Print ISSN 2319-2003 | Online ISSN 2279-0780

IJBCP International Journal of Basic & Clinical Pharmacology

doi: http://dx.doi.org/10.18203/2319-2003.ijbcp20150368

Research Article

Can occupational exposure to antineoplastic drugs increase levels of an inflammatory trigger?

T. Kamalasundar[1], Padmaja Udaykumar[1]*, Prabin Shah[2]

[1]Department of Pharmacology, Father Muller Medical College, Mangalore, Karnataka, India, [2]Department of Biochemistry, Father Muller Medical College, Mangalore, Karnataka, India

Received: 19 December 2014
Revised: 19 June 2015
Accepted: 05 July 2015

***Correspondence to:**
Dr. Padmaja Udaykumar, Email: padmajaudaykumar@gmail.com

ABSTRACT

Background: Antineoplastic drugs (AND) are known to cause collateral damage to normal cells by oxidative stress. This study was conducted to check for oxidative stress in occupational exposure to these drugs using advanced oxidation protein products (AOPP).
Methods: Cross-sectional comparison of serum AOPP levels of 33 nurses occupationally exposed and serum AOPP levels of 30 nurses not exposed using modified AOPP method.
Results: Serum AOPP levels were significantly increased ($p<0.001$) in the exposed group (16.66±3.31) compared to the unexposed group (12.87±2.62).
Conclusion: This study highlights oxidative stress in the form of protein oxidation occurring in nurses exposed to AND.

Keywords: Antineoplastic drugs, Nurses, Advanced oxidation protein products, Protein oxidation

INTRODUCTION

Oxidative stress is the imbalance between oxidant and antioxidant systems inside a cell in which the oxidative systems predominate over the antioxidant systems.[1] Antineoplastic drugs (AND) can create collateral damage to non-cancerous tissue by oxidation of nucleic acids, lipids, and proteins.[2] Nurses occupationally exposed to these drugs during handling are at risk of AND-induced adverse effects. Early determination of oxidative stress can prevent these effects in the exposed nursing professionals.[3] Biomarker of oxidant-induced reactions has the potential to detect oxidative stress. Novel marker of protein oxidation, advanced oxidation protein products (AOPP) can be quantified by absorbance at 340 nm using ultraviolet (UV) spectrophotometer.[4]

Objective

This study intends to use serum AOPP levels to detect oxidative stress in nurses involved in the preparation and administration of AND for more than 3 months and collect data regarding safety measures followed during handling of AND. It is hypothesized that if protein oxidation occurs due to exposure of AND during preparation and administration, the serum AOPP levels of nurses occupationally exposed to AND should be higher than the serum AOPP levels of nurses not exposed to AND.

METHODS

Hospital-based cross-sectional comparison between serum AOPP levels of nurses occupationally exposed to AND

and serum AOPP levels of nurses not exposed to AND was conducted within a time frame of 2 months in 2014 at a tertiary care hospital in Mangalore after obtaining ethical clearance from Father Muller Institutional Ethics Committee. Nurses between 20 and 40 years of either sex were included. Exposed group consisted of nurses with minimum 3 months of history of handling (preparation and administration) of AND. Unexposed group consisted of nurses not involved in the preparation and administration of AND. Nurses with history of alcohol or tobacco usage; history of diabetes mellitus, cardiovascular, hepatic or renal disorders; history of any acute or chronic inflammatory disease were excluded from volunteering. 33 nurses volunteered to be included in the exposed group and 30 nurses volunteered in the unexposed group. After obtaining written informed consent from each subject, data regarding age, gender, marital status, experience with the history of handling AND, and safety procedures followed (for exposed group) were collected. 2 ml of blood sample was collected in coded vacutainers from nurses of both the exposed and unexposed group. Each blood sample was centrifuged at 3000 rpm for 5 mins to separate the serum. Serum was stored in coded 1.5 ml vials at −20°C for the convenience of testing at a later date. Serum was thawed at 4°C for 20 mins before shifting to room temperature.

AOPP was measured using the following modified AOPP method:[5]

1. 320 µl of serum+8 µl of magnesium chloride+32 µl phosphotungstic acidàcentrifuge for 5000 rpm for 20 mins à collect supernatant;
2. 200 µl of supernatant+800 µl of phosphate buffer solution+50 µl of potassium iodide+100 µl of acetic acid → absorbance at 340 nm measured using UV 1700 spectrophotometer. AOPP readings were expressed in chloramine-T equivalent. Statistics: data collected in this study was analyzed by mean, standard deviation, and Student's (unpaired) *t*-test using Statistical Package for Social Sciences version 13. Since the data followed a normal distribution, comparison of two groups by parametric analysis using Student's (unpaired) *t*-test was done.

RESULTS

The demographic data among the female nurses of both exposed and unexposed group matched (Table 1). The exposed group nurses were found to be handling known oxidative stress-inducing drugs (Table 2).

Safety procedures were undertaken by the exposed group: (1) 18 subjects had access to bio-safety cabinet only for past 6 months, which helps in preventing exposure to antineoplastic drugs during the preparation phase. But, the usage of this provision was not adhered by nurses, due to high patient load receiving chemotherapy during a given time and less nurses posted to manage the patient load (as reported by the nurses). 15 subjects did not have access to bio-safety cabinet as they were not provided by the hospital, (2) All 33 subjects reported usage of latex gloves and disposable mask during preparation phase; they also reported use of spill kits in case of spillage of any AND, (3) only 3 subjects reported usage of protective goggles and gown during the preparation phase, (4) All 33 subjects reported usage of latex gloves during the administration of chemotherapy to patients.

AOPP was quantified by spectrophotometer (absorbance at 340 nm) and expressed in units of chloramine-T equivalent (Figures 1 and 2). Serum AOPP level in the exposed group

Figure 1: Serum advanced oxidation protein products levels of 33 exposed group nurses.

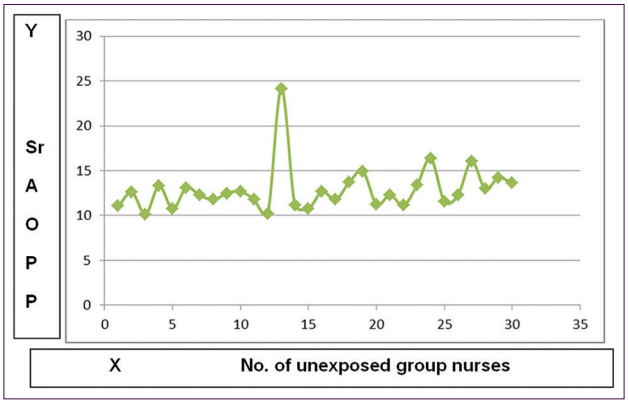

Figure 2: Serum advanced oxidation protein products levels of 30 unexposed group nurses.

Table 1: Demographic data of exposed and unexposed group.

Nurses	Age (years)		Gender		Female nurses planning for pregnancy
	21-30	31-40	Male	Female	
Exposed	31	2	2	31	3
Unexposed	29	1	0	30	1

was found to be significantly higher than serum AOPP level in the unexposed group ($p<0.001$) using Student's *t*-test (Table 3).

The data from exposed group nurses were sub-grouped as follows:

1. Sub-group 1: Nurses handling AND for ≤1 year and those nurses handling AND for > 1 year. There was no significant difference ($p>0.05$) found in this sub-group (Table 4).
2. Sub-group 2: Nurses using bio-safety cabinet (irregularly) and those nurses who did not have access to this equipment. There was no significant difference ($p>0.05$) found in this subgroup (Table 5).

DISCUSSION

Gómez-Oliván et al. and Mahboob et al. had individually monitored the oxidative stress in nurses exposed to AND and observed the elevation of lipid peroxidation-induced oxidative stress marker malondialdehyde (MDA).[3,6] Since AOPP accumulation exists even when MDA levels are stable, protein oxidation products are more accurate marker of oxidative stress than lipid peroxidation products.[6] In the present study, serum AOPP marker is used to check for oxidative stress.

Witko-Sarsat et al. using spectroscopic analysis had observed that human serum albumin exposed to reactive oxygen species (ROS) formed AOPP. AOPP mainly consists of dityrosine containing cross-linked protein products and it has the capacity to trigger respiratory burst in polymorphonuclear cells and monocytes, thereby causes hyperinflammation.[7] Anderstam et al. had concluded that AOPP concentration is largely overestimated due to lipid interferences. Modified AOPP method which requires precipitation of triglycerides before analysis yields AOPP values which more accurately reflect oxidative stress.[5] The present study uses modified AOPP method to check oxidative stress in nurses handling AND.

In the present study, serum AOPP levels of young nurses occupationally exposed to AND was found to be significantly higher than those not exposed to AND. Hence, oxidative stress should be higher in the exposed group compared to the unexposed group. The elevated levels of this protein oxidation marker can probably be due to ROS-induced reactions caused by AND which can enter through inhalation, accidental ingestion, skin contact due to workplace environment contamination since nurses with other etiologies have been excluded.[2,8]

Yoshida et al. had observed lymphocyte DNA damage (increase in tail length) by single cell gel electrophoresis (comet assay) in nurses exposed to AND due to workplace environment contamination. Nurses especially those who are planning for pregnancy, should be aware of genotoxicity risk as it can lead to infertility or fetal damage.[8]

Table 2: Oxidative stress inducing AND handled by the exposed group nurses.

AND handled by the exposed group	Oxidative stress inducing drugs[2] handled
Cisplatin, carboplatin, oxaliplatin, 5-fluorouracil, cytarabine, cyclophosphamide, ifosfamide, etoposide, adriamycin, vincristine, vinblastine, paclitaxel, daunorubicin, methotrexate, L-asparaginase	Cisplatin, carboplatin, oxaliplatin, cytarabine, cyclophosphamide, ifosfamide, daunorubicin

AND: Antineoplastic drugs

Table 3: Comparison between mean serum AOPP levels of exposed and unexposed group.

Group	Sample size	Mean serum AOPP (expressed in chloramine-T equivalent)	SD
Exposed	33	16.66	±3.31
Unexposed	30	12.87	±2.62

AOPP: Advanced oxidation protein products, SD: Standard deviation

Table 4: Sub-group 1 – based on handling period of AND.

Handling period	Number of nurses	Mean AOPP (chloramine-T equivalent)	SD
≤1-year	16	15.8	±2.46
>1-year	17	17.78	±3.59

($p=0.077$), AND: Antineoplastic drugs, AOPP: Advanced oxidation protein products, SD: Standard deviation

Table 5: Sub-group 2 – based on usage of bio-safety cabinet.

Use of bio-safety cabinet	Number of nurses	Mean AOPP (chloramine-T equivalent)	SD
Irregular	18	16.89	±3.4
No	15	16.38	±3.31

$p=0.66$, AOPP: Advanced oxidation protein products, SD: Standard deviation

Prevention of occupational exposure to these hazardous drugs requires strict use of bio-safety cabinet and protective wears (mask, gloves, gown, and goggles).[9] The present study reports irregular usage of bio-safety cabinet and nil usage of protective eyewear by nurses during preparation phase due to practical difficulties. No significant difference was observed between serum AOPP levels of those irregularly using and those not using bio-safety cabinet suggesting the effects of improper use of this equipment.

Mahboob et al. had observed an elevation of lipid peroxidation marker irrespective of the duration of exposure in years.[6] The present study shows no significant difference observed between serum AOPP levels of those handling for ≤1 year and those nurses handling for >1 year. The protein oxidation marker is found to be elevated irrespective of the period of handling. There was no significant difference observed between the values of nurses irregularly using and nurses not having access to bio-safety cabinet. This suggests the effect of improper utilization of this safety equipment.

In the present study, the sample size of both exposed and unexposed group were limited due to less test subjects available in the hospital but optimal as per study Mahboob et al.[6] Further studies with larger sample size are needed to include AOPP in the battery of tests needed for the purpose of monitoring the effects of this occupational exposure and the outcome of safety measures. Antioxidant enzyme activity was not checked in the present study. Mahboob et al. had observed significant depletion of glutathione (GSH) content and GSH-S-transferase activity in serum of nurses occupationally exposed to AND & hence the rise in levels of an inflammatory trigger.[5] Further studies can include total antioxidant capacity of serum to study this effect than an individual antioxidant level.

CONCLUSION

The hypothesis put forth was proved by significantly higher serum AOPP levels in the exposed group compared with the serum AOPP levels in the unexposed group. This highlights oxidative stress in the form of protein oxidation occurring in nurses exposed to AND. Hospital administration can ensure that the basic safety measures are being followed by nurses to prevent occupational exposure to AND by conducting regular inspections and checking them for oxidative stress.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Approved by Father Muller Institutional Ethics Committee

REFERENCES

1. Uttara B, Singh AV, Zamboni P, Mahajan RT. Oxidative stress and neurodegenerative diseases: a review of upstream and downstream antioxidant therapeutic options. Curr Neuropharmacol. 2009;7(1):65-74.
2. Chen Y, Jungsuwadee P, Vore M, Butterfield DA, St Clair DK. Collateral damage in cancer chemotherapy: oxidative stress in nontargeted tissues. Mol Interv. 2007;7(3):147-56.
3. Gómez-Oliván LM, Miranda-Mendoza GD, Cabrera-Galeana PA, Galar-Martínez M, Islas-Flores H, Juan-Reyes NS, et al. Oxidative stress induced in nurses by exposure to preparation and handling of antineoplastic drugs in Mexican hospitals: a multicentric study. Oxid Med Cell Longev. 2014;2014:Article ID: 858604.
4. Capeillère-Blandin C, Gausson V, Descamps-Latscha B, Witko-Sarsat V. Biochemical and spectrophotometric significance of advanced oxidized protein products. Biochim Biophys Acta. 2004;1689(2):91-102.
5. Anderstam B, Ann-Christin BH, Valli A, Stenvinkel P, Lindholm B, Suliman ME. Modification of the oxidative stress biomarker AOPP assay: application in uremic samples. Clin Chim Acta. 2008;393(2):114-8.
6. Mahboob M, Rahman MF, Rekhadevi PV, Sailaja N, Balasubramanyam A, Prabhakar PV, et al. Monitoring of oxidative stress in nurses occupationally exposed to antineoplastic drugs. Toxicol Int. 2012;19(1):20-4.
7. Witko-Sarsat V, Friedlander M, Nguyen Khoa T, Capeillère-Blandin C, Nguyen AT, Canteloup S, et al. Advanced oxidation protein products as novel mediators of inflammation and monocyte activation in chronic renal failure. J Immunol. 1998;161(5):2524-32.
8. Yoshida J, Kosaka H, Tomioka K, Kumagai S. Genotoxic risks to nurses from contamination of the work environment with antineoplastic drugs in Japan. J Occup Health. 2006;48(6):517-22.
9. Connor TH, McDiarmid MA. Preventing occupational exposures to antineoplastic drugs in health care settings. CA Cancer J Clin. 2006;56(6):354-65.

Cite this article as: Kamalasundar T, Udaykumar P, Shah P. Can occupational exposure to antineoplastic drugs increase levels of an inflammatory trigger?. Int J Basic Clin Pharmacol 2015;4:660-3.