More than a decade ago, the Institute for Safe Medication Practices (ISMP) reported a number of serious safety events associated with the use of medications with doses displayed as ratio expressions. At that time, in 2005, there had already been more than 75 reports in the ISMP database dating back at least 10 years. Unfortunately, wrong dose/wrong strength errors have continued to be common, and alarmingly, they include medications frequently used in emergency departments or procedural settings such as calcium, epinephrine, lidocaine, magnesium sulfate, isoproterenol, neostigmine, and sodium bicarbonate. Through continued review and analysis of this issue, ISMP has repeatedly heard from practitioners who report confusion when the drug label expresses the drug strength using percentages (eg, lidocaine 1%) or when ratio expressions are included (eg, isoproterenol 1:5,000). These serious and sometimes even fatal errors did not occur because practitioners were uncaring or irresponsible; instead, these events were often associated with confusion about the drug’s concentration.

Such was the case with epinephrine. Until very recently, the drug’s concentration had been listed on the label using a ratio expression (ie, 1:1,000 and 1:10,000). Numerous incidents were reported in which undiluted epinephrine 1:1,000 (1 mg/mL) was given intravenously to patients instead of using the 1:10,000 (0.1 mg/mL) concentration. In each case, the more diluted epinephrine (1:10,000) was available for use, but staff inadvertently prescribed or selected the 1:1,000 concentration. For example, an error of this type reportedly occurred in an outpatient radiology unit. When visible hives and respiratory distress developed in a patient after an injection of contrast material, a physician prescribed 3 mL of the 1:10,000 concentration intravenously. The nurse in the radiology department rarely administered medications and did not fully understand the difference between the 2 available concentrations of epinephrine. This confusion led to the nurse to inadvertently administer 3 mL of the 1:1,000 concentration in error. In another case, a physician’s assistant ordered the incorrect concentration of epinephrine for a patient in an urgent care clinic, and the nurse administered the undiluted 1:1,000 concentration without recognizing the problem. Both patients experienced rapid heart rates and increased blood pressures, necessitating an overnight stay in the hospital.

Another example occurred during a close call, when a dose of epinephrine was ordered in milliliters during a neonatal code. Despite competent staff and bedside resources, a good deal of confusion was evident between the resident and the nursing staff. A pharmacist who attended the code luckily was able to guide staff regarding the proper dose for the patient, because both 1:1,000 and 1:10,000 dilutions were available on the code cart. Neonatal nurses and physician staff had assumed that only the 1:10,000 dilution was available on their neonatal code cart. This misunderstanding and confusion could have resulted in an irreversible event.

Errors also have resulted when the wrong dose of epinephrine has been used for procedural cases. Treatment for a reported case of priapism turned deadly for a 16-year-old admitted to the emergency department after a urologist ordered and inadvertently administered 4 mL (4 mg) of undiluted epinephrine. Believing the 1:1,000 concentration was “prediluted” to the usual solution strength of 1:1,000,000, the physician performed the intracavernous injection, resulting in a systemic overdose and death.

Although ISMP and others had warned about the potential for confusion with this seemingly antiquated labeling practice for more than a decade, tragically, these warnings were not enough to prevent the most recent
epinephrine death associated with ratio expressions. Recently, ISMP learned of an otherwise healthy 27-year-old young man who had experienced a herniated disk and lumbar radicular syndrome after moving heavy furniture, requiring surgical intervention. At the start of the procedure, the surgeon wanted to infiltrate his skin and subcutaneous tissue with bupivacaine and epinephrine before making the incision. He asked a nurse to obtain 30 mL of epinephrine 1:100,000 and 30 mL of bupivacaine 0.25% with epinephrine. In addition to the bupivacaine with epinephrine, the surgeon also wanted to administer 30 mL of 1:100,000 epinephrine (60 mL total). He administered the combination of medications at the surgical site. Shortly after the medications were administered, the anesthesiologist noted an abnormal heart rhythm. The patient’s surgery was quickly aborted because of the need for resuscitation. Although the patient was initially resuscitated, he unfortunately suffered a significant brain injury and later died. Upon investigation, a bottle of epinephrine 1:1,000 was found in the trash, making it clear that the patient had received 100 times the intended dose.5

Typically, the contents of most injectable medications are given as their mass concentration (milligram or microgram per milliliter). However, a few drugs have concentrations expressed as a dilution ratio or percentage (eg, epinephrine 1:1,000 and lidocaine 1%). Studies have long shown that these type of dose expressions are error prone, even among physicians and emergency medicine residents.6–8 Epinephrine as a pharmaceutical agent was available before the existence of the 1938 Food, Drug, and Cosmetic Act and did not fall under the most recent Food and Drug Administration (FDA) labeling standards, resulting in a lack of authority for the FDA to regulate these drugs or to make significant changes. Because of repetitive confusion and the serious nature of many of these reported events as far back as 2004, ISMP petitioned the United States Pharmacopeia (USP) to request that epinephrine injection concentrations be expressed only in terms of milligram per milliliter (eg, 1 mg/mL) and no longer expressed in terms of ratio (eg, 1:1,000 and 1:10,000), except when combined with local anesthetics.9

Only now, after years of reporting on these events, has a change been possible. The USP and The National Formulary (NF) recently published an updated regulation on the issue (USP39, NF34), which became official on May 1, 2016. This new regulation will no longer allow the use of ratio expressions on single-entity drug products in hopes of eliminating continued dosing confusion. For example, the strength of epinephrine 1:1,000 injection can now only be displayed as 1 mg/mL, and 1:10,000 can now only be displayed as 0.1 mg/mL. Isoproterenol 1:5,000 injection will be expressed as 0.2 mg/mL, and neostigmine 1:1,000 injection will be expressed as 1 mg/mL.10 Be aware, however, that the ratio expression for local anesthetics such as lidocaine 1% with epinephrine 1:100,000 injection and bupivacaine 0.25% with epinephrine 1:200,000 injection will retain ratio expressions for the epinephrine component because a decimal notation for such a reduced strength could easily be misread.10

Although this change is certainly welcome after the occurrence of all of these serious events, ISMP is concerned that if this change is not well communicated and understood, confusion and delay in lifesaving treatments could result. Please make it a priority to help ED staff learn about these changes. Instruct prescribers to refer to these medication doses in metric units only using the updated terminology. For example, if a prescriber leading a code team calls out for “1:10,000 epinephrine” and the product label no longer contains this ratio expression, practitioners could become confused and administer the wrong strength.10 As part of this effort, do not forget to review and update any order sets, policies, procedures, protocols, drug information sheets on resuscitation carts, drug storage locations, emergency kit listings, and all electronic databases so that the new product labels match the dose designation wherever they are used.

The time has finally come to truly eliminate ratio expressions and associated dose confusion. Your help to ensure rapid and thorough communication of this change throughout the emergency department and wherever necessary will support safe medication dose communication, and ultimately move your department one step closer toward ENA’s Safe Practice, Safe Care.

REFERENCES


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