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LETTER TO THE EDITOR

Precipitation in Gallipoli: Sugammadex / Amiodarone & Sugammadex / Dobutamine & Sugammadex / Protamine

Dear Editor,

Sugammadex is a modified gamma cyclodextrin¹⁻³. Cyclodextrins are water soluble cyclic oligosaccharides with a lipophilic core. Sugammadex has quickly found a place in clinical use for selective antagonism of neuromuscular blockade with rocuronium¹⁻³. Sugammadex quickly encapsulates steroidal neuromuscular blockers, increasing the amount of encapsulated steroidal neuromuscular blockers in plasma and separating the blockers from the nicotinic acetylcholine receptors¹⁻³.

Apart from its use with steroidal neuromuscular blockers, it is known that sugammadex interacts with over 40 lipophilic, steroidal and non-steroidal drugs. These drugs include: propofol, thiopental, fentanyl, remifentanyl, vancomycin, gentamicin, salbutamol, aminophylline, atropine, digoxin, ephedrine, phentolamine, verapamil, cortisone and hydrocortisone⁴.

Previous research shows that, apart from steroidal muscle relaxants, sugammadex forms precipitates with protamine⁵.

There is no clinical data on whether sugammadex forms precipitates with other drugs, commonly used in clinical practice. The hypothesis of this study is to investigate whether the chemical and physical properties of sugammadex would contribute to a precipitation reaction with drugs commonly used in clinical practice.

With this aim, simply 0.1 mL containing 100 mg.mL⁻¹ sugammadex was mixed on a glass slide with the same volume of a drug and the presence or absence of precipitation was determined under the microscope. The drugs investigated are all commonly used in clinical anesthesia practice. They include: adrenalin (1 mg.mL⁻¹), atropine (1 mg.mL⁻¹), amiodarone (50 mg.mL⁻¹), aminophylline (24 mg.mL⁻¹), ornidazole (500 mg.3 mL⁻¹), bupivacaine (5 mg.mL⁻¹), cefazolin sodium (250 mg.mL⁻¹), dexmedetomidine (100 µg.mL⁻¹), dobutamine (12.5 mg.mL⁻¹), dopamine (8 mg.mL⁻¹), ephedrine (0.05 g.mL⁻¹), esmolol (10 mg.mL⁻¹), esomeprazole (40 mg.mL⁻¹), etomidate (2 mg.mL⁻¹), fentanyl (50 µg.mL⁻¹), flumazenil (0.1 mg.mL⁻¹),

furosemide (10 mg.mL⁻¹), gentamicin (40 mg.mL⁻¹), glyceryl trinitrate (5 mg.mL⁻¹), heparin (1,000 IU.mL⁻¹), hydrocortisone (250 mg.mL⁻¹), crystallized insulin (100 IU.mL⁻¹), Calcium (Calcium Gluconate Monohydrate 225 mg.10 mL⁻¹ + Calcium levulinate dihydrate 572 mg.10 mL⁻¹), ketamine (50 mg.mL⁻¹), levobupivacaine (7.5 mg.mL⁻¹), magnesium sulphate (1.2 mEq.mL⁻¹), metamizol sodium (0.5 g.mL⁻¹), methylethylgobasin maleate (0.2 mg.mL⁻¹), metoclopramide (5 mg.mL⁻¹), metoprolol (1 mg.mL⁻¹), morphine (0.01 g.mL⁻¹), midazolam (5 mg.mL⁻¹), n-acetylcysteine (100 mg.mL⁻¹), naloxone (0.4 mg.mL⁻¹), neostigmine (0.5 mg.mL⁻¹), nitropruside (12 mg.mL⁻¹), noradrenaline (1 mg.mL⁻¹), oxytocin (5 IU.mL⁻¹), paracetamol (10 mg.mL⁻¹), thiopental sodium (25 mg.mL⁻¹), pethidine (50 mg.mL⁻¹), pheniramine (22.75 mg.mL⁻¹), phenytoin (50 mg.mL⁻¹), piracetam (1 g.5 mL⁻¹), prednisolone (25 mg), prilocaine (20 mg.mL⁻¹), propafenone (3.5 mg.mL⁻¹), protamine hydrochloride (1,000 IU.mL⁻¹), potassium (1 mEq.mL⁻¹), remifentanyl (5 mg.mL⁻¹), cefuroxime axetil (125 mg.mL⁻¹), sulbactam-ampicillin (200 mg.mL⁻¹), succinylcholine (20 mg.mL⁻¹), tenoxicam (10 mg.mL⁻¹), theophylline (24 mg.mL⁻¹), tramadol (50 mg.mL⁻¹), and vitamin K (10 mg.mL⁻¹). A scale of 0-4 was used to evaluate the test, with 0 being no precipitation and 4+ being strong precipitation.

Within seconds, sugammadex (100 mg.mL⁻¹) scored 4+ precipitation with amiodarone (50 mg.mL⁻¹), dobutamine (12.5 mg.mL⁻¹) and protamine hydrochloride (1,000 IU.mL⁻¹).

There are reports on the incompatibility and precipitation of anesthetic drugs⁵⁻⁷. Thiopental, with basic pH, reacts with acidic muscle relaxants such as suxamethonium, mivacurium, vecuronium and rocuronium, causing precipitation⁸. Similarly, thiopental causes precipitation with local anesthetics due to pH differences⁹. Previous experimental studies have shown that thiopental reacting with various drugs may form thiopental acid crystals due to precipitation, which may cause pulmonary embolism¹⁰. Sugammadex has a pH of 7.5 and the precipitation reaction with protamine may be related to the molecules' ionic weight¹⁻⁵.

Our study shows that sugammadex reacts with amiodarone, dobutamine and protamine under in-vitro conditions, causing precipitation. We emphasize that sugammadex should not be given intravenously simultaneously with these drugs. Future studies will characterize their precipitation reaction, which seems to be only the tip of the iceberg. In addition, future studies should be focused on investigating sugammadex compatibility with other drugs by using Gas Chromatography/Mass Spectrometry device. We believe the effects of this precipitation on the drugs' efficacy and circulation warrants further research.

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