Evaluation of the Impact of Ascorbic Acid in the Prevention of Vancomycin Induced Nephrotoxicity

A thesis submitted for the fulfillment of Masters Degree in pharmaceutical sciences (Clinical Pharmacy)

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List of abbreviations

ABW	Adjusted Body Weight.
ACEIs	Angiotensin Converting Enzyme Inhibitors.
AIN	Acute Interstitial Nephritis.
AKI	Acute kidney Injury.
AKIN	Acute Kidney Injury Network.
APACHE II score	Acute Physiology and Chronic Health Evaluation II score.
ASHP	American Society of Health-System Pharmacists.
AUC	Area Under the Concentration time Curve.
BMI	Body Mass Index.
BUN	Blood Urea Nitrogen.
CAPE	Caffeic Acid Phenethyl Ester.
CI	Continuous Infusion.
CIN	Contrast Induced Nephropathy.
Cr.cl	Creatinine Clearance.
CRRT	Continuous Renal Replacement Therapy.
DM	Diabetes Mellitus.
ESKD	End Stage kidney Disease.
EPO	Erythropoietin.
FDA	Food and Drug Administration.
GFR	Glomerulus Filtration Rate.
GSH	Glutathione.
HAP	Hospital Associated Pneumonia.

HMG-CoA	3-Hydroxy-3-MethylGlutaryl Co-enzyme A.
HTN	Hypertension.
IBW	Ideal Body Weight.
ICU	Intensive Care Unit.
IDSA	Infectious Disease Society of America.
IHD	Ischemic Heart Disease.
IT	Intermittent Infusion.
IV	Intravenous.
LC	Liquid Chromatography.
LOS	Length of Stay.
MIC	Minimum Inhibitory Concentration.
MDA	Malondialdehyde.
MDRD	Modification of Diet in Renal Disease.
MRSA	Methicillin Resistant *Staphylococcus Aureus.*
NAG	N-Acetyl-beta-d-Gluconamini dase.
NS	Normal Saline.
NSAIDs	Non-Steroidal Anti-Inflammatory Drugs.
PK	Pharmacokinetic.
PO	Per Os.
PTZ	Piperacillin- Tazobactam.
RCT	Randomized Controlled Trial.
RDA	Recommended Dietary Allowance.
RIFLE	Risk, Injury, Failure, Loss, End stage kidney injury.
ROS	Reactive Oxygen Species.
RPM	Round Per Minute.
S.cr	Serum Creatinine.

SIDP	Society of Infectious Diseases Pharmacists.
SOD	Superoxide Dismutase.
SSTIs	Skin and Soft Tissue Infections.
TBW	Total Body Weight.
TDM	Therapeutic Drug Monitoring.
TLC	Total Leukocytes Count.
UOP	Urinary Output.
US	United States.
VAN	Vancomycin Associated Nephrotoxicity.
VAP	Ventilator Associated Pneumonia.
Vd	Volume of Distribution.
VISA	Vancomycin Intermediate *Staphylococcus Aureus*.
VRSA	Vancomycin Resistant *Staphylococcus Aureus*.
WBCs	White Blood Cells.
Wt	Weight.

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Abstract

Background:

Vancomycin is a cornerstone antibiotic for Methicillin Resistant *Staphylococcus Aureus* treatment in the intensive care unit. However, the common side effect-vancomycin associated nephrotoxicity (VAN)- limits its use. Oxidative stress is the anticipated mechanism of VAN, therefore, antioxidants were thought to have a nephro-protective role against VAN.

Aim of work:

The current study aimed to determine the incidence of VAN, its correlation with piperacillin/tazobactam co-administration and other risk factors in adult critically ill patients, and to investigate the potential nephroprotective role of ascorbic acid against VAN in this population.

Patients and methods:

An observational retrospective study was conducted at Cairo University Hospitals over a period of two years. Critically ill patients who took vancomycin for at least 72 hours were eligible for the study. Patients were classified into two groups according to whether VAN occurred or not. Patients' demographics, clinical features, concurrent potential nephrotoxins and severity of illness data were collected at baseline and till the end of the treatment. The obtained data were analyzed to know the possible risk factors for VAN in critically ill patients.

Afterwards, a prospective open label randomized controlled trial was conducted on critically ill patients at Cairo University hospitals. Eligible patients were assigned on random basis into one of two groups as follows: the intervention group (vancomycin IV 15-20 mg/kg plus ascorbic acid 2 gram before vancomycin administration by half an hour) and the control group (vancomycin IV 15-20 mg/kg only). Patients demographics, clinical features, concurrent potential nephrotoxins and severity of illness data were collected at baseline. The primary outcome was the vancomycin associated nephrotoxicity incidence and the change in the creatinine parameter, while the secondary outcome was to assess the impact of this nephrotoxicity on rate of mortality and length of stay (LOS).

Results:

Hundred seventy-two patients were collected from the electronic database of the critical care medicine department for the cohort study, where only 98 patients had sufficient data for analysis and

met the inclusion and exclusion criteria. Seventy patients didn't suffer from VAN where twenty-eight suffered from VAN. Males were 45 (45.9%) and median (IQR) age was 44 (29-59.25) years. Mean time of nephrotoxicity occurrence was 6.8 days while the mean time to resolve from nephrotoxicity was 3.9 days. Multivariate analysis revealed that piperacillin/tazobactam was identified as a significant risk factor that was associated with VAN [odds ratio (OR) 3.2, 95% CI 1.21-8.46, *P*-value 0.019].

Regarding the randomized controlled trial, 55 patients from the critical care medicine department at Cairo University hospitals were assessed, where only 41 patients were eligible and completed the study. Patients' demographics, clinical features, concurrent potential nephrotoxins and severity of illness data (Acute physiological and chronic health evaluation II score) were all comparable at baseline. Vancomycin trough levels were comparable in both groups (*P*-value 0.948). The incidence of VAN was 1/21 (4.7%) versus 5/20 (25%) in the intervention and control groups, respectively (Relative risk (RR), 0.19; CI, 0.024–1.49; *P*-value = 0.093). Mean absolute difference of S.cr was significant when compared between both groups (*P*-value= 0.036). Mean absolute Cr.cl decline was significant when compared between both groups, *P*-value=0.04. Mortality was higher in the control group than the intervention group, however, it didn't reach statistical significance (*P-value* = 0.141). Also, LOS didn't differ significantly between both study groups (*P-value* = 0.129).

Conclusion:

The results of the cohort study revealed that VAN incidence was high in the critically ill patients (28.6%). Also, Piperacillin/tazobactam was found to increase the odds of VAN by 3.2 times.

The randomized controlled trial proposed that ascorbic acid reduces VAN incidence by 20.3%, however, this reduction didn't reach statistical significance level. Further prospective large multi-center randomized controlled studies are recommended to approve the obtained results.

Keywords:

Vancomycin, Nephrotoxicity, Critically ill patients, Piperacillin/tazobactam, Ascorbic acid.

Introduction

Drug induced nephrotoxicity is a tremendous common complaint that is responsible for a diversity of pathological effects on kidneys. It is described as a renal disease or dysfunction that arises due to a direct or indirect exposure to drugs, and it accounts for around 20% of all acute kidney injury (AKI) cases **(Dhodi *et al.* 2014)**.

Incidence of drug induced nephrotoxicity has been growing with the increasing use of medications such as antibiotics (e.g., vancomycin, amphotericin B, colistimethate sodium and aminoglycosides), chemotherapeutic agents (e.g. methotrexate, cisplatin, carboplatin, etc.), analgesics (e.g., Non-steroidal anti-inflammatory drugs (NSAIDs) and selective cox-2 inhibitors) and immune-suppressants (e.g., sirolimus, and calcineurin inhibitors) **(Sales *et al.* 2020)**.

Furthermost, the drugs which are found to be nephrotoxic exhibit their nephrotoxic properties by one or more of the common pathogenic mechanisms. These mechanisms include alteration in the intra glomerular hemodynamics, tubular cells poisonousness, inflammation, rhabdomyolysis, and thrombotic microangiopathy. Knowing the insulting drugs and their exact renal injury pathogenic mechanism is serious for distinguishing and avoiding drug induced renal damage **(Petejova *et al.* 2019)**.

Vancomycin is one of those drugs that causes drug induced nephrotoxicity and it is frequently used in the intensive care unit (ICU). It is a glycopeptide antibiotic that has been used widely, particularly for Methicillin Resistant *Staphylococcus Aureus* (MRSA) and for numerous strains of pathogenic *staphylococcus epidermis* **(Bal *et al.* 2017).** It is mainly eliminated through the kidneys and in many circumstances, the dose and the duration of administering the therapy are restricted since the medication induces renal dysfunction **(Eyler *et al.* 2019)**. This renal dysfunction was stated to be 10-20% after administering the conventional dose and 30-40% percent after high doses administration of the therapy **(Elyasi *et al.* 2012)**.

The mechanism by which vancomycin associated nephrotoxicity (VAN) happens is not completely tacit. The reason might be attributed to the indirectly generated reactive oxygen species (ROS) accompanied with inflammatory events *in vivo* **(Wu *et al.* 2018).** Diverse risk factors may fasten or potentiate VAN occurrence, such as high serum concentration of vancomycin at trough >20 mg/L, high doses per day particularly more than four grams per day, simultaneous treatment with nephrotoxic remedies, extended duration of therapy (beyond seven days) and admission to an intensive care unit (ICU) specially with prolonged stay **(Elyasi *et al.* 2012, Park *et al.* 2018) .**

Introduction

Antioxidants (such as ascorbic acid, selenium and alpha-tocopherol) have a vital role in defending the components of the cells against free radical harm. Evidence for the role of oxidative stress in renal diseases has led to the idea that antioxidants might be applied as adjunctive therapy for the nephroprotective strategy **(Sung et al. 2013)** .

Animal studies addressing the use of antioxidants in protection from vancomycin induced nephropathy showed the advantageous actions of several antioxidants, such as ascorbic acid, *N*-acetylcysteine, alpha-tocopherol, caffeic acid phenethyl ester, and erythropoietin **(Elyasi *et al.* 2013).** Ascorbic acid and alpha-tocopherol were reported to suppress vancomycin-induced malondialdehyde, BUN and creatinine levels, and prevented high nitric oxide production in another animal study **(Ocak *et al.* 2007).** There was only one retrospective cohort study and it showed that the administration of ascorbic acid decreased the incidence of vancomycin-induced nephrotoxicity **(SaagarAkundi *et al.* 2015).**

Concerning drugs other than vancomycin, animal trials were performed to investigate the effect of administrating alpha-tocopherol on the inhibition of lipid peroxidation level in gentamicin, and cisplatin-induced nephrotoxicities in rats **(Nazıroğlu *et al.* 2004, Maliakel *et al.* 2008)**. Another trial studied the effect of ascorbic acid and alpha-tocopherol co-administration in providing protective effects from gentamicin-induced nephrotoxicity **(Safari *et al.* 2017)**. Similarly, Ascorbic acid was found to demonstrate a protective effect against colistin-induced nephrotoxicity in another animal study **(Aslan *et al.* 2021)**.

The only randomized controlled trial that was conducted regarding drug induced nephrotoxicity was held on 28 patients exploring the probable nephroprotective effect of intravenous ascorbic acid against colistin associated nephrotoxicity and it suggested that ascorbic acid does not show a nephroprotective effect for patients getting intravenous colistin **(Sirijatuphat *et al.* 2015)**.

Up to date, there is no clinical trials investigating the role of antioxidant in preventing vancomycin associated nephrotoxicity.

Review of literature

1.Vancomycin

History of vancomycin

In 1950, limited choices were existing to treat staphylococcal infections resistant to penicillins. This has led companies to create a program in order to discover antibiotics with action against those microbes. In 1952, a sample of dirt was sent to an organic chemist at Eli Lilly and *Streptomyces orientalis* was isolated from that sample. The previously mentioned organism produced a substance which they named "compound 05865". This compound was found to be active against almost all of the gram-positive organisms, including staphylococci resistant to penicillin **(Anderson *et al.* 1961).** This compound was also found to be active against some anaerobic organisms including clostridia and *Neisseria gonorrhoeae* **(Geraci *et al.* 1981)**.

In vitro trials were commenced to decide whether the action of "05865" would be well-maintained despite attempts to induce resistance. Those trials had ended up with that the resistance had increased by 100,000 folds in the penicillin group, compared to only an increase of 4-8 folds in "compound 05865". Subsequent experimental studies proposed that "compound 05865" is probably effective and harmless for humans. Consequently, it was approved by FDA in 1958 **(McGuire *et al.* 1955, Griffith 1957)**.

Initial preparations contained a lot of impurities (up to 70%) and were named the 'Mississippi mud' due to its brown color. Purification process took place, then the subsequent drug was entitled "vancomycin" (derived from the word "vanquish"), and was ready for clinical studies **(Kisil *et al.* 2021)**. At the beginning, those impurities were thought as the cause of the nephrotoxicity arised with the use of vancomycin. Nowadays, purification techniques had improved and the existing preparations have ~90–95% of the active moiety, vancomycin B **(Filippone *et al.* 2017).** After modern fermentation methods and purification techniques, nephrotoxicity had become infrequent, about 5 to 7% and usually reversible **(Lodise *et al.* 2009).**

Though vancomycin was a second-line treatment in the early stage of its life cycle, it became the treatment of choice for serious infections (including endocarditis, osteomyelitis, meningitis, and pneumonia) due to Methicillin resistant *Staphylococcus aureus* (MRSA) in the seventies of the past