


SAFETY SIGNAL DETECTION FOR PLATINUM COMPOUNDS IN CANADIAN SPONTANEOUS ADVERSE EVENT REPORTS

SHARWANKUMAR SINGHAL,1,2 BHASWAT CHAKRABORTY1,2
1Cadila Pharmaceuticals Ltd, Ahmedabad, India, 1389, Trasad Road, Dholka 387810, 2Department of Pharmacology, Institute of Pharmacy, Nirma University, Sarkhej-Gandhinagar Highway, Chandodiya, Gota, Ahmedabad, Gujarat, India
Email: sharwanksinghal@rediffmail.com

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ABSTRACT
Objective: The objective of the study was to identify possible toxic signal induced by cisplatin and carboplatin treatment by searching database from Canadian Adverse Reaction Monitoring Program (CADRMP).

Methods: A total of 10427 reports of patients between January 1970 to March 2010 were downloaded from Canada Adverse reaction Monitoring Program website. These reports contained information of adverse events associated with all other drugs inclusive of platinum compounds. Adverse drug reaction (ADR) signal detection were determined by proportional reporting ratio (PRR), reporting odds ratio (ROD), PRR calculated by chi-square statistics, 95% confidence interval of PRR, observed to expected (O/E) ratio and De Mouchel method calculated PRR. Information component (IC) was given by Bayesian confidence propagation neural network. [As per regulatory criteria, PRR ≥ 2, ROR ≥ 1, chi-square statistics calculated PRR > 4 and lower bound of 95% CI of PRR > 1 to consider particular adverse drug reaction as a signal. Further by ROPIN method if IC > 2SD > 0 then that drug-ADR pair considered as no signal; if 0IC ≤ 2SD ≤ 1.5 then that drug-ADR pair considered as weak signal; if 1.5 ≤ ICSD ≤ 3 then that drug-ADR pair considered as middle signal; if IC > 2SD then that drug-ADR pair considered as strong signal].

Results: A total of 28 reports of cisplatin-induced ototoxicity and 122 reports of carboplatin-induced pruritus were obtained from CADRMP database. For cisplatin, the PRR was found to be 53.44 and by the Du Mouchel Method it was 20.7977. Further, the PRR calculated by chi-square statistics was 244.70 whereas the lower and upper limits of 95% CI of PRR was found to be 3.67 and 4.57, respectively. The O/E ratio was found to be 20.5130 and ROR was found to be 55.63 for cisplatin-induced ototoxicity. For carboplatin, the PRR was found to be 7.04412 and by the Du Mouchel Method it was 16.4360. Further, the PRR calculated by chi-square statistics was 623.36645 whereas the lower and upper limits of 95% CI of PRR was found to be 2.9167 and 3.6475, respectively. The O/E ratio was found to be 16.43854 and reporting odds ratio was found to be 7.60865 for carboplatin-induced pruritus. The value of ICSD was 2.91414 indicates middle signal for cisplatin-induced ototoxicity. However, the value of ICSD is 7.9495 indicates middle signal for carboplatin-induced pruritus.

Conclusion: The signal of ototoxicity coupled with cisplatin and of pruritus coupled with carboplatin was found significant enough to induce ototoxicity and pruritus respectively in the Canadian population.

Keywords: Cisplatin, Carboplatin, Signal detection, Ototoxicity, Pruritus.

INTRODUCTION
Cancer is a leading cause of death worldwide, accounting for 7.6 million deaths (around 13% of all deaths) [1]. Only 5–10% of all cancer cases can be attributed to genetic defects, whereas the remaining 90–95% have their roots in the environment and lifestyle. The lifestyle factors include cigarette smoking, diet (fried foods, red meat), alcohol, sun exposure, environmental pollutants, infections, stress, obesity, and physical inactivity. The evidence indicates that of all cancer-related deaths, about 25–30% are due to tobacco, as many as 30–35% are linked to diet, about 15–20% are due to infections, and the remaining percentage are due to other factors like radiation, stress, physical activity, environmental pollutants etcetera [2]. Platinum analogues have become the mainstay of treatment for many tumors including ovarian cancer, lung cancer, germ cell tumors, head and neck cancer, bladder cancer and to a lesser degree breast cancer and gastric cancer. Cisplatin was introduced into clinical practice with a toxicity profile characterized by nausea and vomiting, renal dysfunction and neurotoxicity and ototoxicity. Carboplatin was the second clinically important platinum analogue. Carboplatin is less nephrotoxic and less emetogenic than cisplatin and neurotoxicity and ototoxicity are virtually absent. Myelosuppression is the major toxic effect of carboplatin and combining carboplatin with other cytotoxic agents may be complicated [3, 4].

Number of adverse event reports (AERs) has been submitted to the US Food and Drug Administration (FDA) to confirm a relation between piomium agents and hypersensitivity reactions. This database created on the basis of reports to the FDA by health professionals, consumers, and manufacturers. This system is referred to as the Adverse Event Reporting System (AERS). These results were evaluated quantitatively by signal detection, where a signal means a drug-associated adverse event [5]. Signal-detection algorithms (SDAs) are recognized as major tools in pharmacovigilance. However, their performance characteristics are generally unknown. By leveraging a unique gold standard recently made public by the Observational Medical Outcomes Partnership (OMOP) and by conducting a unique systematic evaluation, we provide new insights into the diagnostic potential and characteristics of SDAs that are routinely applied to the US Food and Drug Administration (FDA) Adverse Event Reporting System (AERS) [6]. The objective of the study was to identify possible toxic signal detection (SD) of cisplatin and carboplatin by searching database from Canadian Adverse Reaction Monitoring Program (CADRMP).

MATERIALS AND METHODS
Data collection from public database

The CADRMP is the Health Canada post-marketing surveillance program which collects and reviews suspected adverse reaction reports for Canadian marketed health products such as cisplatin and carboplatin. Data was extracted from Canadian Adverse Drug Reaction Monitoring Program. For evaluation following sections were serially accessed from health Canada website [http://www.hc-sc.gc.ca/index-eng.php]: Drug and health products and Med Effect Canada Adverse Reactions [7]. Finally, in the section of Canada vigilance program, the CADRMP online database was extracted.

Procedure followed for signal detection in this study

Individual Case Safety Reports (ICSRs) in this database were
THERAPEUTIC CLASS-SPECIFIC SIGNAL DETECTION OF PACLITAXEL-INDUCED TACHYCARDIA

Sharwan Kumar Singhal*, Bhaswati S. Chakraborty
Department of Clinical Research and Pharmacology, Cadila Pharmaceuticals Ltd. Ahmedabad, Gujarat (India)

ABSTRACT

Introduction: Paclitaxel is one of the most widely used taxane group anti-cancer drug for lung cancer, ovarian cancer, breast cancer and head & neck cancer. Paclitaxel is a mitotic inhibitor used in cancer chemotherapy since 1967. shows a number of serious and non-serious adverse events. Objective: Major objective of this study was to identify possible toxic signal detection (SD) of paclitaxel by searching database from Canadian Adverse Reaction Monitoring Program (CADRMP). Materials and Methods: Data was extracted from CADRMP and appropriate statistical methods were used for Adverse drug reaction (ADR) signal detection such as, proportional reporting ratio (PRR); reporting odds ratio (ROR); the Chi-square (χ²) statistic method; the 95% confidence interval (CI); the observed to expected ratio (O/E); and Du Mouchel method were used to calculate the possible signals. Significance of χ² and other calculated statistics, e.g., PRR and ROR, was based on a composite criterion of regulatory guidelines and not on any particular statistical level of significance. Results: Calculated statistics by different methods were compared with regulatory criteria of a statistic value ≥ 4.0 for χ², and ≥ 3.0 for the rest for SD to be declared significant. The PRR statistic was found to be 4.2607; the ROR method it was 4.4175; the χ² statistic was 77.2786; whereas the lower and upper limits of 95% CI of PRR were found to be 1.7979 and 1.1023, respectively, by the O/E ratio was found to be 3.8029, and PRR with the help of Du Mouchel was found to be 3.8029. Thus, the tachycardia–Paclitaxel Signals calculated in this study were significant. Conclusions: The therapeutic class specific signal of tachycardia coupled with paclitaxel was found potent enough to cause tachycardia.
Signal Detection of Docetaxel in Canadian Spontaneous Adverse Event Reports


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ABSTRACT

Introduction: Cancer is one of the most widespread and feared diseases in the world today. It is due largely to the lack of effective therapies. The reason for this difficulty is that cancer results from the uncontrolled multiplication of subpopulations of normal human cells. One of the main methods of modern cancer treatment is drug therapy (chemotherapy). Docetaxel is a clinically well established anti-tumor chemotherapy medication (that is, it interferes with cell division). It is used mainly for the treatment of breast, ovary, and non-small-cell lung cancer. Docetaxel has FDA approval for treatment of patients who have already advanced or metastatic breast or non-small-cell lung cancer who have undergone anthracycline-based chemotherapy and failed to stop cancer progression or relapsed and a European approval for use in hormone-refractory prostate cancer. Docetaxel binds to microtubules reversibly with high affinity and has a maximum stability of 1 mole docetaxel per mole tubulin in microtubules. This binding stabilizes microtubules and prevents depolymerization of microtubules, decreased temperature and vasoconstriction, preferentially at the plasma of the microtubule. Docetaxel has been found to accumulate in higher concentrations in ovary adenocarcinoma cells than in breast cancer cells, which may contribute to the more effective treatment of ovarian cancer by docetaxel. It has also been found to lead to the phosphorylation of caspase-related BCL-2, which is apoptosis blocking in its inactivate form. Most common adverse reactions across docetaxel indications are infections, neutropenia, anemia, febrile neutropenia, hypersensitivity, thrombocytopenia, neuropathy, dysgeusia, hyperglycemia, anemia, neutropenia, abnormal liver function tests, abdominal pain, nausea, diarrhea, vomiting, mucositis, anorexia, skin reactions, myalgia but flushing is reported in very minor category of hypersensitivity reaction. Objective: Major objective of this study was to extract from Canadian Adverse Reaction Monitoring Program (CADRMP) database for possible toxic signal detection (ST) of docetaxel, evaluate the frequency of the flushing associated with these different acknowledged groups for a positive signal, and generate awareness in healthcare professionals regarding usefulness of ST. Materials and Methods: Appropriate statistical methods were used for Adverse drug reaction (ADR) signal detection such as, proportion reporting ratio (PRR), reporting odds ratio (ROR), chi-square (X2) statistic method, for 95% confidence interval (CI), observed to expected ratio (O/E), and Da Mouchel method were used to calculate the possible signals. Significance of X2 and other calculated statistics e.g., PRR and ROR, was based on a composite criterion of regulatory guidelines and on any particular statistical level of significance. Results: Calculated statistically significant were compared with regulatory criteria of a statistic value + 1.645 for X2, and +1.96 for the ROR for ST to be declared significant. The ROR statistical was found to be: 4.3830, by the ROR method it was 4.3830; the X2 statistic was 205.9988, whereas the lower and upper limits of 95% CI of ROR were found to be 1.213 and 1.6247, respectively, by the O/E ratio was found to be 1.6780, and PR with the help of DaMouchel was found to be 1.6772. Thus, the flushing–docetaxel signal calculated in this study were significant. Conclusions: The therapeutic classes specific signal of flushing associated with docetaxel was found potent enough to cause flushing.

Key words: Adverse drug reactions, Canadian adverse reaction monitoring program, Docetaxel, signal, detection

INTRODUCTION

The WHO defines a toxic signal as: “Reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously.”[1] Usually, more than a single report is required to generate a signal, depending upon the seriousness of the event and quality of the information.

Adverse drug reactions (ADRs) are thought to be the 4th largest cause of death in the USA and are estimated to occur 2-7% of all hospital admissions.[2] More than half of these ADRs are not recognized by the physician on admission, and ADRs may be responsible for deaths of 15 of 1000 patients admitted.[3] There is a need of closer link between the market authorization holder (MAH) and the pharmacovigilance (PV) system, allowing products to be authorized earlier under strict and clearly defined rules for post-authorization safety studies, thus offering hope to patients with currently unmet medical needs.[4]

*Corresponding author:
Sharan Kumar Singh
CRO Cadila Pharmaceuticals Ltd.
1389, Trasad Road, Ahmedabad-380010
Pimp: Ahmedabad, Gujarat, India

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The role of SD and PV do not end by establishing a drug–ADR pair only; prompt regulatory actions need to be taken to appropriately restrict or ban the drug. In the recent past, critical opinions have brought about the side of many drugs from some countries that have been banned in other countries.[5] All over the world, nimesulide has been withdrawn, but unfortunately it still continues to be sold in some countries.[6] Another drug that has been voluntarily withdrawn recently is the manufacturer’s (Mediscan Health) drug, from the world market was valsartan, which was causing unforeseen.[7]

Cancer is a leading cause of death worldwide and accounted for 7.6 million deaths (around 13% of all deaths) in 2008. Tobacco use is a major risk factor for cancer. Harmful alcohol use, poor diet, and physical inactivity are other major risk factors. Cancer is a leading cause of death worldwide and accounted for 7.6 million deaths [around 13% of all deaths] in 2008. The main types of cancer are lung (1.4 million deaths), stomach (746,000 deaths), liver (738,000 deaths), colorectal (530,000 deaths), breast (485,000 deaths). More than 70% of all cancer deaths occurred in low- and middle-income countries. Deaths from cancer worldwide are projected to continue to rise to over 11 million in 2030.[8]

Docetaxel exhibits cytotoxic activity on breast, colorectal, lung, ovarian, gar-
Signal Detection for Cyclophosphamide: Canadian Adverse Reaction Monitoring Program (CADRMP)

Singhal Sharwan1 and Bhaswat Chakraborty 2

1 Department of Clinical Research, Cadila Pharmaceuticals Ltd., Ahmedabad, India
2Department of Pharmacology, Institute of Pharmacy, Nirma University, Sarkhej-Gandhinagar Highway, Chandodiya, Gota, Ahmedabad, Gujarat, India.

ABSTRACT

Objective: The objective of the study was to identify possible toxic signal induced by cyclophosphamide treatment by searching database from Canadian Adverse Reaction Monitoring Program (CADRMP). Method: A total of 10429 reports of patients between January 1970 to March 2010 were downloaded from CADRMP website. These reports contained information of adverse events associated with all other drugs inclusive of cyclophosphamide. Adverse drug reaction (ADR) signal detection were determined by proportional reporting ratio (PRR), reporting odds ratio (ROR), PRR calculated by chi-square statistics. 95% confidence interval of PRR, observed to expected (O/E) ratio and De Mouchel method calculated PRR. Information component (IC) was given by Bayesian confidence propagation neural network. (As per regulatory criteria, PRR ≥ 2, ROR ≥ 1, chi-square statistics calculated PRR ≤ 4 and lower bound of 95% CI of PRR ≥ 1 to consider particular adverse drug reaction as a signal. Further by BCPNN method, if IC ≥ 2SDx0 then that drug-ADR pair considered as no signal, if 0<IC<2SD ≤ 1.5, then that drug-ADR pair considered as weak signal, if 1.5<IC<2SD ≤ 3.0, then that drug-ADR pair considered as middle signal; if IC ≥ 2SD > 3.0, then that drug-ADR pair considered as strong signal). Results: A total of 106 reports of cyclophosphamide-induced neutropenia from CADRMP database. The PRR was found to be 4.7396 and by the De Mouchel Method it was 3.0310. Further, the PRR calculated by chi-square statistics was 2.3682518 whereas the lower and upper limits of 95% CI of PRR was found to be 1.3484 and 1.7634, respectively. The O/E ratio was found to be 3.9322 and ROR was found to be 4.0704. The value of IC/2SD was 1.6953 indicates middle signal for cyclophosphamide-induced neutropenia. The signal of neutropenia coupled with cyclophosphamide was found potent enough to cause neutropenia in Canadian population.

Key words: Bayesian confidence propagation neural network, Cyclophosphamide, Neutropenia, Proportional reporting ratio, Signal detection

INTRODUCTION

Signal detection in pharmcovigilence comprises the processes of selection of a drug-adverse event association of possible interest, the preliminary assessment of the available evidence; and a follow-up of how the signal develops. In the currently used automated systems, the computer selects drug-adverse event pairs that stand out against the background of the database, according prefixed statistical criteria, for example, using proportional reporting ratio (PRR) or, as is the case at the UMC, the information component (IC) calculated by a Bayesian Confidence Propagation Neural Network (BCPNN). Once the computer has at a given moment identified the associations that meet the quantitative criterion, individual assessors have to select those associations that deserve

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*Address for correspondence:
Mr. Sharwan Singhal, CRO-Cadila Pharmaceuticals Ltd., 1389, Trasad Road, Dholka-387810, Dist.: Ahmedabad, Gujarat, India.
E-mail: sharwansinghal@rediffmail.com