Drugs-Induced QT Interval Prolongation among End-Stage Renal Disease Patients in Jordan

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Abstract

Background In spite of high risk of mortality due to drug-induced QT interval prolongation (QTcP) usage among end stage renal disease patients (ESRD), no previous studies were conducted to assess medication safety of this drugs category among this vulnerable patients group. Objectives This study aimed to investigate the appropriateness and potential drug-drug interactions of QTcP-inducing drugs among ESRD patients in Jordan. Method This study was a cross-sectional retrospective study conducted in the outpatient clinics of 200 Jordanian healthcare facilities over three years (2017, 2018, and 2019) using Hakeem© database for data collection. CredibleMeds© was used to identify and categorise QTcP-inducing drugs. Drug-drug interactions and appropriateness of prescribing were assessed by Micromedex Drug Reax© software and a multidisciplinary committee, respectively. Results Of the 407 patients included, 954 drugs with risk of QTcP were dispensed; 618 (64.8%) had interactions with other drugs; 10.4% were major, 29.3% were moderate, and 60.3% were minor drug-drug interactions. Absence of major polypharmacy and co-morbidity decreased the odds of major drug-drug interactions by 61% (OR 0.61; 95% CI 0.23-0.97; p=0.02), and 72% (OR 0.72; 95% CI 0.44-1.23; p=0.04), respectively. After clinical evaluation, 17.6% of the dispensed drugs were considered inappropriate application, 12.9% were classified as inappropriate choice, and 26.4% were judged as inappropriate decision. Urology clinics were more likely to prescribe QTcP-inducing drugs based on inappropriate decision. Conclusion Major drug-drug interactions and dispensing medications with risk of QTcP based on inappropriate prescribing decisions for patients with ESRD were reported to be high in outpatient clinics in Jordan.

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Running title

Medication safety of QTcP-inducing drugs in Jordan

Principal Investigator statement

Dr. S.C.L.M. Cremers

Editor-in-Chief

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I am pleased to submit an original research article entitled "**Drugs-Induced QT Interval Prolongation among End Stage Renal Disease Patients in Jordan**"

In spite of high risk of deadly complications due to drug-induced QT interval prolongation usage among end stage renal disease patients, no previous studies were conducted to assess medication safety of this drugs category among this vulnerable patients group.

In this manuscript, we show that Major drug-drug interactions and dispensing medications with risk of developing QT interval prolongation based on inappropriate prescribing decisions for patients with end stage renal disease were reported to be high in outpatient clinics in Jordan. Therefore, proper pharmaceutical care should be improved to intervene on this events and maintain patient safety.We believe that this manuscript is appropriate for publication by The British Journal of Clinical Pharmacology because it links to the Journal's aims and scope. This manuscript has not been published and is not under consideration for publication elsewhere. We have no conflicts of interest to disclose.

Thank you for your consideration!

Dania Abu-Naser

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Brief description

Section one

- QT interval prolongation inducing drugs can cause sudden death
- Kidney impairment is a risk factor for QT interval prolongation
- Investigation of medication safety for QT interval prolongation inducing drugs among end stage renal disease patients would help reducing mortality and morbidity rates.

Section two

- More than one-quarter of QT interval prolongation inducing drugs were prescribed for patients with end stage renal disease based on inappropriate decisions.
- Around two-thirds of dispensed QT interval prolongation inducing drugs had pharmacokinetic and pharmacodynamics interactions with other drugs, more than one-third of these interactions were major and moderate
- Absence of major polypharmacy and co-morbidity decreased the odds of major drug-drug interactions by 61% and 72%, respectively.

Abstract

Background

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Objectives

This study aimed to investigate the appropriateness and potential drug-drug interactions of QTcP-inducing drugs among ESRD patients in Jordan.

Method

This study was a cross-sectional retrospective study conducted in the outpatient clinics of 200 Jordanian healthcare facilities over three years (2017, 2018, and 2019) using Hakeem© database for data collection. CredibleMeds© was used to identify and categorise QTcP-inducing drugs. Drug-drug interactions and appropriateness of prescribing were assessed by Micromedex Drug Reax© software and a multidisciplinary committee, respectively.

Results

Of the 407 patients included, 954 drugs with risk of QTcP were dispensed; 618 (64.8%) had interactions with other drugs; 10.4% were major, 29.3% were moderate, and 60.3% were minor drug-drug interactions. Absence of major polypharmacy and co-morbidity decreased the odds of major drug-drug interactions by 61% (OR 0.61; 95% CI 0.23-0.97; p=0.02), and 72% (OR 0.72; 95% CI 0.44-1.23; p=0.04), respectively. After clinical evaluation, 17.6% of the dispensed drugs were considered inappropriate application, 12.9% were classified as inappropriate choice, and 26.4% were judged as inappropriate decision. Urology clinics were more likely to prescribe QTcP-inducing drugs based on inappropriate decision.

Conclusion

Major drug-drug interactions and dispensing medications with risk of QTcP based on inappropriate prescribing decisions for patients with ESRD were reported to be high in outpatient clinics in Jordan.

Keywords

End stage renal disease; QT interval prolongation; medication safety; pharmaceutical care; Jordan

Introduction

QT interval prolongation (QTcP) is a congenital or acquired cardiac condition that is associated with potential risks of torsade de pointes (TdP) and sudden cardiac death (SCD) (1). The prevalence of acquired QTcP is high and escalates with the decline in kidney function among chronic kidney disease patients (CKD) who were reported to be suffering from progression to end-stage renal disease (ESRD) which needing emergency care (2,3,12,4–11). For each 1 mg increase in serum creatinine, the QT interval prolongs by an average of 2.9 ms (5). A previous study reported that the risk for QTcP is 2.47 times higher in ESRD patients, than in CKD3 patients, and this may be attributed to the impairment in drug disposition of renal excreted drug-induced QTcP (1). Due to the complexity of drug pharmacokinetics in patients with CKD and because many CKD patients are often prescribed drug-induced QTcP, renal excretion of many used drugs is decreased in CKD which triggers these drugs to cause much more QTcP (13,14).

In Jordan, around 3% of the population were estimated to have ESRD, and the main causes were hypertension and diabetes mellitus (15–17). Furthermore, high rate of drug-induced QTcP usage among geriatric patients was reported, many of them had ESRD (18). However, a recent study indicated that CKD is highly underdiagnosed in Jordan (19). Physicians in Jordan demonstrated poor adherence to current practice guidelines for safe prescription of antibiotics (20–23), proton pump inhibitors (24,25), and non-steroidal anti-inflammatory drugs (26). In addition, high rate of major and moderate drug-drug interactions was found among elderly patients in Jordan (27). As a possible solution, clinical pharmacists in Jordan exhibited the ability to identify and intervene on such inappropriate prescriptions (28,29).

Given the high risk of mortality and morbidity due to inappropriate prescribing of drug-induced QTcP for ESRD patients and scarcity of available data on this area, we believe our multicentric approach to assess prescribing behaviour of drug-induced QTcP is imperative to provide a better understanding of the problem and urge health officials for corrective actions. To our knowledge, there was no previous study that targeted this patient group and assessed their prescriptions meticulously.

Aims

This study aimed to; 1) assess the appropriateness of drug-induced QTcP prescribing, 2) study the predictors for inappropriate prescribing and 3) examine the potential drug-drug interactions in prescriptions of ESRD patients who have been prescribed QTcP inducing drugs.

Ethics approval

The study was approved by the Ministry of Health in Jordan (Moh/REC/2019/176), and the Institutional Review Board (IRB) at Al-Balqa‘ Applied University (. 6540).

Method

Study design and data collection

This study was a cross-sectional retrospective multicentric study conducted in the outpatient clinics of 200 Jordanian healthcare facilities over three years (2017, 2018, and 2019). These facilities were included from the 12 governorates in Jordan and divided as follow; Northern Region (Irbid, Ajloun, Jerash, Mafraq), Southern Region (Karak, Tafilah, Ma'an, Aqaba), Capital Region (West Amman, East Amman) and Central Region (Balqa, Zarqa, Madaba). Data were collected using "Hakeem©" database, which is the electronic prescribing system (EPS) launched by Electronic Health Solutions (EHS) in 2009, and since then it was used by the ministry of health in Jordan. The types of electronic medical information we had access to, included, but were not limited to, the following: comprehensive medical and surgical history, physical examinations, procedural and surgical reports, current medications' names, frequency and dosage, allergies as well as in-patient and out-patient clinic visit notes. However, Hakeem© did not include Clinical Decision Support System (CDSS). The flow of the study approach and design was illustrated in **Figure 1** .

Eligibility criteria

Those who aged [?]18 years, and have been diagnosed with ESRD and prescribed at least one drug with risk of QTcP were included. Those who were documented cases of congenital long QTc were excluded.

Drugs inducing QTcP

To categorise potential drugs induced QTcP, we adopted the most updated CredibleMeds(c) (May 18, 2020), and then we subdivided these medications into the following categories (18): 1) known risky category which includes all medications with proven evidences of causing QTcP, and are associated with a potential causing of TdP, 2) possible risky group which encompasses all drugs with significant evidences of causing QTcP, but with insignificant evidences that these medications have a risk of causing TdP, and 3) conditional risk group which includes all medicines with sufficient evidences that confirm possible causing QTcP, and TdP, but only under certain circumstances (e.g. inappropriate dosage, or being in a drug–drug interaction). Minor polypharmacy prescriptions were assumed to contain 2-4 prescribed drugs, and major polypharmacy prescriptions were defined to have [?] 5 prescribed drugs (30).

Drug-Drug interaction (DDIs)

The detected potential DDIs were classified based on severity of interaction (31,32); 1) major DDI, which can cause life threating problem or severe damage to the patient. 2) Moderate DDI, which can cause some harm to the patient and affect his/her treatment, or his/her clinical status, and 3) mild DDI, which can cause insignificant harm to the patient, and usually unnoticeable. The potential DDIs were also categorised based on scientific evidence of interaction to (31,32); 1) Proven documentation, where the studies clearly established the existence of the interaction, 2) Good Documentation, where strongly suggest the presence of interaction, but controlled study are lacking, and 3) Fair documentation, where studies poorly suggest the interaction, but the clinicians suspect the interaction exists due to other factors. Prescriptions were screened for potential DDI using Micromedex Drug Reax(c) software (Thomson Reuters Inc., 2011). Micromedex provides fast and accurate checking on type, and severity of potential DDI (33).

Appropriateness evaluation

Appropriateness of prescriptions was assessed by a multidisciplinary committee; a consultant nephrologist, a consultant cardiologist, and a senior clinical pharmacist. The main investigator (DAN) arranged three online meetings (April 5-20, 2020) using Zoom(c)Software, 2 hours for each one with the experts to discuss the appropriateness of prescriptions. Their purpose was to judge the prescription appropriateness of QTcP-inducing drugs among the included patients. They reviewed all prescriptions and clinical information (Prescribed medications' name, dosage, frequency, route of administration, diagnosis, lab results and clinical history of patients) provided by the investigator against the British National Formulary (BNF), version 79, and Wilcock et al., guideline for prescribing drugs in ESRD (34). The committee divided the prescriptions to two major categories; 1) appropriate decision which was subcategorised to completely appropriate (Correct decision with correct choice of drug and correct application), inappropriate choice (the drug is needed, but

can be replaced with a safer one), and incorrect application (correct decision and choice, but incorrect dose, frequency, or route of administration), and 2) inappropriate decision (the drug is not needed). Prescriptions with insufficient clinical information were dropped.To ensure the reliability of this approach, the Kappa statistic was used to test interrater reliability of the committee members. Value of kappa Below 0.5 was considered as bad reliability, above 0.5 and below 0.7 moderate reliability, Above 0.7 good, and above 0.8 great reliability (35).

Data analysis

Data were coded and entered into the Statistical Package for Social Science (SPSS$^{(c)}$) version 26 (IBM, Chicago, IL, US) by the main researcher. Descriptive results are presented as proportions (%) with 95% CIs, while logistic regression results are presented as ORs with 95% CI. Statistical significance was considered at $p$value < 0.05 (with a confidence limit at 95%). Logistic regression was used to assess predictors for inappropriate drugs-induced QTcP prescriptions and examine predictors for major DDIs. To improve reliability of regression, categorical variables of appropriate decision (Completely appropriate, Inappropriate choice, and Incorrect application) were combined and coded (No) against the variable inappropriate decision which coded (Yes). Using the same approach, moderate and minor DDIs were combined and coded (No) against major DDIs which coded (Yes). Rao-Scott chi-square test which is a design-adjusted version of the Pearson chi-square (36), was used to assess differences between categorical variables.

Results

Demographic data

As shown in **Table 1** , 407 patients with End Stage Renal Disease (ESRD) and have been prescribed at least one QTcP inducing drug over the past 3 years in outpatient clinics in Jordan, the mean age was 53.8 years (SD: +-15.25); 35.9% (n= 146) of them aged >60 years, 33.2% (n= 135) aged 45-59 years, and only 12.0% (n=49) aged 18-29 years. Approximately half of participants were female (46.9%, n= 191), and more than two-thirds of patients had co-morbidity (70.3%, n=286). Patients from the capital and north regions of Jordan accounted for (40.5%, n=165) and (25.6%, n=140) of participants, respectively.

Prescribed medications

The number of prescriptions collected for the included patients was 954, with a total of 4871 medication orders, 954 (19.6%) were QTcP inducing drugs. The mean number of QTcP inducing drugs usage among included patients was 2.3 (Range: 1-6). The majority of patients consumed at least one drug with risk of QTcP (37.6%, n=153), 20.6% (n= 84) were using two drugs with risk of QTcP, 18.7% (n= 76) were using three drugs and 16.9b% (n= 69) were using four drugs. Furthermore, 21(5.2%) patients were consuming five QTcP-inducing drugs and 4 patients were using 6 drugs with risk of QTcP. The most common prescribed QTcP-inducing drugs for included patients were Furosemide (36.2%, n=345), Lanzoprazole (28.9%, n=276), and Omeprazole (14.9%, n=142), and they were classified as drugs with conventional risk of QTcP. Whereas, Sodium Valproate, Levofloxacin, and Haloperidol were prescribed only once and they were classified as drugs with known risk of QTcP. Drugs-induced QTcP were listed and classified in **Table 2.**

Drug-Drug interactions (DDIs)

Of the 954 QTcP-inducing drugs prescribed, 618 (64.8%) had interactions with other drugs; 10.4% (n=64) were major DDIs, 29.3% (n= 181) were moderate DDIs, and 60.3% (n=373) were minor DDIs (**Table 3**). Prescriptions with minor polypharmacy were less likely to have major DDIs compared to those with major polypharmacy (OR 0.61; 95%CI 0.23-0.97; p=0.02), and prescriptions for patients with no co-morbidity were less likely to have major DDIs compared to those prescribed for patients with co-morbidity (OR 0.72; 95%CI 0.44-1.23; p=0.04). Differences in types of the clinic or clinic location were not significantly related to major DDIs proportion. Of 618 identified DDIs, 257 (41.6%) had good documentation, 201 (32.5%) had proven documentation, and 160 (25.9%) had fair documentation. Examples of DDIs were listed in **Table 4.**

Prescriptions appropriateness

Our results (**Table 3**) indicated that 43.1% (n=411) of dispensed QTcP-inducing drugs were deemed completely appropriate, 17.6% (n=168) were considered inappropriate application, and 12.9% (n=123) were classified as inappropriate choice. Moreover, 26.4% (n=252) of QTcP-inducing drugs were judged as inappropriate decision. Our findings suggested that urology clinics are more likely to prescribe QTcP-inducing drugs based on inappropriate decision (OR 7.71; 95%CI 3.45-11.49; p=0.04). Differences in the number of medication orders in prescriptions or clinic location were not significantly related to inappropriate decision proportion.

Discussion

There is a paucity of research on drug-drug interactions and prescriptions appropriateness among ESRD patients who have been prescribed QTcP-inducing drugs in Jordan. We adopted holistic and valid operational techniques to detect DDIs and evaluate the prescriptions appropriateness. Our findings can be confidently generalised, since the sample in our study was representative, with low margin of error, and randomly selected from all regions in Jordan. However, our study had limitations; this research was conducted in outpatient setting, and thus our data cannot reflect the prescribing behaviour in the inpatient settings. Due to insufficient resources and the limited nature of our data, patients with acquired r congenital QTc prolongation were not clinically identified. Nevertheless, we were tied by the study aims and the nature of the data, and our study can provide comprehensive assessment of prescribing behaviour in the outpatient clinics of Jordan.

In Jordan, Ahmad Al-Azayzih et al., (18), investigated the patterns of QTcP-inducing drugs usage among geriatric patients in North Jordan. DDIs and prescriptions appropriateness were not assessed, and ESRD patients were not screened. Furthermore, their findings cannot be generlised as they targeted patients in geographic area in Jordan. Many previous studies were conducted in the USA (37,38), Colombia (39), Germany (40), and India (41) assessed the patterns of QTcP-inducing drugs prescriptions. Despite that patients with ESRD are at high risk of developing fatal QTcP, none of the recent studies screened for DDIs or prescriptions appropriateness among this patient group particularly.

Among the included patients in our study, 954 QTcP-inducing drugs were prescribed; most of them were furosemide (36.2%) and lanzoprazole (28.9%). This was consistent with Ahmad Al-Azayzih et al., (18), where lanzoprazole (20.7%) and furosemide (15.8%) accounted for the most common prescribed QTcP-inducing drugs. Most of dispensed QTcP-inducing drugs in our study were categorised as conditional risk of QTcP. A recent study reported higher rate of mortality among patients who have been prescribed QTcP-inducing drugs with known or possible risk of QTcP than those who were on drugs with conditional risk or not on QTcP-inducing drugs at all (42). This finding focused on patients in psychiatry clinics, and thus cannot be generlised to other patient groups.

Our results suggested high rate of DDIs (64.8%) between QTcP inducing drugs and other medications; more than one-third of these DDIs were major and moderate. In addition, polypharmacy and co-morbidity were significantly related to this proportion. This result may attributed to low pharmaceutical care interventions, physicians poor adherence to the guidelines, and absence of clinical decision support system in the operated computerized physician order entry system (CPOE) . Our findings are in line with other studies in Jordan that indicated high rate of DDIs and poor adherence to the guidelines by physicians (21,22,27). The difference between the recent studies in Jordan and our study is that the patient group in our research is highly vulnerable to severe deadly complications, and thus urgent precautionary measures are necessary. In Saudi Arabia, pharmacists had a major role in intervening on DDIs in outpatient psychiatry clinics (43). Other studies explained how pharmacists are responsible for identifying DDIs and notifying physicians and patients about the potential consequences (44,45). For safer medication use especially among high risk groups of patients, we believe comprehensive plan to deliver continual professional development courses to pharmacists and physicians as well in outpatient clinics is indispensable.

Our results indicated that more than one-quarter (26.4%) of the dispensed QTcP-inducing drugs were prescribed based on inappropriate decision, and this was significantly associated with urology clinics. A recent

study conducted in Germany, found that inappropriate prescribing can lead to negative adverse drug events including QTcP, hyperkalaemia and haemorrhage in patients with kidney diseases (46). Lower rate of inappropriate prescribing was found in the USA (47). Due to inconsistencies in the operational definitions of prescribing appropriateness, results of different studies are barely comparable.

To sum up, patients with ESRD are underrepresented in most of the previous research and as there is no cleared approach for polypharmacy management, clinical assessment of potentially risk factors regarding inappropriate prescribing behaviour, and DDIs monitoring, health officials should efficiently utilised our data to implement concise patient education programme aiming to improve self-monitor of side effects for early detection of potential harm. Furthermore, pharmacists should be encouraged and trained to intervene on DDIs and erroneous medication orders. Further multicentric study to assess the quality of prescribing in hospital settings is required.

Conclusion

High rates of drug-drug interactions and inappropriate prescribing were reported among ESRD patients who were on QTcP-inducing drugs in outpatient clinics in Jordan. These findings urge policymakers to implement educational programme for patients and continual training courses for pharmacists and physicians to ensure safe delivery of medications to the ESRD patients.

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Conflicts of Interest

The authors declare that they have no conflict of interest.

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Data availability statement

Research data are not shared

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Figure legends

Figure 1. The flow of the research approach

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