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Evaluation of the Precipitation Characteristics of Ertapenem, Tigecycline, Colistin, Daptomycin, Vancomycin and Teicoplanin

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SUMMARY*. Some medications frequently employed in anesthesiology and in intensive care practice may undergo reactions linked to chemical and physical characteristics when they are used with many other medications or in sequential administration and may cause precipitation. Ertapenem, tigecycline, colistin, daptomycin, vancomycin and teicoplanin are important antibiotics, some newly entering use, employed in intensive care for infections by resistant microorganisms. The compatibility of ertapenem, tigecycline, colistin, daptomycin, vancomycin and teicoplanin was researched with all medications used in our surgery using the lam-lamellar technique and visual investigations. Our study determined the precipitation characteristics of ertapenem (20 mg/mL), tigecycline (10 mg/mL), colistin (75 mg/mL), daptomycin (50 mg/mL), vancomycin (10 mg/mL) and teicoplanin (60 mg/mL). With this aim 0.1 mL of each medication was mixed on a slide with the same volume of test drug and the precipitation or the lack of each one was observed through a magnifier. Ertapenem reacted with dobutamine, verapamil, protamine, mannitol and midazolam; tigecycline reacted with diclophenac sodium and thiopental; colistin reacted with amiodorone, dobutamine, ketamine, chlorphenoxamine, protamine and ranitidine; daptomycin reacted with protamine, thiopental and dobutamine; vancomycin reacted with diclophenac sodium, gelofucine, dexketoprofen, daptomycin, ertapenem, furosemide, prednisolone, tenoxycam, dexamethasone, heparin, thiopental and bicarbonate while teicoplanin reacted with dobutamine, atracurium, ketamine, chlorphenoxamine and diltiazem under *in vitro* conditions causing precipitation. The *in vitro* reactions and precipitations observed in our study may be described as the "tip of the iceberg" of medication interactions. Future studies should determine the factors involved in the *in vitro* precipitations observed in our study and also the characteristic properties of these reactions.

RESUMEN. Algunos medicamentos frecuentemente utilizados en anestesiología y en la práctica de cuidados intensivos pueden sufrir reacciones vinculadas a las características químicas y físicas cuando se utilizan con otros medicamentos o en administración secuencial y pueden provocar la precipitación. Ertapenem, tigeciclina, colistina, daptomicina, vancomicina y teicoplanina son antibióticos importantes, algunos recientemente empleados en cuidados intensivos para las infecciones por microorganismos resistentes. La compatibilidad de ertapenem, tigeciclina, colistina, daptomicina, vancomicina y teicoplanina fue investigada con todos los medicamentos utilizados en cirugía mediante la técnica lam-lamelar e investigaciones visuales. Se determinaron las características de precipitación de ertapenem (20 mg/mL), tigeciclina (10 mg/mL), colistina (75 mg/mL), daptomicina (50 mg/mL), vancomicina (10 mg/mL) y teicoplanina (60 mg/mL). Con este objetivo, 0,1 mL de cada medicamento se mezcló en portaobjetos con el mismo volumen de fármaco de prueba y la precipitación o la falta de cada uno de ellos se observó a través de una lupa. Ertapenem reaccionó con dobutamina, verapamilo, protamina, manitol y midazolam; tigeciclina reaccionór con diclofenaco sódico y tiopental; colistina reaccionó con amiodorona, dobutamina, ketamina, chlorfexamina, protamina y ranitidina; daptomicina reaccionó con protamina, tiopental y dobutamina; vancomicina reaccionó con diclofenac sódico, gelofucina, dexketoprofeno, daptomicina, ertapenem, furosemida, prednisolona, tenoxicam, dexametasona, heparina, tiopental y bicarbonato, mientras teicoplanina reaccionó con dobutamina, atracurio, ketamina, diltiazem chlorfexamina. Las reacciones *in vitro* y las precipitacion observadas en este estudio pueden ser descritos como la "punta del iceberg" de las interacciones de medicamentos. Estudios futuros deben determinar los factores que intervienen en las precipitaciones *in vitro* observada en nuestro estudio y también las propiedades características de estas reacciones.

KEY WORDS: Colistin, Daptomycin, Ertapenem, Precipitation, Teicoplanin, Tigecycline, Vancomycin.

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INTRODUCTION

Some medications frequently employed in anesthesiology and intensive care practice may undergo reactions linked to chemical and physical characteristics when they are used with many other medications or in sequential administration and may cause precipitation [1-4]. Precipitation may cause blockage of the vein used, and loss of the medication efficacy [1,5,6]. In addition previous experimental studies have shown that the crystals formed during the precipitation reactions can cause pulmonary embolism and this resulting embolism may lead to mortality or morbidity [7].

As a result knowing the reactions with other medications and precipitation characteristics of medications used in anesthesiology and intensive care practice is important to provide quality patient care and prevent unwanted reactions [1].

Thiopental has a basic pH value among medications employed in anesthetic practice and precipitates with many medications and is at the top of the list of incompatible drugs [5,7]. It is known that thiopental reacts with alfentanil, atracurium, cisatracurium, suxamethonium, mivacurium, vecuronium, rocuronium, pancuronium, atropine, dopamine, dobutamine, ephedrine, midazolam, morphine and sufentanil; medications frequently used in anesthetic practice [5,8-10]. Thiopental forms also precipitation with local anesthetics linked to pH differences [6]. Propofol can react with alfentanil, atracurium, atropine, digoxin, diphenhydramine, dopamine, dobutamine, ephedrine, esmolol, famotidine, fentanyl, ketamine, midazolam, morphine, pancuronium, remifentanil, sufentanil and vecuronium [10-12]. Midazolam can react with sodium bicarbonate, dobutamine, morphine, propofol and thiopental [8,11,13,14].

Our previous studies have determined that sugammadex, a medication newly entering anesthetic practice, can form a precipitation reaction with amiodarone, dobutamine and protamine [1,2].

Ertapenem, tigecycline, colistin, daptomycin, vancomycin and teicoplanin are important antibiotics, some newly entering use, from different groups employed in intensive care for infections by resistant microorganisms [15]. For a variety of reasons it may be necessary to use ertapenem, tigecycline, colistin, daptomycin, vancomycin and teicoplanin simultaneously with other medications in anesthesiology and intensive care practice. It is to note that the physicochemical compatibility with some medications frequently used in anesthesiology and intensive care practice has not been researched and the scientific data on this topic is limited. For effective treatment of patients in anesthesiology and intensive care, it is necessary to determine clearly the physicochemical compatibility of the medications employed in this area , specially for those cases where antibiotics such as ertapenem, tigecycline, colistin, daptomycin, vancomycin and teicoplanin are needed; and to ensure patient safety [1].

The hypothesis of our study is that medications frequently employed in anesthesiology and in intensive care practice may produce precipitation reactions linked to physical and chemical characteristics with antibiotics such as ertapenem, tigecycline, colistin, daptomycin, vancomycin and teicoplanin. To test this hypothesis it was researched the compatibility of ertapenem, tigecycline, colistin, daptomycin, vancomycin and teicoplanin with all medications used in our surgery, using the lam-lamellar technique and visual investigations.

MATERIAL AND METHODS

Our study was carried out in the operating room of Dokuz Eylul University Faculty of Medicine on 24 January 2014 and was granted by "Dokuz Eylul University Non-Interventional Research Ethics Committee" (Date: 09/01/2014; Decision No. 2014/02-07, Chair: B Önvural). We determine the precipitation characteristics of ertapenem (20 mg/mL), tigecycline (10 mg/mL), colistin (75 mg/mL), daptomycin (50 mg/mL), vancomycin (10 mg/mL) and teicoplanin (60 mg/mL), with this aim 0.1 mL of each medication was mixed on a slide with the same volume of test drug and the precipitation or the lack of each one was observed through a magnifier [1].

Ertapenem (20 mg/mL), tigecycline (10 mg/mL), colistin (75 mg/mL), daptomycin (50 mg/mL), vancomycin (10 mg/mL) and teicoplanin (60 mg/mL) were mixed with medications frequently used in clinical practice of anesthesiology and intensive care such as adrenalin (1 mg/mL), atropine (1 mg/mL), amiodarone (50 mg/mL), aminophylline (24 mg/mL), acetaminophen (10 mg/mL), atracurium (10 mg/mL), daptomycin (50 mg/mL), dexmedetomidine (100 μg/mL), dexamethasone (4 mg/mL), dobutamine (12.5 mg/mL), dopamine (8 mg/mL), dexketoprofen (25 mg/mL), diclophenac sodium (25 mg/mL), diltiazem HCl (25 mg/mL), digoxin (0.25 mg/mL), ephedrine (0.05 g/mL), ertapenem (20 mg/mL), enoxaparin

(100 mg/mL), fentanyl (50 µg/mL), pheniramine (22.75 mg/mL), phenytoin (50 mg/mL), furosemide (10 mg/mL), glycerine trinitrate (5 mg/mL), gelofusine (succinylated gelatine (modified liquid gelatine) 40 mg/mL, sodium chloride 7 mg/mL, sodium hydroxide 1.36 mg/mL) heparin (1000 IU/mL), hydrocortisone (250 mg/mL), calcium amp (calcium gluconate monohydrate 225 mg/10 mL + calcium levulinate dihydrate 572 mg/10 mL), ketamine (50 mg/mL), chlorphenoxamine hydrochloride (10 mg/mL), colistin (75 mg/mL), lidocaine (20 mg/mL), magnesium sulfate (1.2 mEq/mL), mannitol (20 g/100 mL), metamizol sodium (0.5 g/mL), methylergobasin maleate (0.2 mg/mL), metoclopramide (5 mg/mL), metoprolol (1 mg/mL), morphine (0.01 g/mL), midazolam (1 mg/mL), $NaHCO_3$ (0.84 g/10 mL), n-acetylcisteine (100 mg/mL), neostigmine (0.5 mg/mL), nitroprusside (12 mg/mL), noradrenalin (1 mg/mL), oxytocin (5 IU/mL), paracetamol (10 mg/mL), pethidine (50 mg/mL), prednisolone (25 mg/mL), protamine hydrochloride (1000 IU/mL), potassium (1 mEq/mL), propofol (20 mg/mL), ranitidine (10 mg/mL), remifentanil (5 mg/mL), rocuronium (10 mg/mL), butylscopolamine bromide (20 mg/mL), sugammadex (100 mg/mL) succinylcholine (20 mg/mL), teicoplanin (60 mg/mL), tenoxycam (10 mg/mL), tigecycline (10 mg/mL), thiopental sodium (25 mg/mL), tranexamic acid (100 mg/mL), tramadol (50 mg/mL), vancomycin (10 mg/mL), and verapamil (2.5 mg/mL) at the same volume.

Precipitation was scored similarly to previous studies: so if precipitation did not form a score of 0 was given and if strong precipitation formed a score of 4+ was given [1].

RESULTS

In our study the precipitation characteristics of ertapenem (20 mg/mL), tigecycline (10 mg/mL), colistin (75 mg/mL), daptomycin (50 mg/mL), vancomycin (10 mg/mL) and teicoplanin (60 mg/mL) were evaluated. Ertapenem entered precipitation reactions with dobutamine (++++), vancomycin (+++), verapamil and protamine (++), mannitol and midazolam (+). Tigecycline had a precipitation reaction with diclophenac sodium (++++) and thiopental (+++). Colistin entered a precipitation reaction with amiodarone, dobutamine, ketamine, chlorphenoxamine and protamine (+++), and ranitidine (++). Daptomycin had a precipitation reaction with protamine and vancomycin (+++), thiopental (++), and dobutamine (+). Vancomycin had precipitation reactions with diclophenac sodium, gelofusine (++++), dexketoprofen, daptomycin, ertapenem, furosemide and prednisolone (+++), tenoxycam, heparin and dexamethasone (++), thiopental and bicarbonate (+). Teicoplanin precipitated with dobutamine and chlorphenoxamine (++++), atracurium and ketamine (+++), and diltiazem (++).

The precipitation characteristics of the study drugs, ertapenem (20 mg/mL), tigecycline (10 mg/mL), colistin (75 mg/mL), daptomycin (50 mg/mL), vancomycin (10 mg/mL) and teicoplanin (60 mg/mL) , are summarized in Table 1.

DISCUSSION

Our study shows that the precipitation reactions of ertapenem, tigecycline, colistin, daptomycin, vancomycin and teicoplanin with medications frequently used in anesthesiology and in intensive care practice were determined.

Ertapenem, in the carbapenem group with a narrow effective spectrum, is an antibiotic used for intra-abdominal infections, acute pelvic infections, complicated skin infections, community-acquired pneumonia and complicated urinary tract infections [15,16]. Previous studies have determined incompatibility with anidulafungin, caspofungin acetate and mannitol [17-19]. In addition there is no wide-ranging study researching the drug incompatibility of ertapenem. In our study we also determined that ertapenem produced a precipitation reaction with dobutamine (++++), vancomycin (+++), verapamil and protamine (++) and mannitol and midazolam (+).

Tigecycline, a prototype of glycylcycline group antibiotics, is a broad-spectrum antibiotic effective against methicillin-resistant *Staphylococcus aureus,* vancomycin-resistant *Enterococcus* spp., *Acinetobacter baumannii* and ESBL-producing gram-negative bacterial strains. Tigecycline is used in adults for complicated intra-abdominal infections, complicated skin infections, and community-acquired bacterial pneumonia [20]. Studies on the precipitation characteristics of tigecycline are very limited. Apart from the manufacturer's incompatibility guidelines there is no study data. Our results, the first on the topic, showed that tigecycline precipitated with diclophenac sodium (++++) and thiopental (+++).

Colistin is a polypeptide antibiotic in the polymyxin group mainly effective against gram negative organisms. Parenteral colistin is used for treatment of ventilator-related pneumonia caused by multiple drug-resistant bacteria such

Drug	Ertapenem (20 mg/mL)	Tigecycline (10 mg/mL)	Colistin (75 mg/mL)	Daptomycin (50 mg/mL)	Vancomycin (10 mg/mL)	Teicoplanin (60 mg/mL)
Amiodarone (50 mg/mL)	-	-	+++	-	-	-
Atracurium (10 mg/mL)	-	-	-	-	-	+++
Chlorphenoxamine hydrochloride (10 mg/mL)	-	-	+++	-	-	++++
Daptomycin (50 mg/mL)	-	-	-	-	+++	-
Dexamethasone (4mg/mL)	-	-	-	-	++	-
Dexketoprofen (25 mg/mL)	-	-	-	-	+++	-
Diclophenac sodium (25 mg/mL)	-	++++	-	-	++++	-
Diltiazem HCl (25 mg/mL)	-	-	-	-	-	++
Dobutamine (12.5 mg/mL)	++++	-	+++	+	-	++++
Ertapenem (20 mg/mL)	-	-	-	-	+++	-
Furosemide (10mg/mL)	-	-	-	-	+++	-
Gelofusine succinylated gelatine (modified liquid gelatine) 40 mg/mL	-	-	-	-	++++	-
Heparin (1000 IU/mL)	-	-	-	-	++	-
Ketamine (50 mg/mL)	-	-	+++	-	-	+++
Mannitol (20g/100 mL)	+	-	-	-	-	-
Midazolam (1 mg/mL)	+	-	-	-	-	-
NaHCO3 (0.84g/10 mL)	-	-	-	-	+	-
Tenoxycam (10 mg/mL)	-	-	-	-	++	-
Prednisolone (25 mg/mL),	-	-	-	-	+++	-
Protamine hydrochloride (1000 IU/mL)	++	-	+++	+++	-	+++
Ranitidine (10 mg/mL)	-	-	++	-	-	+++
Rocuronium (10 mg/mL)	-	-	-	-	-	+++
Thiopental sodium (25 mg/mL)	-	+++	-	++	+	-
Vancomycin (10 mg/mL)	+++	-	-	+++	-	-
Verapamil (2.5 mg/mL)	++	-	-	-	-	-

Table 1. The precipitation characteristics of Ertapenem, Tigecycline, Colistin, Daptomycin, Vancomycin and Teicoplanin.

as *Pseudomonas aeruginosa, Klebsiella pneumoniae* and *Acinetobacter baumannii* [21]. Previous studies have determined incompatibility between colistin and cromoglycate sodium and telavancin hydrochloride [22,23]. There is no other broad-range study on the precipitation characteristics of colistin. In our study, colistin precipitated with amiodarone, dobutamine, ketamine, chlorphenoxamine and protamine (+++), and ranitidine (++).

Daptomycin is a branched, cyclic anionic lipopeptide antibiotic and received FDA approval in 2003. It is effective against aerobic and anerobic gram-positive bacteria including methicillin-resistant Staphylococcus aureus and vancomycin-resistant enterococci [24]. The single study on daptomycin's drug incompatibility reported no incompatibility with the study drugs; aztreonam, ceftazidime, ceftriaxone, dopamine, gentamicin, fluconazole, heparin, levofloxacin and lidocaine [25]. We observed a precipitation reaction for daptomycin with protamine and vancomycin (+++), thiopental (++), and dobutamine (+).

Vancomycin is a glycopeptide-group antibiotic in widespread use since the 1950's. In spite of the fact that many new anti-gram positive antibiotics have been discovered since vancomycin entered use, it continues to be the gold standard for treatment of methicillin-resistant staphylococcal infections [26]. Vancomycin is one of the leading drugs requiring care when it is employed with other medications. Previous studies have described incompatibility of vancomycin with many drugs. A series of studies have reported vancomycin incompatibility with aminophylline, amphotericin B, amobarbital sodium, ampicillin, ascorbic acid, aztreonam, bivalirudin, cefazolin sodium, cefepime, cefmethazole sodium, cefonicid sodium, cefuroxime sodium, ceftazidime, ceftizoxim sodium, ceftriaxone disodium, cefuroxim sodium, chloramphenicol sodium succinate, chlortiazide sodium, chloxacillin sodium, defibrotide, dexamethasone sodium phosphate, dimenhydrinate, flucloxyacillin sodium, phoscarnet sodium, furosemide, heparin, hydrocortisone, idarubicin, lansoprozole, methotrexate, methylprednisolone, moxifloxacin, nafcillin,

omeprazole, pantoprozol, penicillin G, phenytoin sodium, piperacillin/tazobaktam, propofol, rocuronium, salbutamol, sargramostim, temocillin, heophylin, thiamine, ticarcillin/clavulanic acid, warfarin and gelofucin [27-43]. Our results showed vancomycin had a precipitation reaction with diclophenac sodium, gelofusine (++++), dexketoprofen, daptomycin, ertapenem, furosemide and prednisolone (+++), tenoxycam, heparin and dexamethasone (++), thiopental and bicarbonate (+). Vancomycin had the highest number of precipitation reactions of all the study antibiotics.

Teicoplanin is a glycopeptide antibiotic [44,45], that as with other beta lactams, is used for treatment of severe antibiotic-resistant gram-positive bacterial infections [45]. Previous studies have reported teicoplanin incompatibility with amikacin, ceftazidime, ciprofloxacin, gentamicin, kanamycin and netilmicin [46,47]. However we observed a precipitation reaction between teicoplanin and dobutamine and chlorphenoxamine (++++), atracurium and ketamine (+++), and diltiazem (++).

In our study, while some precipitations were emphasized by previous studies, some reactions were determined for the first time in this study with ertapenem (20 mg/mL), tigecycline (10 mg/mL), colistin (75 mg/mL), daptomycin (50 mg/mL), vancomycin (10 mg/mL), and teicoplanin (60 mg/mL).

We can concluded that ertapenem reacted with dobutamine, verapamil, protamine, mannitol and midazolam; tigecycline reacted with diclophenac sodium and thiopental; colistin reacted with amiodorone, dobutamine, ketamine, chlorphenoxamine, protamine and ranitidine; daptomycin reacted with protamine, thiopental and dobutamine; vancomycin reacted with diclophenac sodium, gelofucine, dexketoprofen, daptomycin, ertapenem, furosemide, prednisolone, tenoxycam, dexamethasone, heparin, thiopental and bicarbonate while teicoplanin reacted with dobutamine, atracurium, ketamine, chlorphenoxamine and diltiazem under *in vitro* conditions causing precipitation. We emphasize that care must be taken when these medication are administered simultaneously through intravenous methods. The *in vitro* reactions and precipitations observed in our study may be described as the "tip of the iceberg" of medication interactions. Future studies should determine the factors involved in the *in vitro* precipitations observed in our study and the characteristic properties of these reactions. Further studies should use advanced tools such as gas chromatography/mass spectrometry to shed light on the possible reactions of these antibiotics with other drugs. Additionally we believe that the effects of the drug interactions in this study on the medication efficacy and on the circulation require further research.

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