Annals of Internal Medicine | ARTICLE

The Effect of Drug Concentration Expression on Epinephrine Dosing Errors

A Randomized Trial

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Background: The expression of drug concentration as a ratio may cause dosing errors.

Objective: To examine the effect of ratio expressions on drug administration.

Design: Randomized, blinded, controlled study.

Setting: Simulation center in an urban hospital.

Participants: 28 physicians.

Intervention: Participants managed a simulated pediatric acute anaphylaxis scenario by using epinephrine ampules labeled with mass concentration (1 mg in 1 mL) or a ratio (1 mL of a 1:1000 solution).

Measurements: The amount of epinephrine given and the time taken to administer it.

Results: Compared with providers using ampules with mass concentration labels, those using ratio labels gave more epinephrine (adjusted mean dose, 213 μg above target [95% CI, 76.4 to 350.1 μg]; $P = 0.003$), and took longer to do so (adjusted mean delay, 91 seconds, [CI, 61.0 to 122.1 seconds]; $P \leq 0.0001$).

Limitations: Performance in simulated scenarios may not reflect clinical practice. In reality, ampule labels provide both expressions of concentration.

Conclusion: The use of ratios to express drug concentration may be a source of drug administration error. Patient safety might be improved by expressing drug concentrations exclusively as mass concentration.

Ann Intern Med. 2008;148:11-14. www.annals.org
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Clinical error and negligence are responsible for disabling injuries in about 1 in 25 hospital admissions (1). Most of these injuries are caused by adverse drug events, which prolong hospital stay, increase care costs, and nearly double a patient's risk for death (2, 3). About one third of adverse drug events occur during drug administration, when interception is unlikely (4). The confusion caused by expressing the concentrations of drug solutions in different ways is an important cause of dose errors (5–10). Converting among ratios, percentages, international units, mols, micrograms, and milligrams causes substantial difficulty, especially for less experienced physicians or those most removed from acute care. Epinephrine, lidocaine, heparin, and potassium chloride are frequently associated with drug error (11). It may be no coincidence that the strengths of these drug solutions are typically expressed in ratios, percentages, international units, and millimols, respectively.

Any physician could be confronted with a patient in cardiac arrest or anaphylaxis, in whom the consequences of a dosing error are grave. In an emergency, dose calculation must be easy. Despite widespread concern expressed over many years (5–8, 12), ampule labels have changed little, possibly because research in this field has relied on surveys and questionnaires, which rank unfavorably in the hierarchy of evidence-based medicine.

We evaluated the effect of ampule labeling on physicians' clinical performance in a simulated critical incident in a randomized, single-blinded, controlled trial. We randomly assigned providers to receive an ampule of epinephrine labeled as 1 mg in 1 mL or as 1 mL of 1:1000, and presented them with a scenario requiring the acute management of a child with anaphylaxis. A pediatric case was chosen because participants would be less likely to know the epinephrine dose and more likely to have to consult a resuscitation protocol and calculate the dose. We then measured the quantity of epinephrine administered and the time taken to give it.

Methods

The study received institutional ethical approval. The scenario was enacted by using a pediatric mannequin in the hospital's high-fidelity patient simulator center (Human Patient Simulator, Medical Education Technologies, Sarasota, Florida), which was configured as a rural emergency room. Hospital-affiliated physicians in our institution

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Context

The use of ratios to express drug concentrations makes dosing calculations confusing and may cause drug errors.

Contribution

The researchers labeled epinephrine ampules with ratios only (1 mL of 1:1000) or concentration only (1 mg in 1 mL) and randomly assigned providers to use one or the other in a simulated anaphylactic arrest. Providers using ratios made many more errors and took longer to give the drug than providers using concentrations.

Caution

The case was simulated, and in reality, ampules are labeled with both expressions.

Implication

The use of ratios to express epinephrine concentration is confusing, and the revision of labeling to express concentration in more clinically intuitive ways may reduce errors.

—The Editors

without pediatric experience volunteered to participate without payment. The **Appendix** (available at www.annals.org) shows the volunteers' briefing.

Scenario

Participants were asked to manage the case of a 5-year-old child with known peanut allergy who is brought in for care after peanut exposure. The patient simulator was programmed to mimic development of acute anaphylaxis with hypotension profound enough to warrant 0.12 mg of intramuscular epinephrine, according to the protocol (13). Participants needed to calculate the correct volume of epinephrine to administer (0.12 mL) by using the ampule label to which they were randomly assigned (mass concentration only [1 mg in 1 mL] or ratio only [1 mL of 1:1000]). The trial ampules were made to resemble real epinephrine ampules in every way except this labeling change. The protocol stated that the dose required was 0.12 mg without referring to ratios or volumes (**Appendix Figure**, available at www.annals.org). An actor playing a nurse was available to provide help; participating physicians also had access to a pharmacopeia, calculator, paper, and pencil. Participants who requested other epinephrine presentations were told that none were available.

Data Collection

We recorded the participants' age, seniority, specialty, and sex. Audiovisual recordings of the scenarios were made. Investigators who were blinded to each participant's randomization status subsequently recorded the dose of epinephrine administered and the time taken for it to be given.

Statistical Analysis

Power calculations indicated that 14 participants were required in each group to achieve a significance level of 5% and study power of 80%. This was based on observations from another study that suggested differences of 50% in the probability of a dose error and 20 seconds in dose administration time between the groups (14). A randomization sequence of 28 unsorted nonunique numbers ranging from 0 to 1 was generated online (Research Randomizer, Social Psychology Network; available at www.randomizer.org) and implemented by a researcher who was not involved in data collection.

We assessed the effect of ampule labeling on the accuracy of the epinephrine dose by using logistic regression, in which the dependent variable was dose given and was categorized as within 10% of the correct 120-μg dose (considered acceptable because of the practical difficulty of measuring a very small volume in a 1-mL syringe) or more than 10% (dose error), and by using linear regression, in which the dependent variable was the absolute value of dose error (dose given minus target dose). We initially fitted the logistic model with ampule labeling and provider characteristics (age, seniority, specialty, and sex) as independent variables. However, there was no association between provider characteristics and dosing errors, and inclusion of provider variables only appeared to inflate the estimate of the risk for error with labeling. Therefore, ampule labeling is the only independent variable in the final model reported here. We included ampule labeling and provider characteristics (age, seniority, specialty, and sex) as independent variables in the linear model.

We also used linear regression to assess the effect of ampule labeling (independent variable) on the time taken to administer epinephrine (dependent variable). Goodness-of-fit of the models was confirmed by examination of deviance residuals (logistic model) and standardized residuals (regression models). We performed all analyses by using the R 2.2.1 statistical package (15).

Role of the Funding Source

The Association of Anaesthetists of Great Britain and Ireland provided funding but had no role in study design, conduct, or analysis, or the decision to submit the manuscript for publication.

RESULTS

Twenty-eight physicians consented to participate, and 14 were randomly allocated to each group. All completed their scenario. Their median age was 32.0 years (interquartile range [IQR], 8.5 years) and their median time in practice since graduating was 6.0 years (IQR, 6.5 years). Fifteen (53.6%) physicians had a background in critical care, 7 (25.0%) in internal medicine, and 6 (21.4%) in surgery. Sixteen (57.1%) were men and 12 were women. Demographic characteristics did not statistically significantly differ between the groups. Nine of the 14 physicians (64.3%) who were given the ratio-labeled ampules asked for an alternative, but no physician in the mass concentration group did so ($P < 0.001$, Fisher exact test). One participant from each group (8.3%) did not consult the protocol.

Table. **The Influence of Ampule Presentation on Administration of Epinephrine**

Label	Time Taken		Dose Given			
	Mean Increase (95% CI), *s**	*P* Value	Mean Absolute Dose Error (95% CI), *μg**	*P* Value	Odds Ratio for Dose Error (95% CI)	*P* Value
Ratio rather than mass concentration	91.0 (61.0–122.1)	<0.001	213.0 (76.4–350.1)	0.003	13.4 (2.2–81.7)	0.005

* Estimates are adjusted for provider characteristics (age, seniority, sex, and specialty). No provider characteristic was associated with epinephrine dose or timing.

The **Appendix Table** (available at www.annals.org) shows the dose given by each provider and time taken to administer it.

Dose of Epinephrine Administered

Eleven of 14 (79%) providers in the mass concentration group calculated a dose within 10% of that recommended by the protocol, compared with 2 (14%) in the ratio group ($P = 0.009$, chi-square test). All participants who gave the wrong dose of epinephrine gave too much; 1 participant gave 1 mg. The median dose given by providers using mass concentration was 122.5 μg (IQR, 120.0 to 125.0 μg) compared with 250.0 μg (IQR, 250.0 to 500.0 μg) for those using ratios ($P = 0.003$) (**Figure**). The risk for dose error was greater among providers using ratios (odds ratio for error, 13.4 [95% CI, 2.2 to 81.7]). Providers using ratio labels gave more epinephrine (adjusted mean, 213 μg above target dose [CI, 76.4 to 350.1 μg]; $P = 0.003$) than those using mass concentration labels. Provider characteristics (age, seniority, specialty, and sex) were not associated with dosing errors (data not shown).

Time Taken to Administer Epinephrine

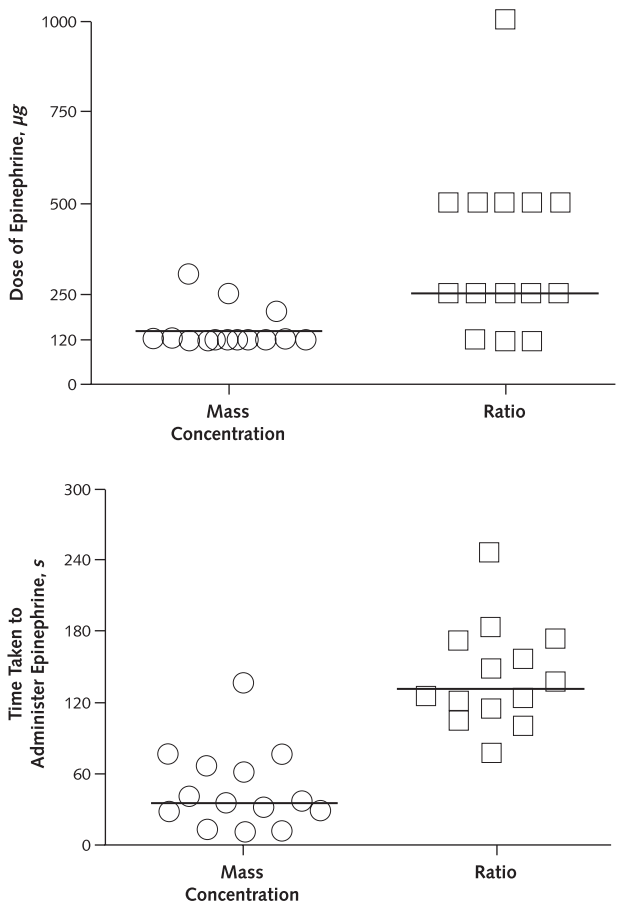
Physicians using ampules labeled with mass concentration calculated and administered the dose more quickly than those receiving epinephrine labeled as 1 mL of 1:1000 (**Figure**). The median time taken to administer epinephrine for the mass concentration group was 35.5 seconds (IQR, 27.0 to 65.0 seconds) compared with 130.0 seconds (IQR, 112.0 to 171.0 seconds) for the ratio group ($P \leq 0.001$). The adjusted mean time was 91.0 seconds (CI, 61.0 to 122.1 seconds) (**Table**) greater in the group using a ratio rather than mass concentration label. Provider characteristics were not associated with differences in timing of administration (data not shown). Observation of trial participants indicated that difficulty with arithmetic and a lack of understanding of ratios led to the observed delays, but we did not attempt to systematically describe these steps in the calculations and delays.

Discussion

We found that physicians are more likely to give the wrong dose of epinephrine—and take longer to do so—when the strength of epinephrine is expressed as a ratio. The differences seem not only statistically but also clinically significant, given that the consequences of a delay in treatment or an overdose of epinephrine in an emergency are potentially catastrophic.

Many physicians know that the dose of epinephrine used to treat anaphylaxis in an adult is 0.5 mL of a 1:1000 solution, without knowing how many milligrams this is (9). By asking providers who care for adults to manage simulated anaphylactic arrest in a child, we compelled most

Figure. **Dose and timing of epinephrine administration.**



Top. Dose of epinephrine. Bars indicate median doses (122.5 μg [IQR, 120.0 to 125.0 μg] in the mass concentration group vs. 250.0 μg [IQR, 250.0 to 500.0 μg] in the ratio group; $P = 0.003$); 120 μg was the correct dose. The adjusted mean difference in dose made by the ratio group was 213 μg (95% CI, 76.4 to 350.1 μg) greater than the 120-μg target dose. **Bottom. Time taken to give epinephrine.** Bars indicate median times (35.5 seconds [IQR, 27.0 to 65.0 seconds] in the mass concentration group vs. 130.0 seconds [IQR, 112.0 to 171.0 seconds] in the ratio group; $P < 0.001$). The adjusted mean time was 91.0 seconds (CI, 61.0 to 122.1 seconds) greater in the ratio than in the mass concentration group.

participants to consult a resuscitation protocol, and we required 1 group to calculate an unfamiliar dose by using the drug concentration expressed only as a ratio.

There is no international standard for the labeling of drug solutions. The World Health Organization and the European Union declare that packaging should state the name, strength, quantity, and physical description or identification of the medicinal product, and that labels should identify the active ingredients and dosage form (16, 17). Neither mention ratios. Ratios and percentages are used in most countries, but inconsistently. For example, the concentration of epinephrine is expressed as a percentage in some Scandinavian countries (18). No regulatory authority has ruled to remove ratios from ampules, although the new local anesthetic levobupivacaine (Abbott Laboratories, Abbott Park, Illinois) is supplied in ampules labeled with mass concentration only, and there are no reports in the literature yet of dose errors caused by the labeling of levobupivacaine ampules. The concentrations of local anesthetics are traditionally expressed as percentages, which can be even more confusing than ratios (9, 10, 19). Survey and questionnaire studies have provided evidence of the confusion caused by different ways of expressing the concentrations of drug solutions (5–10), yet these findings have not influenced labeling policy or practice.

Our study has limitations. We used a pediatric scenario, and in real life, the clinical consequences of epinephrine overdoses similar to those administered in this study are typically less grave in children than in adults. In addition, epinephrine ampules are labeled using both systems, so that providers are not forced to calculate doses from ratios alone. Finally, the study was small and was conducted at a single site, the generalizability of the findings is unknown, and data were too few to determine the distribution of observations and thus the accuracy of some of the estimates from our multivariable analyses.

Nonetheless, we clearly observed confusion among the participants who were required to calculate epinephrine doses by ratio alone under time pressure. Ratios and percentages were useful when drug doses were expressed in imperial units, but we believe that this format is now outdated and should not be used to express the concentration of drug solutions on ampules, even when dual labeling is present. Using milligrams per milliliter alone might not be the answer, because conversions among milligrams, mols, and micrograms also cause difficulties (9, 20) and the concentrations of some drugs, such as insulin and heparin, are more conveniently expressed in international units. A better solution might be for pharmacopeias, formularies, and protocols to express the concentration of each drug in terms of the most straightforward expression of mass, and for this to be reproduced on ampule labels.

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Potential Financial Conflicts of Interest: None disclosed.

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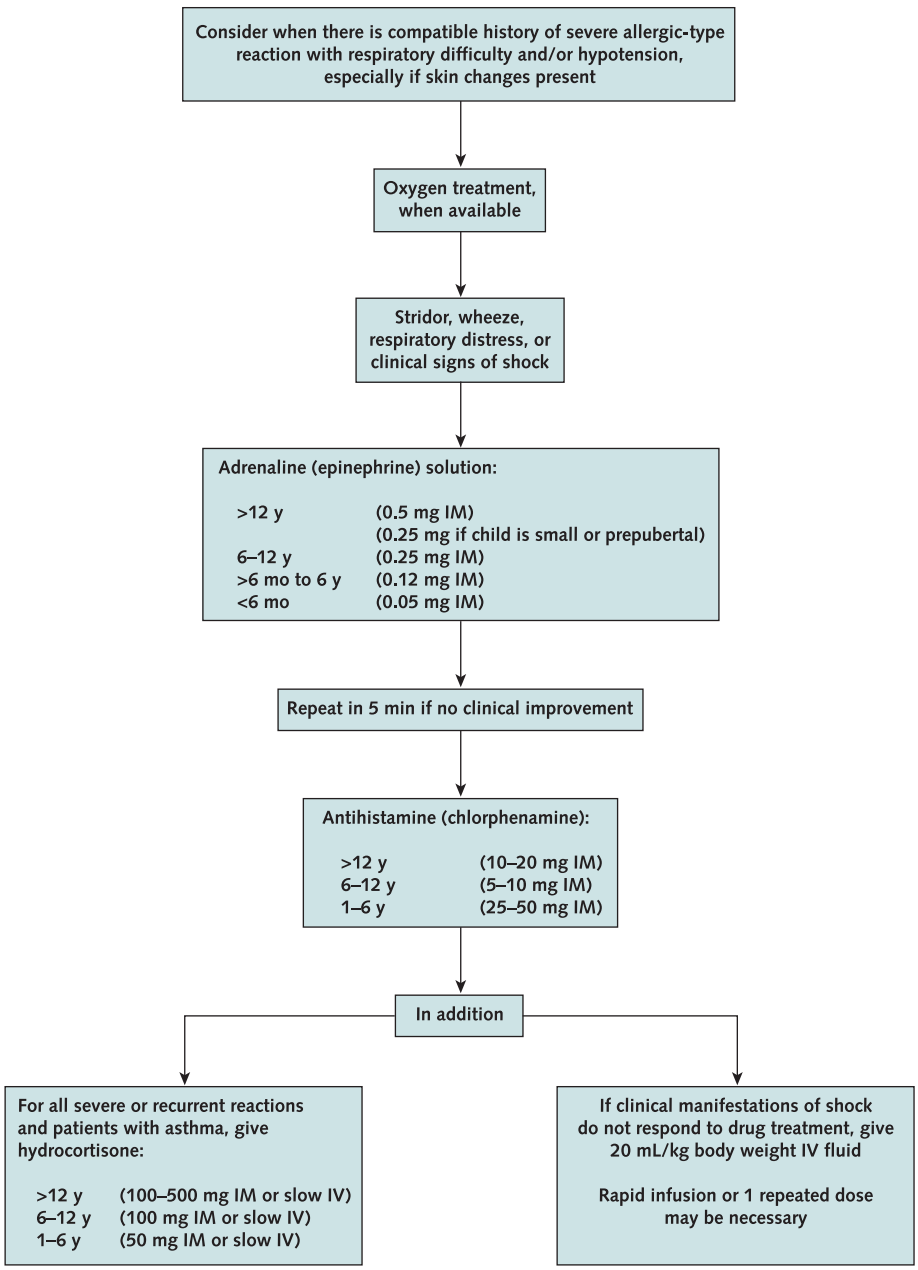
Appendix: Briefing of Participants

Participants were briefed as follows: "You are at a small rural hospital conducting an outreach clinic. The hospital has some inpatient beds for rehabilitation and an adult minor injuries unit, but no resident physician. You are the only physician in the hospital at the moment. You have been called to the minor injuries unit to review Jack, a 5-year-old brought in after eating a peanut while unsupervised at a friend's party. He is known to have a peanut allergy. He was brought in by a family friend, who has returned to the party. His parents are on the way but have not yet arrived. The nurse present has experience in the management of minor injuries but little in critical care or pediatrics. She has instituted electrocardiography, noninvasive blood pressure and peripheral oxygen saturation monitoring, and brought out the resuscitation equipment and drugs. Please begin the immediate management of Jack."

Appendix Figure. **Protocol for determining the dose of epinephrine.**



IM = intramuscular; IV = intravenous.

Appendix Table. **Epinephrine Administration, by Individual Providers***

Group	Dose Administered (Time Taken) by Each Provider, μg (s)
Mass concentration	120 (12), 120 (13), 120 (14), 120 (27), 120 (39), 120 (60), 120 (75), 125 (27), 125 (35), 125 (65), 125 (76), 200 (135), 250 (36), 300 (30)
Ratio	120 (112), 120 (244), 125 (76), 250 (118), 250 (124), 250 (136), 250 (145), 250 (181), 500 (98), 500 (122), 500 (154), 500 (171), 500 (171), 1000 (103)

* The correct dose was 120 μg.