



Original article

Assessment of the risk of QT-interval prolongation associated with potential drug-drug interactions in patients admitted to Intensive Care Units



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ABSTRACT

Objectives: To evaluate the relationship between drug interactions and QT-interval prolongation in patients admitted to a general intensive care unit (ICU).

Methods: This study was approved by the Institutional Review Board and written informed consent was obtained from all patients. From May 2015 to July 2016, all patients over 18 years-old admitted to the ICU for more than 24 h and in whom the QT-interval on the ECG could be read were prospectively included in this observational, cross-sectional study. All medications administered in the 24 h prior to admission were recorded and the QT-interval was measured upon ICU admission and corrected with Bazette's formula (QTc). Drug-drug interactions involving drugs potentially associated with QTc prolongation (DDIQT) were searched and QTc increase associated with pharmacokinetic (PK-DDIQT) and pharmacodynamic (PD-DDIQT) interactions was assessed with multiple regression adjusted by patient variables.

Results: The study population consisted of 283 patients, 54.4% males, mean age 57.6 ± 16.7 years-old. Forty five (15.9%) patients presented 65 DDIQT with predominance of pharmacodynamic (66.1%). The risk of DDIQT prescription increased with lower systolic blood pressure, in hypokalemia, in non-diabetics and with the number of medications. PK-DDIQT alone did not affect the QTc interval (7.75 ms, 95%CI: -22.4 to 37.9 ms, $p = 0.61$), but PD-DDIQT increased QTc by 28.4 ms (95%CI: 9.67 to 47.4 ms, $p = 0.003$). Most PD-DDIQT involved metoclopramide with ondansetron or amiodarone, and ondansetron with ciprofloxacin.

Conclusions: In patients exposed to drugs associated with prolonged QTc in the 24 h prior to ICU admission, pharmacodynamic DDIQT are associated with increased risk of QTc prolongation.

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1. Introduction

The QT interval on the electrocardiogram is the duration from the beginning of the QRS complex to the end of the T-wave and

represents ventricular depolarization and repolarization (Smithburger et al., 2010b). In critically ill patients, the use of intensive care medications increases the chance of drug-drug interactions (DDI), and some of these may potentiate the risk of QT-interval prolongation (Van Der Sijs et al., 2009; Smithburger et al., 2010a; Armahizer et al., 2013; Wiśniowska et al., 2016), a condition known as acquired long QT syndrome (LQTS). A corrected QT (QTc) interval with a duration greater than 500 ms (ms) increases the risk of Torsade de Pointes (TdP), a rare but lethal form of cardiac arrhythmia (Isbister and Page, 2013; Roden, 2016). In addition, prolongation of the QT interval significantly increases length of hospital stay and mortality of critically ill patients (Pickham et al., 2012).

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DDIs that increase the QT interval (DDIQT) may be classified as pharmacokinetic or pharmacodynamic (Armahizer et al., 2013). Pharmacokinetic DDIQT (PK-DDIQT) occur when a drug capable of prolonging the QT interval is administered concomitantly with a metabolic inhibitor, resulting in increased serum concentration of the drug. Pharmacodynamic DDI (PD-DDIQT) are characterized by the use of two drugs that cause QT prolongation (Smithburger et al., 2012). In clinical practice, DDIs occur primarily for two reasons: (a) prescribers are unaware of the effects of the combination of the two drugs or (b) in some situations it is considered that the expected benefit outweighs the potential risk of a DDI (Armahizer et al., 2013).

The prescription of drug interactions that increase the risk of QTc prolongation is likely to be frequent. One retrospective study on a large geriatric patient database found a prevalence of PD-DDIQT in approximately 20% of patients (Schächtele et al., 2016), while a retrospective cohort study using an outpatient database of one of the largest pharmacy benefit managers in the United States identified a prevalence of DDIQT of 9.4% (103119/1.1 million individuals) in 1999 (Curtis et al., 2003). Other retrospective studies conducted in Intensive Care Units (ICUs) showed prevalences of 38.8% (21/54) (Ridruejo et al., 2005) and 18.6% (1139/6125) (Freeman et al., 2008).

Critically ill patients are a particular population that is at increased risk of developing drug-drug interactions because of the large number of medications typically administered to these patients, as well as of pharmacokinetic changes due to failure of organic functions and to hemodynamic instability, among other causes. Notwithstanding, there is a paucity of papers approaching this problem, leaving large knowledge gaps. The vast majority of papers are restricted to describing the profile of DDIs that could potentially increase QT-interval duration, but no outcomes have been investigated. In addition, much of the reporting on the role of DDIQTs lacks practical applicability (Isbister and Page, 2013).

The objective of our study was to assess, in intensive care patients, the prevalence and profile of DDIQT, the impact of DDIQT on the duration of the QT interval, and risk factors for DDIQT prescription.

2. Material and Methods

2.1. Study setting and subjects

This project was approved by the Institutional Review Board, with authorization number 666.969, and written informed consent was obtained from all patients or their legal representatives. This observational, cross-sectional study with prospectively collected data was conducted from May 2014 through to July 2016 in the Intensive Care Unit (ICU) of Onofre Lopes University Hospital, a general ICU with 19 beds and an average of 127 admissions per month. All patients admitted to the ICU, aged over 18 years-old who had been prescribed with a drug associated with QT-interval prolongation were considered eligible. Patients with congenital QT prolongation syndrome were excluded, as well as cases of impossibility of measuring the QT-interval (cardiac conduction defects), pacemaker users, patients admitted for monitoring after diagnostic or therapeutic procedures, patients admitted after elective surgery and duplicate patients.

2.2. Qtc interval evaluation

A standard 12-lead electrocardiogram (ECG) with a 10 s rhythm strip in DII was obtained with a Cardio-Care 2000 Bionet (Macrosul, Curitiba, Brazil) electrocardiograph within 24 h of admission in all study patients to measure the QT-interval. Measurements

were done manually by the same cardiologist throughout the study, and the median length of QT intervals in six consecutive QRS complexes was determined. The calculation of corrected QT-interval (QTc) was done with Bazett's formula (Beitland et al., 2014). For the definition of QT prolongation, a value greater than 460 ms for men and greater than 470 ms for women was adopted.

2.3. DDIQT identification

All medications administered to the patient in the 24 h prior to ICU admission were recorded. The identification of drugs associated with QT-interval prolongation was based on the drug list maintained by CredibleMeds (Woosley and Romero, 2014) and included drugs classified in the categories known, possible and conditional risk of TdP.

The prescription of DDIQT was assessed within the 24 h prior to admission to the ICU. The drug interactions included in the analysis were only those related to QT-interval prolongation. Micromedex® (Thomson Reuters Healthcare & Science, Philadelphia, PA, USA) and Lexi-Interact® (Wolters Kluwer N.V., Alphen aan den Rijn, The Netherlands) databases were used to evaluate the prescription of each patient in search of DDIQT. DDIQT were classified as of minor, moderate or major seriousness or as contraindicated. The mechanism of each DDIQT was classified as pharmacokinetic or pharmacodynamic. Pharmacokinetic DDIs were defined as those that occurred due to alterations in the CYP-mediated metabolism of medications known to prolong the QTc interval. Pharmacodynamic DDIs were defined as those that occurred due to the additive effects of two medications either identified as contributing to or directly causing prolongation of the QTc interval.

2.4. Data collection

To reduce the interference of the clinical condition and other risk factors in the estimation of the risk of QTc interval prolongation associated with the presence of drug interaction, confounding factors were assessed at patient admission: the Simplified Acute Physiology Score (SAPS II) (Allyn et al., 2016), the Sequential Organ Failure Assessment (SOFA) score (Vincent et al., 1996) the Charlson comorbidity index (Charlson et al., 1987), and risk factors of QTc prolongation described in literature (gender, hypokalaemia, hypomagnesemia and heart failure) (Pickham et al., 2012; Beitland et al., 2014). Other data needed to characterize the study population, such as clinical diagnosis, blood pressure, heart rate, body temperature, blood biochemistry, length of hospital stay and ICU mortality were collected.

2.5. Statistical analysis

Assuming a standard deviation of the QTc interval of about 50 ms and a percentage of 20% of patients prescribed with DDIQT, a sample size of 270 patients affords 80% power to detect a difference of at least 23 ms in QTc interval, with a two-tailed test and at the 5% significance level.

Variables are described as absolute and relative frequencies, or as mean \pm standard deviation. The identification of the risk factors for DDIQT prescription was performed by univariate and multivariate logistic regression analysis. Only the variables presenting a p-value < 0.10 in the univariate analysis were included in the multivariate model. Results are presented as odds-ratios (OR) or adjusted odds-ratios (AOR) and 95% confidence intervals (CI). Multiple linear regression, with adjustment by the identified risk factors for DDIQT prescription, was used for assessing the influence of the DDIQT prescription and the interaction mechanisms involved (pharmacokinetic and pharmacodynamic) on QTc interval. Results are presented as mean difference and 95% CI. All tests

are two-tailed. No corrections for multiple comparisons were done. The significance level was set at the 5% level. Stata 11 (Stata Corp., Colleague Station, TX, USA) was used for the statistical analysis.

3. Results

During the data collection period, 283 patients who were administered medicines associated with QT-interval prolongation in the 24 h prior to ICU admission were included in the study. The study population consisted of 54.4% males and the mean age was 57.5 ± 16.7 years-old. The main admission diagnoses were myocardial infarction (74, 26.2%), diabetes mellitus (96, 33.9%), kidney disease (72, 25.4%), and heart failure (56, 19.8%). The mean Charlson index was 3.8 ± 2.4 . The characteristics of the study population are described in Table 1.

The study population was divided among those exposed to DDIQT in the 24 h prior to ICU admission (45 patients, 15.9%) and those not exposed (238 patients, 84.1%). In the non-exposed group, the average duration of the QTc interval was 440.8 ± 48.2 ms (95% CI 434.7 to 447.0 ms), while in the group exposed to DDIQT the average was 461.2 ± 52.9 ms (95% CI 445.4 to 477.1 ms, $p = 0.01$). Sixty-five DDIQT were detected in this group with predominance of pharmacodynamic interactions: 43 PD-DDIQT in 33 patients versus 22 pharmacokinetic interactions in 12 patients. The mean QTc interval in patients with PD-DDIQT and PK-DDIQT were 466.6 ± 57.6 ms (95% CI 446.2 to 487.0 ms) and 446.6 ± 35.2 ms (95% CI 424.2 to 469.0 ms), respectively (Table 2).

Univariate analysis (Table 3) showed an association between the prescription of DDIQT in the 24 h prior to ICU admission and

lower systolic blood pressure (OR 0.988, $p = 0.04$), increased heart rate (OR 1.017, $p = 0.02$), no diabetes mellitus (OR 0.505, $p = 0.07$), no myocardial infarction (OR 0.385, $p = 0.04$), low serum potassium (OR 0.704, $p = 0.08$) and number of medicines (OR 1.175, $p < 0.001$). In multivariate analysis, the variables independently associated with increased risk of DDIQT prescription were lower systolic blood pressure (AOR 0.988, 95% CI 0.976 – 0.999, $p = 0.05$), no diabetes mellitus (AOR 0.440, 95% CI 0.196 – 0.991, $p = 0.05$), lower serum potassium (AOR 0.602, 95% CI 0.385 – 0.941, $p = 0.03$) and greater number of medicines in the 24 h prior to ICU admission (AOR 1.201, 95% CI 1.085 – 1.330, $p < 0.001$).

Table 4 describes the profile of DDIQT. Moderate risk DDIQTs were predominant (47.7%), followed by major (38.5%) and minor (13.8%) risk DDIQT. The PK-DDIQT were characterized by the prescription of the metabolic inhibitor metronidazole along with ondansetron (4, 18.2%), metoclopramide (4, 18.2%) or ciprofloxacin (2, 9.1%). Most PD-DDIQT involved antiemetics, mainly metoclopramide with ondansetron (10, 23.3%) or with amiodarone (5, 11.6%), and ondansetron with ciprofloxacin (4, 9.3%).

According to the multiple regression model adjusted by the patient variables that were statistically different between DDIQT and non-DDIQT patients, occurrence of DDIQT in the 24 h prior to ICU admission leads to a mean increase of the QTc interval of 23.6 ms (95% CI 7.0 to 40.2 ms, $p = 0.005$) over the QTc interval in non-DDIQT patients. Again, compared to non-DDIQT patients, PD-DDIQT increased QTc interval duration by an average of 28.4 ms (95% CI 9.67 to 47.1 ms, $p = 0.003$). However, we did not observe an impact of PK-DDIQT on the QTc interval (7.75 ms, 95% CI –22.4 to 37.9 ms, $p = 0.61$).

4. Discussion

Published studies on LQTS-related drug interactions are limited to reports of isolated cases, literature reviews, as secondary results from other research or descriptive studies. In the last 5 years, only 1 literature review (Barni et al., 2016), 2 case reports (Woosley and Romero, 2014), 1 descriptive retrospective study, 4 studies on specific drug interactions associated with LQTS (Beitland et al., 2014; Uijtendaal et al., 2014; Schächtele et al., 2016; Roden, 2016), and 2 studies on the development of alert systems for prescribing interactions associated with LQTS (Ahn et al., 2014; Riad et al., 2017) were published.

Studies in intensive care are even scarcer. A 10 years retrospective study in an ICU that predominantly cares heart diseases, which observed patients presenting $QTc \geq 500$ ms throughout hospitalization, reported a prevalence of LQTS of 37.3% (187/501) and, in these patients, 1798 interactions. A percentage of 43% of patients experienced pharmacodynamic interactions and 47% pharmacokinetic interactions, the drugs most commonly involved being ondansetron, amiodarone, metronidazole and haloperidol (Armahizer et al., 2013).

Our results are based on prospectively collected data from 283 consecutive ICU admissions throughout a full year who were

Table 1
Characteristics of the study population (n = 283).

Characteristics	Values	
Male (n, %)	154	54.4
Age, years	57.5	16.7
Charlson comorbidity index	3.9	2.5
Charlson probability	54.3	37.1
SAPS II	40.5	19.3
SOFA	7.26	4.22
<i>Diagnosis (n, %)</i>		
Diabetes mellitus	96	33.9
Myocardial infarction	74	26.2
Kidney disease	72	25.4
Congestive heart failure	56	19.8
Cancer	37	13.1
Chronic liver disease	28	9.9
Cerebrovascular disease	20	7.1
Others	43	15.2
Number of medicines	9.55	3.37
QT-interval prolongation (n, %)	82	29.0
Length of stay	9.5	10.7
Death (n, %)	43	19.6

Values are mean and standard deviation unless otherwise specified. SAPS: Simplified Acute Physiology Score; SOFA: Sequential Organ Failure Assessment.

Table 2
QTc duration in patients prescribed with QT-prolonging drugs in the 24 h prior to ICU admission.

Patient group	Number of		QTc duration (ms)		
	patients	DDI	mean	sd	95% CI
Study population	283	65	444.1	49.5	438.3 – 449.8
No DDIQT	206	0	440.8	48.2	434.7 – 447.0
DDIQT	45	65	461.2	65.0	445.4 – 477.1
PD-DDIQT	33	43	466.6	57.6	446.2 – 487.0
PK-DDIQT	12	22	446.6	35.2	424.2 – 469.0

DDI: drug-drug interaction; sd: standard deviation. CI: confidence interval; DDIQT: drug-drug interaction potentially related to QTc prolongation; PD: pharmacodynamic; PK: pharmacokinetic.

Table 3
Univariate analysis of variables associated with DDIQT in ICU patients prescribed in the 24 h prior to admission with medicines associated with QTc prolongation.

Characteristics (n = 283)	No DDIQT		DDIQT		p
	n = 238		n = 45		
Female (n, %)	111	46.6	18	40.0	0.41
Age (years)	58.1	16.9	54.2	15.7	0.15
<i>Vital signs</i>					
Systolic pressure (mmHg)	129.1	34	117.7	23.6	0.04
Diastolic pressure (mmHg)	73.1	19.6	69.9	16.6	0.31
Heart rate (bpm)	92.8	22.6	101.3	21.4	0.02
Temperature (°C)	35.7	0.97	35.9	1.14	0.31
<i>Diagnosis (n, %)</i>					
Diabetes mellitus	86	36.1	10	22.2	0.07
Myocardial infarction	68	28.6	6	13.3	0.03
Kidney disease	58	24.4	14	31.1	0.34
Congestive heart failure	49	20.6	7	15.6	0.44
Cancer	26	13.9	5	11.1	0.36
Cerebrovascular disease	17	7.1	3	6.7	0.91
Chronic liver disease	21	8.8	7	15.6	0.17
<i>Blood biochemistry</i>					
Sodium (mmol/L)	138.2	7.37	139.1	7.24	0.47
Potassium (mmol/L)	4.52	0.95	4.24	0.79	0.08
Calcium (mg/dL)	8.81	1.25	8.86	0.97	0.80
Magnesium (mmol/L)	2.04	0.46	2.04	0.46	0.99
Charlson comorbidity index	3.92	2.47	3.29	2.22	0.11
SAPS II	40.9	19.5	38.9	18.1	0.56
SOFA	7.40	4.36	6.38	3.22	0.37
Number of medicines	9.26	3.31	11.1	3.28	<0.001

Values are mean and standard deviation unless otherwise specified. DDIQT: drug-drug interaction potentially related to QTc prolongation; SAPS: Simplified Acute Physiology Score; SOFA: Sequential Organ Failure Assessment.

Table 4
Profile of DDIQT within 24 h prior to ICU admission.

Characteristics	n	%
<i>Risk class</i>		
Minor	9	13.8
Moderate	31	47.7
Major	25	38.5
Contraindicated	0	0.0
Total	65	100.0
<i>Pharmacodynamic DDIQTs</i>		
Metoclopramide + Ondansetron	10	23.3
Metoclopramide + Amiodarone	5	11.6
Ondansetron + Ciprofloxacin	4	9.3
Ondansetron + Amiodarone	4	9.3
Others	20	46.5
Total	43	100.0
<i>Pharmacokinetic DDIQTs</i>		
Metronidazole + Ondansetron	4	18.2
Metronidazole + Metoclopramide	4	18.2
Metronidazole + Ciprofloxacin	2	9.1
Others	12	54.5
Total	22	100.0

DDIQT: drug-drug interaction potentially related to QTc prolongation.

systematically evaluated for QTc interval prolongation and prescription of LQTS-related drug interactions. The main finding was that the QTc interval in patients newly admitted to an ICU is increased by the prescription of DDIQT in the 24 h prior to admission, but only pharmacodynamic interactions were found to prolong the QTc interval. This contradicts the result of a retrospective study based on a Chicago hospital database that quantified the risk of QTc prolongation in patients receiving medicines associated with LQTS classified as “known risk”, and found no statistically significant difference in the QTc interval among patients prescribed with multiple medications associated with the LQTS (Riad et al., 2017). That study is also contradicted by a retrospective case-control study conducted at a university

hospital in Amsterdam, which quantified the risk of cardiac arrest associated with the use of non-arrhythmic LQTS inducers in a total of 140 patients resuscitated from cardiac arrest at the hospital, where the risk of cardiac arrest increased with the number of prescribed LQTS-associated drugs (OR 4.8, 95% CI 1.6 to 14) and when there was a pharmacokinetic interaction involved (OR 4.0, 95% CI 1.2 to 13) (De Bruin et al., 2007).

Our data shows that combinations of ondansetron, metoclopramide and amiodarone were the most frequent found PD-DDIQTs. The combination of metronidazole with these drugs characterized the major PK-DDIQTs. It is known that the increase of the drug-induced QTc interval is most commonly related to the reduction of potassium efflux via blocking of the human ether-a-go-go-related-gene (hERG) (Rodén, 2016; Wiśniowska et al., 2016), and main drugs involved in the interactions (ondansetron, metoclopramide, amiodarone and ciprofloxacin) are largely associated with increased QTc interval through that mechanism (Anderson et al., 2001; Barni et al., 2016) and are widely administered in ICU (Armahizer et al., 2013). The concomitant use of these drugs may imply a potentiating effect on potassium channel blockade. At least in animal studies, administration of two potassium channel blockers simultaneously markedly potentiates the increase of the QTc interval (Lengyel et al., 2007). In our study, the presence of PD-DDIQT was associated with a statistically significant increase of 28 ms in QTc interval. Only one study has reviewed the literature for the mean increase from baseline in the QTc interval induced by drugs strongly associated with TdP, and reported an average of 12 ms on monotherapy, most remarkably with mesoridazine (46.6 ms, 95% CI 44.1 to 49.1 ms) and methadone (41.7 ms, 95% CI 26.0 to 57.4 ms). When in the presence of a metabolic inhibitor, the QTc increase averaged 25 ms, with emphasis on ketoconazole and terfenadine (82 ms, 95% CI 56.6 to 97.1 ms) (Lin and Kung, 2009). However, we were not able to observe an impact of pharmacokinetic interactions on the mean duration of the QTc interval. This could be because of the small number of patients with PK-DDIQT in our study, or because

pharmacokinetic interactions described in databases, such as those consulted in our study, use as information sources a multitude of studies with different methodologies, such as reports of clinical observations and *in silico*, *in vitro* or *in vivo* methodologies, and the criteria used are often not very explicit and have marked divergences across databases (Vitry, 2007). Another reason might be that the main interactions observed in our ICU patients were characterized by the administration of an ion channel blocker (ondansetron, metoclopramide and ciprofloxacin) and the metabolic inhibitor metronidazole. Yet, one study that evaluated the quality of the information specifically related to pharmacokinetic interactions concluded that metronidazole would be a weak metabolic inhibitor of CYP3A4 and CYP2C9 isoforms, rarely clinically relevant (Polasek et al., 2011).

Another relevant finding of our study was that the risk of DDIQT prescription in newly admitted ICU patients increases in non diabetics, with lower systolic blood pressure, lower serum potassium and greater number of prescribed drugs. A review of the electrophysiological consequences induced by DDIQT reported a high variability of effects due to the complexity of the phenomenon and to the innumerable variables involved, especially when pharmacodynamic interactions are concerned, with adequate monitoring and the need to evaluate other risk factors being suggested (Wiśniowska et al., 2016). As far as we know, our study is the first to present risk factors for the occurrence of DDIQT. A greater number of drugs implies an increased likelihood of DDI, including those related to QTc prolongation as noted by others (Smithburger et al., 2012; Uijtendaal et al., 2014), but we have also found that the occurrence of DDIQT is also related to systolic arterial pressure, serum potassium level and diabetes mellitus.

Despite the recommended use of software that supports prescribers and pharmacists in detecting DDI, most alerts are ignored due to information overload (Paterno et al., 2009; Smithburger et al., 2012; Ahn et al., 2014). The same is true for DDIQT-related alerts. A retrospective database study found that only 33% of patients prescribed with two or more medications associated with QT prolongation had electrocardiographic monitoring, even after the support of an electronic system alert (Van Der Sijs et al., 2009). Therefore, it seems reasonable to suggest that those softwares should prioritize DDI alerts with greater potential for changes in clinical parameters. Regarding DDIQT, we suggest that interactions related to pharmacodynamic mechanisms are more clinically relevant than those associated with the prescription of a metabolic inhibitor.

Our study has some limitations. Our data were collected in a general ICU of a university hospital with great diversity of patients, which contributes to the generalization of our findings. However, this generalization potential is somewhat diminished because it is a single study site. QT interval was measured on a single ECG and, because of the variability of the duration of the QT interval, continuous ECG monitoring might provide more accurate readings. Some aspects of our methodology contribute to the validity of our results: data was collected prospectively, patient enrolment lasted for a whole year, thereby eliminating any seasonal trends in drug prescription, measurement of the QTc interval was performed manually by an experienced cardiologist, which is considered the method with greatest accuracy (Isbister and Page, 2013). The inclusion of patients as they were admitted to the ICU and the evaluation of the occurrence of DDIQT in the 24 h prior to admission, are important aspects of our methodology. In fact, the administration of vasoactive drugs and other drugs that affect hemodynamics, the presence of comorbidities and the occurrence of electrolyte imbalances are common in ICU, and these factors hinder the identification of QTc interval increase attributable to DDIQT. Therefore, the inclusion of patients just admitted to the ICU allowed the

evaluation of a population at risk for torsades de pointes, but still with little influence of those confounding variables.

5. Conclusions

In summary, the QTc interval of patients on ICU admission is increased by the prescription of pharmacodynamic DDIQT in the prior 24 h. The pharmacodynamic mechanism involved in the interaction is blockade of the potassium channels (ondansetron, metoclopramide, ciprofloxacin and amiodarone). We found no evidence of an effect on QTc interval of the prescription of pharmacokinetic DDIQT characterized by metabolic inhibition (metronidazole).

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