

High Dose Tigecycline-Induced Mitochondrial Dysfunction-Associated Acute Metabolic Acidosis: A Retrospective Study

Hasan MJ*, Rabbani R, Bachar SC and Huq SMR

Department of Clinical Pharmacy, Square Hospitals Ltd., West Panthapath, Dhaka, Bangladesh

Abstract

Background: Tigecycline (TGC) is a last resort antibiotic having broad spectrum antibacterial activity against gram-negative bacteria. Beyond its standard dosing regimen, a double dosing regimen has been practicing for last couple of years to achieve adequate drug concentration in the targeted body tissues. TGC interferes with the mitochondrial protein translation process and may lead to non-anion gap acute metabolic acidosis (NAGAMA) with low blood-pH level. The main objective of this retrospective study was to evaluate the frequency of high dose TGC-induced NAGAMA events in the South Asian critically ill patients.

Methods: The retrospective data of 24 critically ill patients of an intensive care unit (ICU) were considered for this study. Patients of this study received high dose of TGC. Including all necessary laboratory data, patients' anion gap, blood-pH level data in pre and post-TGC therapy were also recorded from the ICU's clinical-record archive. All the data were analyzed to find out the significance of NAGAMA event with high dose TGC therapy.

Results: Among the patients administered with high dose TGC, 45.83% (11; n=24) of patients were experienced with NAGAMA event and in every 2.18 patients, 1 patient developed this event. Among those 11 patients, 63.64% of patients were recovered within 24 hours after stopping the TGC therapy and the rest of the patients (36.36%) were recovered within 48 hours, where 4 patients required therapeutic intervention to overcome the NAGAMA event.

Conclusion: High dose TGC-induced NAGAMA event is an unusual event, globally. Mitochondrial toxicity is a TGC-associated adverse event and the related NAGAMA is a detrimental clinical consequence. However, the complete mechanism of this event is even not fully clear but, caution should be taken in the use of high dose TGC mostly in the critically ill patients.

Keywords: Tigecycline; High dose; Metabolic acidosis; Anion gap; Mitochondrial dysfunction

Introduction

Tigecycline (TGC) is the first glycylcycline antibiotic under the class of tetracycline antibiotic. TGC is approved by the Food and Drug Administration (FDA) of United States (US) and in Europe for the treatment of complicated skin and skin structure infections (cSSSI) and complicated intraabdominal infections (cIAI), at a standard dose (SD) of 50 mg twice daily following a single 100 mg loading dose [1]. Recently, TGC has been found also effective in the treatment of community-acquired bacterial pneumonia (CABP) [2]. This is one of the few last resort antibiotics that remain potent against the multidrug-resistant (MDR) gram negative bacteria [1,2]. Multiple studies found a superior therapeutic outcome with high dose (HD) TGC (100 mg, intravenously, twice daily following a 200 mg single loading dose) against gram-negative MDR pathogens in severe infections of critically ill patients [1-3].

Metabolic acidosis may be defined as increased production or decreased excretion of non-volatile acid in the body which is manifested as low serum bicarbonate concentration with low serum pH [4]. Drug-induced acute metabolic acidosis (DIAMA) is a common incidence but in some rare cases, it may be life threatening when detection and management of DIAMA is delayed. DIAMA is a typical adverse drug reaction (ADR) and culprit drugs can be classified into four major groups according to their pharmacological characteristics:

- (1) Drugs act as exogenous acid source.
- (2) Drugs leading to excrete-out bicarbonate, significantly.
- (3) Drugs enhancing endogenous acid production.

- (4) Drugs reducing acid excretion through kidneys [4].

According to the level of serum anion gap, DIAMA can be classified into two major categories: non-anion gap and high anion gap acute metabolic acidosis [5]. Non-anion gap acute metabolic acidosis (NAGAMA) is an acid-base disorder where the anion gap is within the normal range [6].

Multiple studies found tigecycline inhibiting mitochondrial protein synthesis [7]. Recently, it was found in a study that tigecycline inhibits the expression of the enzyme complexes leading to mitochondrial toxicity, and as a consequence, tigecycline-induced acute metabolic acidosis is a rare phenomenon [8]. There is very limited data on the molecular mechanism of TGC-induced acute metabolic acidosis; and the main objective of this study was to analyze the association between the high dose of TGC and the frequency of NAGAMA event through mitochondrial dysfunction in critically ill patients.

Materials and Methods

This retrospective study was conducted on 6-month's (April, 2018 to

***Corresponding author:** Md. Jahidul Hasan, Clinical Pharmacist, Department of Clinical Pharmacy, Square Hospitals Ltd., 18/F Bir Uttam Qazi Nuruzzaman Sarak, West Panthapath, Dhaka-1205, Bangladesh, Tel: +8801911011167; E-mail: jahidjr@gmail.com

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September, 2018) collected data on HD TGC therapy in 24 (n) critically ill patients of the intensive care unit (ICU) of a tertiary level hospital in Dhaka, Bangladesh.

Patients and HD TGC therapy

All the patient-wise retrospective data (microbiological, laboratory investigation and routine clinical monitoring) for this study was collected from the ICU's patients' clinical-record archive. All patients considered for this study were Asian (local citizen). All those 24 patients of this study had previous or current experience of sepsis. Apache II Score was calculated for all the patients as per the ICU protocol to determine the severity of their diseases. Routine arterial blood gas (ABG) and anion gap was monitored for all 24 patients in the ICU and recorded, accordingly. The equation used to analyze the anion gap was: Anion gap (mmol/L)=[Na⁺ + [K⁺]] - ([HCO₃⁻] + [Cl⁻]); where [Na⁺], [K⁺], [HCO₃⁻], and [Cl⁻] are the mmol/L concentrations of these ions in blood.

The blood pH records were found in the ABG reports and blood pH was monitored routinely for every patient as per ICU protocol. All the patients of this study received HD TGC (100 mg, intravenously, twice daily following a single 200 mg loading dose) as the last resort susceptible antibiotic for their gram-negative MDR bacterial infections in blood stream and respiratory tract, as per the microbiological culture sensitivity report. Patients received conventional dose of TGC were not considered for this study.

Data analysis technique

Patients' data inclusion criteria for this study was based on no moderate to severe hepatic or renal impairment, no existing blood-pH abnormality, no presence of anion gap in blood, no existing blood-pH modifying drug-therapy and no other additional factors contributing to acute blood-pH modification. After collecting all the relevant data of all the patients of this study, we correlated the patient-wise HD TGC therapy data with the anion gap and pH records to determine either NAGAMA or no metabolic acidosis. All the concomitant drug therapies of the 24 patients' prescriptions were cross-checked for finding any other prescribed drug contributing to metabolic acidosis.

The ethical approval for this study was taken from the hospital ethical committee on January, 2018. IBM SPSS statistics (version 22) software was used for orienting all the retrospective-study data.

Results

All the patients considered for this study were middle aged (between 45-65 years) and the number of female (14; n= 24) patients were slightly higher than the number of male (10; n=24) patients (Table 1). The mean procalcitonin (infection marker) for the patients was 52.63 ng/mL with the highest recorded level 98.60 ng/mL and this indicates that HD TGC was used for treating moderate to severe infections in those critically ill patients of the study. In most of the cases, patients with higher procalcitonin level comprised the more severity level (through determining the apache II scores) of the disease (p-value: 0.054). The apache II scores of the 24 patients considered for this study was recorded just before administering HD TGC to the patients which represented the patients' severity of diseases, and highest score was found 28.0 (range: 0-71) with the mean score 15.75 (p-value=0.034) (Table 1). Bilirubin level represented the hepatic function of the patients. The mean bilirubin level of the patients was 1.34 mg/dL with a maximum of 2.1 mg/dL and no moderate to severe hepatic impairment was observed

in any patient. Through performing ABG, anion gaps were calculated, and those records showed the presence of NAGAMA events in the patients at that time after the HD TGC therapy. The highest anion gap was recorded 12.60 mmol/L (normal range: 10–16 mmol/L) (mean value=10.29 mmol/L) and no significant association was observed between the recorded anion gaps and the low blood-pH levels in the patients (p-value=0.775) (Table 1). The lowest recorded blood-pH was 7.2 (normal range: 7.35-7.45) with a mean pH 7.33 after the HD TGC therapy, and the significance of occurrences of high acidic blood-pH was closed in most of the cases with the higher level of the severity of diseases (determined by calculating apache II score) (p-value=0.034) (Table 1).

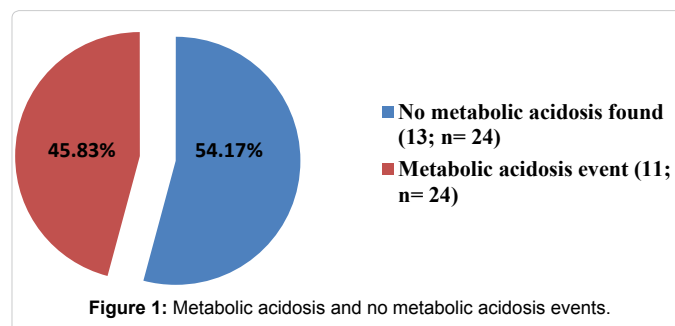
In this study, out of 24 patients, 11 patients (45.83%; n=24) developed NAGAMA event within the first 24 hours after initiation of the HD TGC therapy and the rest of the patients (13; n=24) did not develop any metabolic acidosis during the HD TGC therapy days. Following HD TGC therapy, 1 NAGAMA event was found in every 2.18 patients (45.87%) (Figure 1 and Table 2).

After discontinuing the HD TGC therapy (because of developing HD TGC-induced NAGAMA events) in 11 patients, 63.64% NAGAMA event was resolved within 24 hours. The rest of the events (36.36%)

| Characteristics | Variable | p-value |
|---|------------|---------|
| Age (year) | | |
| Mean | 54.62 | -- |
| Range (min ^a -max ^b) | 47-65 | -- |
| Gender | | |
| Male | 10 | -- |
| Female | 14 | -- |
| Procalcitonin (<0.1 ng/mL) | | |
| Mean | 52.63 | 0.054 |
| Range (min-max) | 5.20-98.60 | |
| Apache II Score (0-71) | | |
| Mean | 15.75 | 0.034 |
| Range (min-max) | 8.0-28.0 | |
| Bilirubin (0.2–1.2 mg/dL) | | |
| Mean | 1.34 | 0.488 |
| Range (min-max) | 0.4-2.1 | |
| Anion gap (10–16 mmol/L) | | |
| Mean | 10.29 | 0.775 |
| Range (min-max) | 8.6-12.60 | |
| Blood pH (7.35-7.45) | | |
| Mean | 7.33 | 0.034 |
| Range (min-max) | 7.2-7.45 | |

Note: min^a-max^b: minimum- maximum

Table 1: Demographic information of patients.



| Number of NAGAMA event (n=24) | Probability of NAGAMA event in patients with HD TGC (%) | After discontinuation of TGC therapy | | |
|----------------------------------|---|---|---|---|
| | | Number of NAGAMA resolved within 24 hours (%) | Number of NAGAMA resolved within 48 hours (%) | Intervention required in number of NAGAMA event (%) |
| 11 | 1 per 2.18 (45.87) | 7 (63.64) | 4 (36.36) | 4 (36.36) |

Table 2: Non-anion gap acute metabolic acidosis event and related management.

were resolved within 48 hours and specific therapeutic intervention was taken after first 24 hours to 4 uncontrolled acidic patients for saving them from the related harms (Table 2).

Discussion

In this study, we found that HD TGC-induced NAGAMA was an acute adverse drug reaction where metabolic or systemic acidosis was not associated with anion gap in blood. FDA disclosed a black boxed warning on the approved or nonapproved use of TGC due to TGC-associated increased risk of mortality and the major causes behind this higher mortality rate is still specifically undiscovered [9]. Shortage of potential antibiotics especially against the MDR and extensively drug-resistant (XDR) gram-negative bacteria, and TGC's broad spectrum of bactericidal activity inspire to use TGC as a last resort antibiotic [2,10,11]. Optimization of antibiotic therapies based on the clinical evidences is an effective way to fight against the severe infections, but increased risk of antibiotic-associated mortality and morbidity plays a vital role in selecting the right antibiotic with the right dose [12]. Standard dosing of antibiotics is sufficient to meet the desired therapeutic drug concentration for achieving optimum therapeutic response in mild to moderate bacterial infections, but in critically ill patients, due to massive pathophysiological alteration and the related pharmacokinetic/pharmacodynamic modification of drugs, the SD of antibiotics in most of the cases may not be sufficient enough to get the desired level of *in vivo* drug-tissue distribution and the optimum therapeutic outcomes [2,13,14]. The recommended SD regimen of TGC as per the package insert might be inadequate in the critically ill patients especially, those are suffering from severe infections like, sepsis, and this may result in under dosing of TGC which may ultimately leads to therapeutic failure [2].

A double dosing regimen (200 mg as loading dose and 100 mg twice daily as maintenance dose) of TGC is a new dose-optimizing approach of TGC in severe MDR or XDR gram-negative infections found in many studies, but related adverse events were not significant [1-3]. However, in our study, 11 patients were experienced with NAGAMA event during HD TGC therapy and in most of the cases, the extremely down-graded levels of blood pH were very crucial for the patients at their present critical clinical conditions. The population samples (patients) considered for our study was completely South Asian and there is no specific pharmacological or clinical studies' data of TGC on this subcontinent's populations at present. Since the last few decades, pharmacogenetic researches on different racial and ethnic groups concerning the metabolism, drug-induced adverse reactions, side effects and clinical effectiveness of many clinically important drugs have been expanded, tremendously and found much dissimilarity among these groups [15]. Study found that Caucasians have relatively higher drug-plasma protein binding characteristic than other ethnic groups and their drug-plasma free fraction is relatively lower [16]. Our study might be the first one on South Asian population where 45.87% probability of HD TGC-associated NAGAMA event was recorded.

TGC is broad-spectrum antibiotic having high selective affinity and potent inhibitory mechanism on bacterial 30S ribosomal subunit, and its potency is 3 and 20-fold higher than that of minocycline and tetracycline, respectively [8,17]. HD TGC shows 'concentration-dependent killing' and nausea and vomiting are the most common side effects [2]. To determine the activity of TGC in eukaryotic cells, haplo-insufficiency profiling (HIP) technique was applied to screen yeast's genome and researchers found that TGC acts on mitochondrial protein translation, makes mitochondria dysfunctional and finally, selectively inhibits the growth and visibility of eukaryotic cells [18]. The role of increasing concentration of TGC on cellular cytochrome c oxidase (Cox)-1, 2 and 4 was analyzed through a study. In mitochondria, Cox-1 and Cox-2 are the subunits of respiratory complex IV of the electron transport chain system, translated by mitochondrial ribosomes [19]. Cox-4 is encoded and translated by nuclear genome and nuclear ribosomes, respectively under the same mitochondrial respiratory complex system [18]. Thus, TGC causes a decrease in the level of Cox-1 and Cox-2, which is higher than Cox-4 level. TGC do not have any role on the expression of other proteins translated by cytosolic ribosomes. The reduction of Cox-1 and Cox-2 protein levels lead to increase the level of mRNA expression of these proteins, whereas mRNA level of Cox-4 protein is not raised, significantly in the same cell. This increased expression level of mitochondrial encoded mRNA causes the main harm to mitochondrial translation process [18]. Another study showed the similar type of TGC's negative response on mitochondrial translation process [20]. Severe metabolic acidosis may be the systemic consequence of this mitochondrial dysfunction or damage [21]. A more recent study showed that a lethal metabolic acidosis was developed with the prolonged treatment of TGC in a middle-aged patient. That study used Oxidative phosphorylation system (OXPHOS) to observe the molecular mechanism of TGC-induced metabolic acidosis. In that study, the OXPHOS demonstrated that the levels of Cox- I, III, IV and V enzyme complexes were reduced (except II which is encoded by nuclear DNA and regains its full functionality) significantly through the action of TGC and lead to a damage in mtDNA translation, and that lethal mitochondrial toxicity caused the unexplained metabolic acidosis [8]. Same study also explained that defected mtDNA replication, transcription and mitochondrial translation ultimately lead to losing capacities for operating oxidative phosphorylation process, and at that time, mitochondrial translation process completely depends on anaerobic glycolysis for adenosine triphosphate production [8]. Another study on TGC-resistant cell (RTEX+TIG) found that even in RTEX+TIG, TGC inhibited the mitochondrial protein translation system and oxidative phosphorylation was undistinguishable [7]. Multiple studies established that mitochondrial toxicity may leads to different acute or chronic metabolic diseases including, metabolic acidosis [7,22-24]. In our study, we found NAGAMA in 11 patients (n=24; 45.83%) with HD TGC therapy and all the events were diminished within 48 hours after discontinuing the TGC therapy.

DIAMA is a difficult state to identify and to initiate the required management in critically ill patients [4]. HD TGC is an effective concept of treatment in the severe infection management and beyond its huge evidences of mortality and morbidity; data on TGC-associated acute metabolic acidosis is very rare. NAGAMA may be the complex consequence of TGC-associated mitochondrial toxicity and further mega study is required urgently to analyze the in-depth molecular-relationship as well as the clear mechanism of this TGC-associated NAGAMA event mostly in critically ill patients.

Conclusion

HD TGC-associated NAGAMA is a rare detrimental event developed through mitochondrial toxicity. In this study, we found NAGAMA event in South Asian critically ill patients, at a significant rate. Though HD TGC is a potential last line antibiotic therapy, nevertheless, HD TGC-induced NAGAMA event should be considered sincerely to minimize the rate TGC-associated morbidity and mortality mostly in the critically ill patients.

Conflicts of Interest

No conflicts of interest.

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