prevent permanent impairment/damage	11
	Other serious	977	Other serious	1281
Concomitant drugs†	Carboplatin	964	Gemcitabine	1986
	Dexamethasone	396	Carboplatin	507
	Diphenhydramine	314	Ondansetron	491
	Ranitidine	166	Dexamethasone	440
	Ondansetron	152	Prochlorperazine	258
	Trastuzumab	152	Lorazepam	210

C: concomitant; FAERS: US Food and Drug Administration Adverse Event Reporting System; I: interacting; nab-PTX: nanoparticle albumin-bound paclitaxel; PS: primary suspect; sb-PTX: solvent-based paclitaxel; SS: Secondary suspect.

*Mean ± SD, †top six drugs.

corresponding 95% CI were >1.²⁵ Two or more cases were required to define the signal.¹⁴

Results

FAERS data used in this study consisted of 8,867,135 reports from January 2004 to December 2016. After excluding duplicate reports according to the FDA recommendations, 7,348,357 reports were analyzed, of which 3469 and 4447 AE cases corresponded to sb-PTX and nab-PTX, respectively (Table S1). Demographic information of sb-PTX and nab-PTX in the FAERS database is summarized in Table 1. The 50 most frequently reported AEs for PTX formulations are listed in Table S1. For sb-PTX, the most commonly reported AEs were dyspnea, nausea, pyrexia, and vomiting, whereas for nab-PTX, the most commonly reported AEs were death, neutropenia, nausea, and anemia.

The reporting ratio of spontaneous AE reports of sb-PTX transiently decreased (Figure 1(a)), whereas the number of

nab-PTX AE reports and reporting ratio transiently increased (Figure 1(b)).

The RORs (95% CI) for *anaphylactic reaction* (SMQ code: 20000021) associated with the use of sb-PTX and nab-PTX ROR were 1.69 (1.56–1.84) and 0.75 (0.68–0.83), respectively. RORs (95% CI) for *hematopoietic leucopenia* (SMQ code: 20000030) associated with the use of sb-PTX and nab-PTX were 5.36 (4.76–6.04) and 11.07 (10.22–11.98), respectively (Table 2). RORs (95% CI) for *acute renal failure* (SMQ: 20000003) associated with the use of sb-PTX and nab-PTX were 0.75 (0.58–0.98) and 1.60 (1.37–1.89), respectively. The lower limits of RORs for *peripheral neuropathy*, *acute renal failure*, *hematopoietic erythropenia*, *hematopoietic leucopenia*, *hematopoietic thrombocytopenia*, *hematopoietic cytopenias affecting more than one type of blood cell*, and *interstitial lung disease* associated with the use of nab-PTX were >1. The lower limits of RORs for *peripheral neuropathy*, *hematopoietic erythropenia*, *hematopoietic leucopenia*, *hematopoietic thrombocytopenia*,

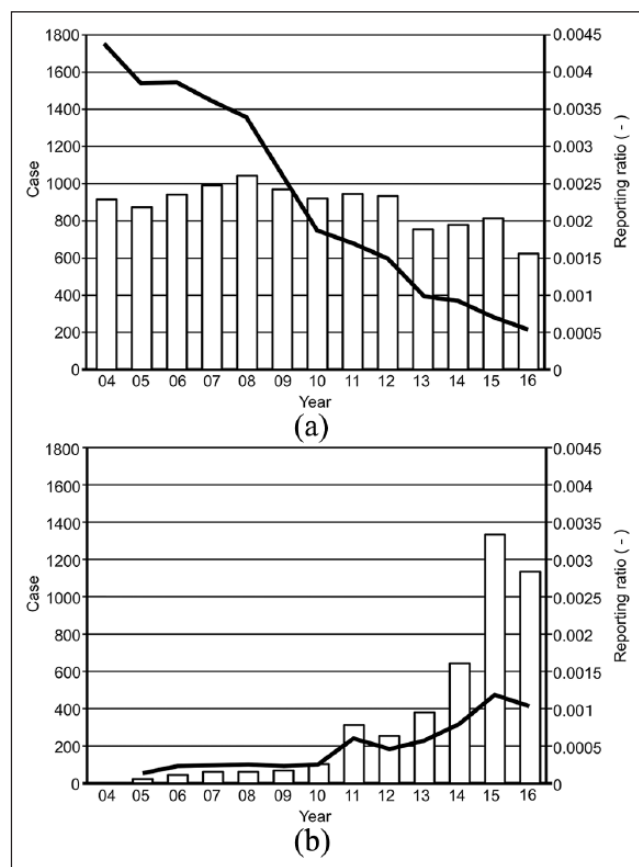


Figure 1. Changes in number of yearly reports of adverse events and reporting ratio of solvent-based paclitaxel (a) and nanoparticle albumin-bound paclitaxel (b).

hematopoietic cytopenias affecting more than one type of blood cell, and interstitial lung disease associated with sb-PTX use were >1 .

Discussion

In this study, we analyzed the AE profiles of sb-PTX and nab-PTX using FAERS data. For both PTX formulations, the lower limits of ROR 95% CI for *hematopoietic erythropenia, hematopoietic leucopenia, hematopoietic thrombocytopenia, hematopoietic cytopenias affecting more than one type of blood cell, and interstitial lung disease* were >1 , suggesting that both sb-PTX and nab-PTX carry potential risks for these AEs. These hematopoietic AEs of PTX have been previously reported in multiple clinical trials.^{6,26–28}

Spontaneous reporting of AEs is influenced by external factors such as duration of the drug in the market. The Weber effect is an epidemiological phenomenon describing a substantial increase in spontaneous reporting of AEs when the drug is first approved, which then plateaus and eventually declines.^{29–31} This effect may explain the decreased reporting ratio of AEs associated with sb-PTX (Figure 1(a)). However, the Weber effect is not always observed,³¹ and the number of

reports generally increases over the first 2 years after launching the drug.^{32,33} In our study, the decline in the reporting ratio was observed after 2004. Since sb-PTX was approved by the FDA in 1992, it might be difficult to explain this decrease based on the Weber effect.

In contrast, the number of nab-PTX AE reports and the reporting ratio transiently increased (Figure 1(b)). nab-PTX was initially approved by the FDA in 2005²⁷ and its therapeutic applications were subsequently extended to include the treatment of non-small-cell lung cancer in 2012 and advanced pancreatic cancer in 2013, potentially increasing AE reporting. This increase of nab-PTX AE reports may be associated with the increased awareness of novel drugs by clinicians.

According to our findings, ROR signal for *anaphylactic reaction* was detected for sb-PTX and not for nab-PTX, which is in agreement with previous literature data. In a clinical trial on metastatic breast cancer, nab-PTX displayed a better safety profile for *anaphylactic reaction* than sb-PTX.^{12,34–36} Because of the high lipophilicity and poor solubility of PTX, sb-PTX employs a CrEL:ethanol vehicle. As CrEL is biologically and pharmacologically active, hypersensitivity reactions have been reported. Prolonged infusion times (3 h) and premedication with corticosteroids and antihistamines are required to reduce the risk of hypersensitivity reactions to sb-PTX.^{9,12,26,37,38} Corticosteroid use is inconvenient for patients and presents a drawback of this formulation.

ROR signal for *acute renal failure* was detected for nab-PTX. However, it was not detected for sb-PTX. Although ROR is a rough indication and does not provide sufficient evidence on causality, the risk of nab-PTX for *acute renal failure* might be a notable observation in the interpretation of our results. Additional studies are required to confirm this finding.

It has been reported that CrEL contributes to the development of peripheral neuropathies.^{13,26,39,40} sb-PTX was shown to cause neutropenia and neuropathy that may be associated with axonal degeneration.^{13,26,39,40} In this study, no difference was observed in ROR for *peripheral neuropathy* between nab-PTX and sb-PTX.

Differences in safety profiles of the studied PTX formulations may be caused by various formulation parameters. nab-PTX demonstrated a larger volume of distribution, more rapid clearance, a higher fraction of unbound drug, higher systemic exposure, and maximal concentration of unbound drug relative to sb-PTX.^{41,42} nab-PTX was shown to improve the pharmacokinetics and biodistribution of PTX compared to sb-PTX.^{41,42} However, we do not have a conclusive explanation for our data. More detailed analyses focusing on these factors are required.

The FAERS database is subject to various biases such as under-reporting, over-reporting, reporting bias favoring newer agents, notoriety bias, exclusion of healthy individuals, and confounding by comorbidities.^{14,25} There are several approaches to control confounding factors, such as stratification,¹⁴ multiple logistic regression,^{22,43} and Bayesian logistic regression.⁴⁴ ROR

Table 2. Reporting odds ratio of sb-PTX and nab-PTX in the FAERS database.

Standardized MedDRA queries code	Total	sb-PTX				nab-PTX			
		Cases*	Reporting ratio (%)	ROR†	95% CI‡	Cases*	Reporting ratio (%)	ROR †	95% CI‡
20000021 Anaphylactic reaction	1,025,984	748	0.07	1.69	(1.56–1.84)§	484	0.05	0.75	(0.68–0.83)¶
20000034 Peripheral neuropathy	307,473	306	0.10	2.22	(1.97–2.49)§	420	0.14	2.39	(2.16–2.64)§
20000003 Acute renal failure	159,652	57	0.04	0.75	(0.58–0.98)¶	153	0.10	1.60	(1.37–1.89)§
20000029 Hematopoietic erythropenia	133,889	118	0.09	1.90	(1.58–2.28)§	347	0.26	4.57	(4.09–5.10)§
20000030 Hematopoietic leucopenia	128,182	301	0.23	5.36	(4.76–6.04)§	727	0.57	11.07	(10.22–11.98)§
20000031 Hematopoietic thrombocytopenia	79,332	81	0.10	2.19	(1.76–2.73)§	307	0.39	6.82	(6.07–7.66)§
20000028 Hematopoietic cytopenias affecting more than one type of blood cell	56,782	76	0.13	2.88	(2.29–3.61)§	154	0.27	4.62	(3.93–5.42)§
20000042 Interstitial lung disease	53,531	215	0.40	9.04	(7.87–10.38)§	155	0.29	4.93	(4.20–5.79)§
20000046 Taste and smell disorders	48,835	13	0.03	0.56	(0.33–0.97)¶	38	0.08	1.29	(0.94–1.77)

CI: confidence interval; FAERS: US Food and Drug Administration Adverse Event Reporting System; MedDRA: Medical Dictionary for Regulatory Activities; nab-PTX: nanoparticle albumin-bound paclitaxel; ROR: reporting odds ratio; sb-PTX: solvent-based paclitaxel.

*Number of patients with adverse events, †reporting odds ratio, ‡CI, §the lower limit of 95% CI was > 1, ¶the upper limit of 95% CI was < 1.

is a well-defined and easily applicable technique that allows for adjustment of covariates through logistic regression analysis. Recently, the Breslow–Day test was introduced to compare the homogeneity of RORs.^{45,46} These approaches might be useful for the analysis of FAERS database.

Cases reported in the FAERS database do not always contain sufficient information regarding patient background and dose response to allow for proper evaluation. In particular, PTX dose may greatly affect AE profiles. However, FAERS database is an SRS, making it difficult to obtain and evaluate the doses and duration of drug treatments. A new therapeutic indication or regimen may influence the AE reporting profile. Close attention should be paid to investigate temporal axis when planning a pharmacovigilance analysis.⁴⁷ More detailed analysis focusing on these factors is a subject for future investigation.

It should be noted that disproportionality analysis only suggests the necessity for well-organized clinical studies with respect to association. ROR differs from odds ratio commonly used in epidemiological studies. In absolute terms, ROR indicates an increased risk of AE reporting, not a risk of AE occurrence.¹⁴ ROR is not applicable to inferences of comparative degrees of causality and only offers a rough indication of signal strength. We have chosen the threshold of two cases for the calculation of ROR.¹⁴ However, efficiency of signal detection was strongly dependent on the thresholds used to define statistical significance.⁴⁸ Using the proportional reporting ratio (PRR), signal is detected if the number of cases are ≥ 3 , and the PRR is at least 2 with an associated chi-square value of 4 or more.⁴⁹ A recent article discussed a potential increase in the number of cases from 3

to 5.⁵⁰ When four or more cases were present, no clear differences in disproportionality measures such as ROR and PRR were found.²⁴ In the future, it would be necessary to reference these thresholds in order to assess how well they perform in the SRS database. These are the limitations of the methodology used in this study.

Michel et al.⁵¹ reported that disproportionality cannot be used for comparative drug safety analysis beyond basic hypothesis generation. de Boer⁵² emphasized that disproportionality measures used in SRS databases have important limitations, and more advanced methods might generate new and relevant information. In contrast, Montastruc et al.⁵³ reported that none of the methods (e.g. clinical trials, case-control studies, and cohort studies) if taken alone should be considered definitive for evaluating drug risk, and disproportionality studies are, therefore, important. Despite the inherent limitations of SRS data, our findings are in agreement with those of previous studies. The FAERS database is the largest SRS in the world and can reflect real-world setting. With larger numbers of accurate reports, the FAERS database would help to optimize pharmacotherapy.

Conclusion

This is the first study to evaluate the AE profile of nab-PTX using FAERS data. Considering that the FAERS database does not allow to infer causality or risk ranking, the different reporting frequencies of *anaphylactic reaction* and *acute renal failure* between sb-PTX and nab-PTX must be further investigated via analytical observational research.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical approval

Ethical approval was not sought for this study because the study was an observational study without any research subjects.

Not applicable. All results were obtained from data openly available online from the FDA website (www.fda.gov). All data from the FAERS database were fully anonymized by the regulatory authority before we accessed them.

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Informed consent

Not applicable. Written informed was not sought for this study because the study was an observational study without any research subjects.

Supplemental material

Supplemental material for this article is available online.

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