Innovare Academic Sciences

International Journal of Pharmacy and Pharmaceutical Sciences

ISSN- 0975-1491 Vol 7, Issue 6, 2015

Original Article

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

SHARWANKUMAR SINGHAL[1,2], BHASWAT CHAKRABORTY[1,2]

[1]Cadila Pharmaceuticals Ltd., Ahmedabad, India, 1389, Trasad Road, Dholka 387810, [2]Department of Pharmacology, Institute of Pharmacy, Nirma University, Sarkhej-Gandhinagar Highway, Chandlodia, Gota, Ahmedabad, Gujarat, India
Email: sharwansinghal@rediffmail.com

Received: 27 Jan 2015 Revised and Accepted: 28 Apr 2015

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 10429 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 (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 − 2SD ≤ 0 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 28 reports of cisplatin-induced ototoxicity and 122 reports of carboplatin-induced pruritis 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 544.70 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 20.9130 and ROR was found to be 55.03 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 7.6065 for carboplatin-induced pruritis. The value of IC-2SD was 2.9141 indicates middle signal for cisplatin-induced ototoxicity. However, the value of IC-2SD is 2.1995 indicates middle signal for carboplatin-induced pruritis.

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

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

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, almost 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 platinum 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 assesses suspected adverse reaction reports for Canadian marketed health products such as cisplatin and carboplatin. Date was extracted from Canadian Adverse Drug Reaction Monitoring Program. For extraction 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

collected from the official website of health Canada. The text freely available was converted into a structured format. On the structured format statistical methods were applied to calculate an actual measure of signals. Therapeutic class-specific SD calculations were then carried out as shown in fig. 1. Signal detection analysis were performed by different methods. These methods of calculations were selected following a systematic literature review [8-10]. In the present study attempt was made to maintain the originality of data collected from CADRMP database while computing actual standard deviation (SD).

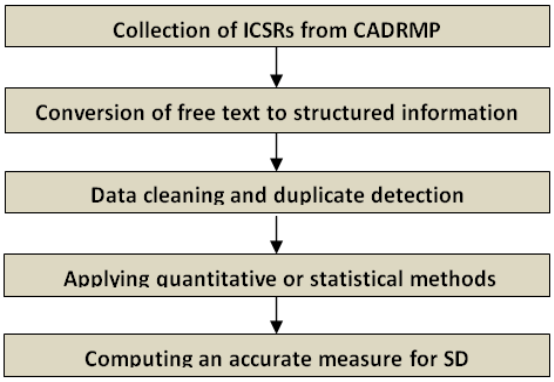

Fig. 1: Procedure followed for signal detection by statistical and quantitative methods

Calculation of signal detection

Disproportionality

These are the frequency or relative frequency of a particular drug–event pair. The signal would be considered significant if the statistics from different calculations such as Proportional Reporting Ratio (PRR), Reporting Odds Ratio (ROR), PRR calculated by chi-square statistics (χ^2), the 95% confidence interval for PRR (lower limit and upper limit), the observed-to-expected (O/E ratio) and Du-Mouchel method calculated PRR exceeded a certain value ((As per regulatory criteria, PRR ≥ 2 , ROR ≥ 1, chi -square statistics calculated PRR≥ 4 and lower bound limit of 95% CI of PRR≥ 1 to consider particular adverse drug reaction as a signal. Further by BCPNN method, if IC–2SD ≤ 0 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), then the signal would be considered significant [9].

PRR calculation

As shown in table 1 and table 2, a 2*2 contingency table was prepared to capture the incidences (targeted event Y) of Ototoxicity (for cisplatin) or Pruritis (for carboplatin) and all other events for the targeted drug X, i.e., Cisplatin or Carboplatin, in the database to calculate PRR [8]. After that, the PRR was calculated as follows:

$$\mathbf{PRR} = \frac{\mathbf{a / a+b}}{\mathbf{c / c+d}}$$

a = Targeted event (Y) associated with targeted drug

b = Other adverse drug reactions (ADRs) associated with targeted drug

c = Targeted event (Y) associated with other than targeted drug

d = Other adverse drug reactions (ADRs) with other than targeted drug

ROR calculation

The procedure is followed to calculate ROR was similar to that of the PRR method [8]. The same contingency table (table 1 and table 2) prepared for PRR, was also followed in the case of ROR calculations. The ROR was calculated as follows:

$$\mathbf{ROR} = \frac{\mathbf{a / b}}{\mathbf{c / d}}$$

a = Targeted event (Y) associated with targeted drug

b = Other adverse drug reactions (ADRs) associated with targeted drug

c = Targeted event (Y) associated with other than targeted drug

d = Other adverse drug reactions (ADRs) with other than targeted drug

The Chi-square (χ^2) statistic calculated PRR

The Chi-square statistic was applied to test the independence of categorical variables [9]. χ^2 was used as an alternative measure of heterogeneity in the contingency table which built with the medicinal product X and the adverse event Y. PRR calculated by chi-square statistics was calculated as follows:

$$\mathbf{Chi-Square} = \sum \frac{\mathbf{(Observed - Expected)^2}}{\mathbf{(Expected)}}$$

95% confidence interval of the PRR calculation

The standard error of the natural logarithm of the PRR was estimated based on the following formula:

$$\mathbf{SE} = \sqrt{\mathbf{1/A + 1/C - 1/(A+B) - 1/(C+D)}}$$

A = Targeted event (Y) associated with targeted drug

B = Targeted event (Y) associated with other than targeted drug

C = Targeted event (Y) and other adverse drug reactions (ADRs) associated with targeted drug

D = Targeted event (Y) and other adverse drug reactions (ADRs) associated with other than targeted Drug

The 95% CI for ln (PRR) was then estimated as ln (PRR)±1.96SE, and its exponential was taken [12]. The 95% confidence interval of the PRR can be calculated as per below equation:

Lower and upper limits of 95% CI for PRR = {PRR/exp (1.96SE), PRR/exp (1.96SE)} [5]

The observed-to-expected (O/E) ratio calculation

The O/E was [11] calculated as follows:

$$\mathbf{OE} = \frac{\mathbf{A/(A+B)}}{\mathbf{(A+C)/(A+B+C+D)}}$$

A = Targeted event (Y) associated with targeted drug

B = Other adverse drug reactions (ADRs) associated with targeted drug

C = Targeted event (Y) associated with other than targeted drug

D = Other Adverse drug reactions (ADRs) with other than targeted drug

Du Mouchel Method for PRR calculation

This method was based on 2*2 contingency table values as well as the ratio of values of A and expected A was taken into consideration for calculations. The PRR as per Du Mouchel Method was calculated as per below equation:

$$\mathbf{PRR} = \frac{\mathbf{A/(A+B)}}{\mathbf{(A+C)/N}} \quad \mathbf{E(a)} = \frac{\mathbf{(A+B)/(A+C)}}{\mathbf{N}} \quad \mathbf{PRR} = \frac{\mathbf{A}}{\mathbf{E(a)}}$$

A = Targeted Event (Y) associated with Targetted Drug

B = Other Adverse Drug Reactions (ADRs) associated with Targetted Drug

C = Targeted Event (Y) associated with other than Targetted Drug

D = Other Adverse Drug Reactions (ADRs) with other than Targetted Drug

N = Total sum of adverse drug reactions associated with drug and other than Targetted Drug

Signal detection by bayesian confidence propagation neural network method (BCPNN)

BCPNN has been chosen for ADR signal detection which realized through calculating the Information Components (IC) compared the calculating IC value with the BCPNN corresponding evaluation standard of signal detection to judge if the signal established or not [11]. The specific algorithm of BCPNN as follows:

N_{comb} (C_i) = A= Targeted Event (Y) associated with Targetted Drug

N_{drug} (C_j) = A+B= Targeted Event (Y) and Other Adverse Drug Reactions (ADRs) associated with Targetted Drug

N_{adr}(C_k) = A+C = Targeted Event (Y) associated with drug and other than Targetted Drug

N_{tot}(C) = A+B+C+D= Total sum of adverse drug reactions associated with drug and other than Targetted Drug

And considering: $\lambda = 1$, $\alpha = \beta = 1$, $\eta = \delta = 2$. Following different formulas used for signal detection by BCPNN methods

IC = $\log_2 ((N_{comb}+0.5)/(N_{adr}/N_{tot}*N_{drug}+0.5))$

γ $= \lambda(N+\delta)(N+\eta)/(C_j+\alpha)(C_k+\beta)$

E(IC) $= \log_2 (C_i+\lambda)(N+\delta)(N+\eta)/(N+\gamma)(C_j+\alpha)(C_k+\beta) = \log_2 {}^{\gamma(Ci+\lambda)/(N+\gamma)}$

V(IC) = $N\text{-}C_i+\gamma-\delta/(C_i+\lambda)$ $(1+N+\lambda)+N\text{-}C_j+\delta-\alpha/(C_j+\alpha)$ $(1+N+\delta)+N\text{-}C_k+\eta\text{-}\beta/(C_j+\beta)$ $(1+N+\eta)$

Statistical calculation

The statistical significance of PRR, ROR, Chi-square calculated PRR, O/E ratio, Du-Mouchel calculated PRR and information component statistics by BCPNN method was based on regulatory guidelines [9].

RESULTS

Proportional reporting ratio (PRR) and Reporting odds ratio (ROR)

The total of 10429 patient's reports were extracted from CADRMP. 970 reports of adverse event associated with cisplatin inclusive ototoxicity and 1442 reports of adverse event associated with carboplatin inclusive pruritis were noted. The relevant details for calculation of PRR and ROR are mentioned in table 1 and table 2 and table 3 and table 4. The signal detected with the help of "Proportional reporting ratio" for ototoxicity associated with cisplatin was found to be 53.44 and "Reporting Odds Ratio" for Ototoxicity associated with cisplatin was found to be 55.0370. However, the PRR with the help of Du Mouchel Method was found to be 20.9130.

For carboplatin, the signal detected with the help of "Proportional reporting ratio" for Pruritis associated with carboplatin was found to be 7.04412 and "Reporting Odds Ratio" for Pruritis associated with carboplatin was found to be 7.6065. However, the PRR with the help of Du Mouchel Method was found to be 16.4360.

As per above results for cisplatin and carboplatin, the value of PRR was ≥ 2 and value of ROR was ≥ 1 indicate toxic signal for ototoxicity associated with cisplatin and pruritis associated with carboplatin.

Table 1: Cisplatin-Data obtained from CADRMP to calculate PRR and ROR

Drug Name	Ototoxicity	Not Ototoxicity
Cisplatin	28	942
Not Cisplatin	17	31435

Table 2: Carboplatin-Data obtained from CADRMP to calculate PRR and ROR

Drug Name	Pruritis	Not Pruritis
Carboplatin	122	1320
Not Carboplatin	381	31341

Table 3: Cisplatin database reports details

Description	Numbers
Total Reports included in database	10429
Ototoxicity associated with Cisplatin	28
Other ADR's reported with Cisplatin	942
Ototoxicity associated with other than Cisplatin	17
Other ADR's associated with other than Cisplatin	31435

Table 4: Carboplatin database reports details

Description	Numbers
Total Reports included in database	10429
Pruritis associated with Carboplatin	122
Other ADR's reported with Carboplatin	1320
Pruritis associated with other than Carboplatin	381
Other ADR's associated with other than Carboplatin	31341

Chi-square statistics calculated PRR

For cisplatin, the relevant details for calculation of PRR by chi-square statistics is mentioned in table 5. The PRR value by chi-square statistics was 544.7096 for cisplatin. For carboplatin, the relevant details for calculation of PRR by chi-square statistics is mentioned in table 6. The value of PRR by chi-square statistics was 623.36645 for carboplatin.

The value of chi-square statistics calculated PRR was≥ 4 for both drugs which also indicates toxic signal for ototoxicity associated with cisplatin and pruritis associated with carboplatin.

Table 5: Cisplatin-data obtained from CADRMP to calculate signal detection (chi-square statistics)

Drug name	Ototoxicity	Not Ototoxicity	Total
Cisplatin	28	942	970
Not Cisplatin	17	31435	31452
Total	503	32661	32422

Table 6: Carboplatin-Data obtained from CADRMP to calculate signal detection (chi-square statistics)

Drug name	Pruritis	Not pruritis	Total
Carboplatin	122	1320	1442
Not Carboplatin	381	31341	31722
Total	503	32661	33164

95% Confidence interval for PRR

Cisplatin

The lower limit of 95% Confidence Interval of PRR was found to be 3.6728 and Upper limit was found to be 4.5776. 95% Confidence Interval of PRR has been computed as per mentioned below steps:

$$SE = \sqrt{1/A + 1/C - 1/(A+B) - 1/(C+D)}$$

$$= \sqrt{1/28 + 1/17 - 1/970 - 1/31452}$$

$$= \sqrt{0.03571 + 0.05882 - 0.001030 - 0.000031}$$

$$= \sqrt{0.09453 - 0.001061}$$

$$= \sqrt{0.09346}$$

SE = 0.3057

Therefore, 1.96 SE = 0.3057 x 1.96

= 0.5991

Hence, 95% Confidence Interval for PRR = ln(PRR)±1.96 SE

= ln(53.44)±1.96 (0.3057)

= 3.9785±0.5991

= 4.5776 and 3.6728

Carboplatin

The lower limit of 95% Confidence Interval of PRR was found to be 2.9167 and Upper limit was found to be 3.6475. 95% Confidence Interval of PRR has been computed as per mentioned below steps:

$$SE = \sqrt{1/A + 1/C - 1/(A+B) - 1/(C+D)}$$

$$= \sqrt{1/43 + 1/77 - 1/702 - 1/31497}$$

$$= \sqrt{0.02325 + 0.01298 - 0.00142 - 0.000031}$$

$$= \sqrt{0.03623 - 0.001451}$$

$$= \sqrt{0.03477}$$

SE = 0.18646

Therefore, 1.96 SE = 0.18646 x 1.96

= 0.3654

Hence, 95% Confidence Interval for PRR = ln (PRR)±1.96 SE

= ln (26.6326)±1.96 (0.18646)

= 3.2821±0.3654

= 3.6475 and 2.9167

The lower limit of 95% CI of PRR was ≥ 1 for both drugs indicates toxic signal for cisplatin-induced ototoxicity and carboplatin-induced pruritis.

Observed to expected ratio

Cisplatin

The Observed-to-expected ratio of PRR was found to be 20.9130. Observed to expected ratio has been computed as per mentioned below steps:

$$OE = \frac{28/(28+942)}{(28+17)/(28+942+17+31435)}$$

$$= \frac{28/970}{45/32422}$$

$$= \frac{0.02886}{0.00138}$$

OE = 20.9130

Carboplatin

The Observed-to-expected ratio of PRR was found to be 16.43854. Observed to expected ratio has been computed as per mentioned below steps:

$$OE = \frac{43/(43+659)}{(43+77)/(43+659+77+31420)}$$

$$= \frac{43/702}{120/32199}$$

$$= \frac{0.06125}{0.00372}$$

= 16.43854

Data by gender and age

The data obtained from CADRMP were stratified by years (table 7, 8and fig. 2, 3), age (table 9, 10, fig. 4 and 5) and gender (table 11 and table 12). Highest cases of ototoxicity were reported between 2006 and 2010 and however highest cases of pruritis were reported between 1996 to 2000.

Males were prone to cisplatin-ototoxicity whereas females were prone to carboplatin associated with pruritis. The results of age-stratified cases of cisplatin-induced ototoxicity and carboplatin-induced pruritis were mentioned in table fig. 4 and fig. 5, respectively.

Table 7: Year specific data of cisplatin-induced ototoxicity

Year	Cases	Ototoxicity	Other ADRs
1976-1980	4	1	6
1981-1985	22	0	30
1986-1990	18	1	18
1991-1995	55	2	176
1996-2000	64	2	203
2001-2005	66	0	247
2006-2010	64	22	211

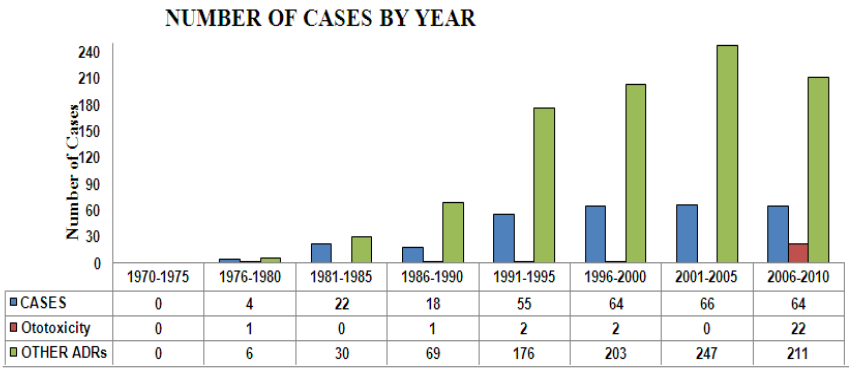

Fig. 2: Year specific data of cisplatin-induced ototoxicity

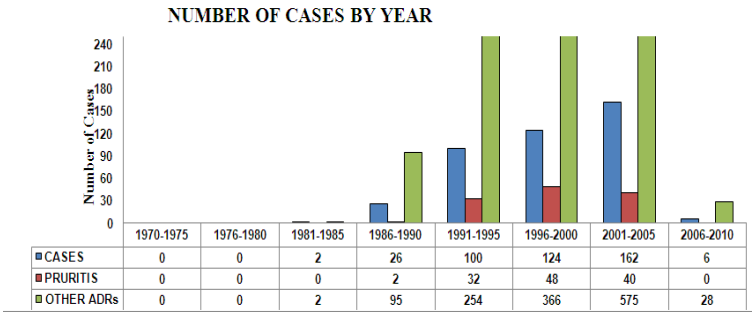

Fig. 3: Year specific data of carboplatin-induced pruritis

Table 8: Year specific data of carboplatin-induced pruritis

Year	Cases	Pruritis	Other ADRs
1985-1990	28	2	97
1991-1995	100	32	254
1996-2000	124	48	366
2001-2006	168	40	603

Table 9: Age specific data of cisplatin-induced ototoxicity

Age Range	No. of Cases	Ototoxicity	%
0-18 Years	30	22	10.2
19-60 Years	193	6	65.9
>61 Years	70	0	23.9
Total	293	28	100.0

Table 10: Age specific data of carboplatin-induced pruritis

Age Range	No. of Cases	Pruritis	%
0-18 Years	14	4	3.3
19-60 Years	233	72	55.5
>61 Years	173	46	41.2
Total	420	122	100.0

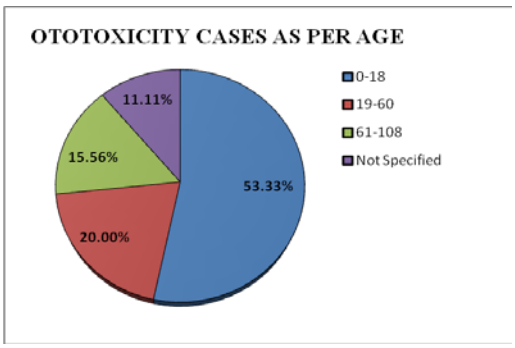

Fig. 4: Age specific data of cisplatin-induced ototoxicity

Table 11: Gender specific data of cisplatin-induced ototoxicity

Gender	No. of Cases	Ototoxicity	%
Females	171	13	58.4
Males	122	15	41.6
Total	293	28	100.0

Table 12: Gender specific data of carboplatin-induced pruritis

Gender	No. of Cases	Pruritis	%
Females	149	42	35.5
Males	271	4	64.5
Total	420	46	100.0

Signal detection by bayesian confidence propagation neural network

The value of information component (IC) by BCPNN for cisplatin and carboplatin were mentioned in table 13, 14, and table 15. For cisplatin, the value of IC was 4.4031, the value of IC-2SD was observed 2.9141 means middle signal for ototoxicity in Canadian data base (1.5<IC−2SD ≤ 3.0). For carboplatin, the value of IC was 2.4851, the value of IC-2SD was observed 2.1995 means middle signal for Pruritis in Canadian data base (1.5<IC−2SD ≤ 3.0). The conclusive summary for both drugs were mentioned in table 16.

Table 13: Cisplatin-data obtained from CADRMP to calculate signal detection by BCPNN method

Drug name	Ototoxicity	Not Ototoxicity	Total
Cisplatin	28	942	970
Not Cisplatin	17	31435	31452

Table 14: Carboplatin-data obtained from CADRMP to calculate signal detection by BCPNN method

Drug name	Pruritis	Not Pruritis	Total
Carboplatin	122	1320	1442
Not Carboplatin	381	31341	31722

Table 15: Cisplatin and carboplatin-data derived by BCPNN Method

Drug name	IC	γ	E (IC)	V(IC)	SD	IC−2 SD	IC+2 SD
Cisplatin	4.4031	23392.311	3.6122	0.12185	0.3490	2.9141	4.2303
Carboplatin	2.4851	1512.4789	2.4235	0.02040	0.1428	2.1995	2.7707

Table 16: Cisplatin and carboplatin-conclusive summary

Drug Name	PRR	ROR	Chi-Square Test	95% CI	O/E Ratio	DM Method (PRR)	BCPNN Method (IC-2SD value)	Signal Output significance	p-Value
Cisplatin	53.44	55.03	544.70	4.57 & 3.67	20.9130	20.7977	2.91	Middle	<0.001
Carboplatin	7.04	7.60	458.43	1.97 & 1.93	16.43854	16.4360	2.19	Middle	<0.001

P-value calculated by chi-square test, likelihood chi-square test, continuity-adjusted chi-square test and Mantel–Haenszel chi-square test for both drugs

Statistical analysis

As per statistical analysis by SAS version 9.2 software, the chi-square value was observed 544.70 for cisplatin and 486.62 for carboplatin which was further supported by p value 0.001 which showed significant signal of ototoxicity associated with cisplatin and pruritis associated with carboplatin.

DISCUSSION

The Canadian Adverse Drug Reaction Monitoring Program (CADRMP) of the Marketed Health Products Directorate (MHPD) of Health Canada collects reports of suspected adverse events to health products (including pharmaceuticals, biologics, natural health products, and radiopharmaceuticals) marketed in Canada. Adverse events include adverse reactions and medication incidents. Adverse reactions are noxious and unintended responses and include any undesirable patient effects suspected to be associated with the use of health products. Medication incidents are preventable events that may cause or lead to inappropriate use or patient harm, and are the most common (known) single preventable cause of patient injury [12].

Pharmacovigilance analysis aims to search for previously unknown patterns and automatically detect important signals, i.e., drug-associated adverse events, from such a large database. Recently developed data mining tools for pharmacovigilance have been successful at detecting signals that could not be found by individual case reviews and that warrant further investigation together with continuous surveillance. For this reason, data mining tools are being routinely used for pharmacovigilance, supporting signal detection and decision-making at companies, regulatory agencies, and pharmacovigilance centers [13-19]. Despite of limitation to report spontaneously, the CADRMP is the wealthy resource and the data mining tools provide a string means of identifying potential associations between drugs and adverse events.

Cancer chemotherapeutic drugs like cisplatin have a very high potential for drug toxicity [20]. However, the number of ADR reports from the cancer wards to the pharmacovigilance center of our hospital was minimal. The reason for this paradox was not clear. It could be either due to gross underreporting of adverse drug reactions or due to effective preventive measures being adopted for the patients receiving cancer chemotherapy. Platinum compounds (cisplatin and carboplatin) are most commonly used drugs for cancer chemotherapy. Cisplatin is a commonly used anti neoplastic agent. Some of the well documented cisplatin-induced ADRs include nausea, vomiting,renal toxicity, ototoxicity, peripheral neuropathy, hypersensitivity reactions and electrolyte disturbances [20].

Cisplatin-induced nausea and vomiting are preventable ADRs due to better predictability and thorough mechanisms to explain their cause. However, ADRs such as ototoxicity, hypersensitivity reactions, and electrolyte disturbances are not preventable due to the poor predictability of the ADRs, poorly understood mechanisms and due to lack of reporting of these ADRs.[20] However, as per previous certain reports, it is concluded that cisplatin-induced ototoxicity is due to genetic variants of thiopurine Smethyltransferase (TPMT) and catechol O-methyltransferase (COMT) [21]. As per recent study in India, 9.8 percentage of patients reported ototoxicity possibly due to cisplatin [20]. Recent study at Cape Town, authors reported that cisplatin shows associated with a high incidence of ototoxicity, characterized by irreversible bilateral hearing loss and affecting 23-50% of adults who receive the drug [22].

Hypersensitivity reactions (HSRs) are considered uncommon during treatment with anticancer agents, platinum agents, taxanes, procarbazine, asparaginase, and epipodophyllotoxins are thought to increase the susceptibility to such reactions [23]. Previously pharmacoepidemiological analyses were performed to confirm the HSRs caused by these agents, using more than a million AERs submitted to the FDA.[23] Carboplatin reported Hypersensitivity reactions (rash, urticaria, erythema, pruritus, and rarely bronchospasm and hypotension) in 2% of the patients [24]. The clinical features of carboplatin-induced HSRs are highly variable and difficult clinical management issue [25].

In this study, twenty eight reports of ototoxicity associated with cisplatin and 122 reports of Pruritis associated with the carboplatin were reported as per data received from CADRMP in 30 years (01/01/1970–01/03/2010). Further, 17 reports of ototoxicity were not associated with cisplatin whereas 381 reports of pruritis were not associated with carboplatin.

For cisplatin, the values of PRR (53.44), ROR (55.03), PRR calculated by chi-square statistics (544.70), 95% confidence interval of PRR (3.67 & 4.57), O/E ratio (20.9130), PRR by Du-Mouchel Method (20.7977) suggest toxic signal for ototoxicity. Further, the value of IC-2SD value was 2.91 for cisplatin which also suggest middle intensity for ototoxicity associated with cisplatin. For carboplatin, the values of PRR (7.04), ROR (7.60), PRR calculated by chi-square statistics (458.43), 95% confidence interval of PRR (1.93 & 1.97), O/E ratio (16.43854), PRR by Du-Mouchel Method (16.4360) suggest toxic signal for pruritis. Further, the value of IC-2SD value was 2.19 for carboplatin which also suggest middle intensity for pruritis associated with carboplatin.

Based on above analysis and available literature for cisplatin-induced ototoxicity and carboplatin-induced pruritis. It is recommended that treating physician should anticipate and counsel the patient adequately prior to starting of therapy to minimize above uncommon adverse effects.

ACKNOWLEDGMENT

The authors thank Mr. Hardik Dodiya and Mr. Vipul Modh for his support throughout the conduct of study.

CONFLICT OF INTERESTS

Declared None

REFERENCES

1. World Health Organization Fact sheet. 2013. Available from: http://www.who.int/mediacentre/factsheets/fs297/en/# [Last accessed 15 Apr 2013].
2. Anand P, Kunnumakara AB, Sundaram C, Harikumar KB, Tharakan ST, Lai OS, *et al.* Cancer is a preventable disease that requires major lifestyle changes. Pharm Res 2008;25:2097–116.
3. Connie Henke Yarbro. Carboplatin: A clinical review. Seminars Oncology Nursing 1989;5:63–9.
4. Lokich J, Anderson N. Carboplatin versus cisplatin in solid tumors: an analysis of the literature. Annals of Oncology 1998;9:13-21.
5. Sakaeda T, Kadoyama K, Okuno Y. Adverse event profiles of platinum agents: data mining of the public version of the FDA adverse event reporting system, AERS, and reproducibility of clinical observations. Int J Med Sci 2011;8:487-91.
6. Harpaz R, DuMouchel W, LePendu P, Bauer-Mehren A, Ryan P, Shah NH. Performance of pharmacovigilance signal-detection algorithms for the FDA adverse event reporting system. Clin Pharmacol Ther 2013;93:539-46.
7. Health Canada. Available from: http://www.hc-sc.gc.ca/index-eng. php. [Last accessed 15 Apr 2013].
8. Norén GN. Statistical methods for knowledge discovery in adverse drug reaction surveillance typeset by LATEX, Department of Mathematics, Stockholm University, Stockholm; 2007. p. 1–41. Available from: http://www.diva-portal.org/smash/get/diva2:197004/FULLTEXT01.pdf
9. Eudravigilance Expert Working Group (EV-EWG), European Medicine Agency Guidelines, London; 2006. p. 1-22.
10. Health Canada. Canadian adverse event reporting program. Available from: Http://www.CADRMP/index_e.jsp.
11. Bate A, Lindquist M, Edwards IR, Orre R. A data mining approach for signal detection and analysis. Drug Saf 2002;25:393-7.
12. Health Canada. Canadian adverse event reporting program. Available from: www.hc-sc.gc.ca/ahc-asc/activit/atip-aiprp/priv-prot/pia-efvp-a-eng.php
13. Evans SJ, Waller PC, Davis S. Use of proportional reporting ratios (PRRs) for signal generation from spontaneous adverse drug reaction reports. Pharmacoepidemiol Drug Saf 2001;10:483-6.
14. Van Puijenbroek EP, Bate A, Leufkens HG, Lindquist M, Orre R, Egberts AC. A comparison of measures of disproportionality for signal detection in spontaneous reporting systems for adverse drug reactions. Pharmacoepidemiol Drug Saf 2002;11:3-10.

15. Bate A, Lindquist M, Edwards IR, Olsson S, Orre R, Lansner A, *et al.* A Bayesian neural network method for adverse drug reaction signal generation. Eur J Clin Pharmacol 1998;54:315-21.
16. Szarfman A, Machado SG, O'Neill RT. Use of screening algorithms and computer systems to efficiently signal higher-than-expected combinations of drugs and events in the US FDA's spontaneous reports database. Drug Saf 2002;25:381-92.
17. Bate A, Evans SJ. Quantitative signal detection using spontaneous ADR reporting. Pharmacoepidemiol Drug Saf 2009;18:427-36.
18. Gould AL. Practical pharmacovigilance analysis strategies. Pharmacoepidemiol Drug Saf 2003;12:559-74.
19. Almenoff JS, Pattishall EN, Gibbs TG, DuMouchel W, Evans SJ, Yuen N. Novel statistical tools for monitoring the safety of marketed drugs. Clin Pharmacol Ther 2007;82:157-66.
20. Surendiran A, Balamurugan N, Gunaseelan K, Akhtar S, Reddy KS, Adithan C. Adverse drug reaction profile of cisplatin-based chemotherapy regimen in a tertiary care hospital in India: An evaluative study. Indian J Pharmacol 2010;42:40-3.
21. European Medicine Agency: Pharmacovigilance working party (PhVWP). plenarymeeting. Cisplatin–Risk of increased ototoxicity in patients with genetic variants of TMPT and COMT. 2010. Available from: http://www.ema.europa.eu/htms/human/phv/reports.htm
22. Whitehorn H, Sibanda M, Lacerda M, Spracklen T, Ramma L, Dalvie S, *et al.* High prevalence of cisplatin-induced ototoxicity in Cape Town, South Africa. S Afr Med J 2014;104:288-91.
23. Kadoyama K, Kuwahara A, Yamamori M, Brown JB, Sakaeda T, Okuno Y. Hypersensitivity reactions to anticancer agents: Data mining of the public version of the FDA adverse event reporting system, AERS. J Exp Clin Cancer Res 2011;30:93-8.
24. Paraplatin: Product Monograph. Available from: http://www.fda.gov/ohrms/dockets/ac/05/briefing/20054180b_03_05_Carboplatin%20label%201-9-04%20FDA.pdf
25. Maurie M, Kennedy A, Webster K, Elson P, Peterson G, Kulp B, *et al.* Clinical Features of hypersensitivity reactions to carboplatin. J Clin Oncol 1999;17:1141-5.