The One Pill Can Kill Myth

Milton Tenenbein, MD

Abstract: "One Pill Can Kill" is a meme originating in the 1990s. This construct lists pharmaceuticals that have the alleged potential for fatality after the ingestion of a single pill by a toddler. However, its foundation is fundamentally flawed because it contravenes a basic principle of pediatric pharmacology, allometric scaling. Other than opioids, there are no literature examples of one pill killing a toddler. The negative outcome of the one pill can kill construct is inappropriate management manifested by over-referral of young children by poison centers to emergency departments for care, overly prolonged emergency department observation and needless hospital admissions. A more accurate construct is that one pill of anything other than opioids will not kill anybody with the caveat being that we are referring to regulated pharmaceuticals.

"One Pill Can Kill" is a meme originating in the 1990s. This construct lists pharmaceuticals that have the alleged potential for fatality after the ingestion of a single pill by a toddler. It is based on a 1993 publication.[1] The attractiveness of this meme resulted in its propagation in the traditional[2–6] and virtual literature.[7–9] Indeed, it is a not an infrequent presentation at continuing professional development events. However, this construct lacks face validity. Moreover, its foundation is fundamentally flawed because it contravenes a basic principle of pediatric pharmacology, allometric scaling (see below). Thus, one pill can kill is a myth. Indeed, a more accurate construct is that one pill of anything will not kill anybody[10] with the caveat being that we are referring to regulated pharmaceuticals. As for any "rule of thumb," there is always an exception with opioids being an obvious example.[11] The negative outcome of the one pill can kill construct is inappropriate management manifested by overreferral of young children by poison centers to emergency departments for care, overly prolonged emergency department observation and needless hospital admissions.

SEMINAL PUBLICATION[1]

Its title is "Medications that Can Kill a Toddler with One Tablet or Teaspoonful." Ten "medicinal preparations" were identified (Table 1) and remarkably opioids were not included. This construct lacks face validity. If one pill can kill a toddler, it would have the potential for significant adverse effects in a frail senior. Such pharmaceuticals would have a therapeutic index so narrow that they would not gain regulatory approval. And importantly, there are no reports in the peer reviewed literature of one pill killing a toddler. These factors mandate a critical review of this publication.

The methods consisted of first identifying medication overdoses that are highly hazardous in toddlers. The adult fatal dose in mg/kg was extrapolated by isometric scaling (Fig. 1) to "establish" a fatal dose in children. Then the largest available unit dose was identified from US and Canadian pharmacopeias.

There are several issues. The largest available unit dose is not commonly prescribed. For example, Imipramine (one of the one pill can kill medications) is available as 10, 25, 50, 75, 100, 125, and 150 mg unit doses. The routine unit dose is 25 or 50 mg. The 150-mg dose was used in this publication, which is 3 to 6 times greater than the commonly prescribed dose.

The precise fatal dose is rarely if ever known. Fatal doses are typically expressed as ranges. "The lowest described or estimated fatal dose (per kg) was used" which introduces another bias. And there is no citation support for these fatal dose data.

However, the above shortcomings pale in comparison to the use of isometric scaling to establish fatal doses in toddlers. Isometric scaling, depicted in Figure 1, assumes a direct linear relationship between the parameters of interest—in this case, fatal doses in adults and children. However, a fundamental principle of pediatric pharmacology is that isometric scaling to establish drug dosing for young children is invalid. "Pediatric dose cannot be scaled down directly from an adult using weight (eg, mg/kg). This results in a dose too small in infants and children because elimination does not change in direct proportion to weight."[12] Thus, using isometric scaling is a fatal flaw of this publication. In fact, young children require higher mg/kg drug doses than adults. The methods depicted in Figure 1 were those that were used to calculate the "toxic dose of acetaminophen in children," which has been shown to be an underestimate.[13]

YOUNG CHILDREN REQUIRE GREATER MG/KG DOSES THAN ADULTS

This is an established but underappreciated principle of pediatric pharmacology. It is well known to pediatric anesthesiologists[14] and has been recognized by others for more than a century. Dawson,[15] in 1940, published an extensive review on this topic citing literature as early as Falck et al in 1884 and Dreyer et al in 1914. Although Dawson clearly described this principle, he did not have an explanation for it. "Why children require or tolerate in proportion to their size higher dosage of some drugs than do adults cannot at present be explained." He concluded that "the effective, usually lethal doses of various drugs are usually less per kg in the larger animals of a species."

This principle is confirmed by our training and practice. We are taught to dose children on a mg/kg basis but to not exceed the adult dose. The adult dose is typically achieved in the older pre-school or in the younger school aged child. Table 2 is a comparison of recommended adult and pediatric weight-based doses for several drugs.[16] The recommended pediatric weight-based doses considerably exceed their counterparts in adults. The reason for this is explained by allometric scaling.

ALLOMETRIC SCALING

Allometry is the relationship between the size of an organism and its various characteristics.[17–19] Proportionality between size and these characteristics varies with size. Human development does not have a linear (isometric) relationship with growth.

From the Pediatrics and Child Health, Emergency Medicine and Community Health Sciences, Max Rady College of Medicine, University of Manitoba, Winnipeg, Manitoba Canada.

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Reprints: Milton Tenenbein, MD, Pediatrics and Child Health, Emergency Medicine and Community Health Sciences, Max Rady College of Medicine, University of Manitoba, Winnipeg, Manitoba Canada (e-mail: mtenenbein@hsc.mb.ca).

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TABLE 1. Medicinal Preparations Which Can Be Fatal to a Toddler Upon Ingestion of 1–2 Tablets, Capsules or Teaspoonfuls[1]

Camphor
Chloroquine
Hydroxychloroquine
Imipramine
Desipramine
Quinine
Methyl salicylate
Theophylline
Thioridazine
Chlorpromazine

Obvious examples are the discordance between development and growth are that maturity of ambulation and speech occurs long before the attainment of adult size. Maturation of physiology is relevant to pediatric pharmacology. A 2-year old has adult renal and hepatic function[20] but has an average weight of 13 kg, which is 19% of a 70-kg adult. And, another pertinent factor is that the two-year old's liver and kidney sizes are proportionately greater than those of an adult[21] (Table 3).

A passage in Anderson et al[22] describes contributing factors: "Clearance of drugs is a nonlinear function of weight that decreases with increasing weight, whereas doses are commonly expressed as a linear function of weight. As a consequence, to achieve similar concentrations, younger children require larger doses on a weight basis than older children and adults." This is the explanation for Table 2.

DISCUSSION

The use of isometric scaling in the seminal publication[1] is a fatal flaw of the study design. Rather, allometric scaling, a fundamental and established principle of pediatric pharmacology is the appropriate model. Isometric scaling underestimates therapeutic and fatal drug doses for young children. This is why one pill will not kill. The age-old pediatrician's aphorism—children are not small adults—rings true.

Isometric scaling is a simple linear relationship, whereas allometric is logarithmic. It is described by a complex formula $Y = aW^b$.[23] Y is the parameter of interest, W is body weight, and a and b are the coefficient and exponent of the allometric equation. It lacks utility for predicting pediatric drug doses because the exponents vary widely and are data dependent. Thus, the requirement to test new drugs in children.

In addition to opioids, 2 other medications not included in the seminal publication[1] deserve comment. These are clonidine and sulfonylureas. There are no literature examples of one pill being fatal for either. Clonidine is indeed hazardous in very low doses and a 12-year review of 27,825 clonidine exposures in children documented 3 deaths. Interestingly, the authors stated "we found no evidence to support the inclusion of clonidine as a pharmaceutical where one pill can kill."[24] A single dose of a sulfonylurea resulted in mildly symptomatic hypoglycemia.[25]

Adult Fatal Dose:	10 g (10,000 mg)
Assumed Adult Weight	70 Kg
Calculated Child's Fatal Dose	10,000 / 70 = 143 mg/kg

FIGURE 1. Calculation of the Fatal Dose in a Child by Isometric Scaling.

TABLE 2. Recommended Adult and Pediatric Doses for Several drugs[15]

Drug	Adult Dose	Adult Dose (mg/kg)	Pediatric Dose (mg/kg)
gentamicin	1 mg/kg/dose	1 mg/kg/dose	2.5 mg/kg/dose
acetaminophen	650 mg/dose	9.3 mg/kg/dose	15 mg/kg/dose
amoxicillin	500 mg/dose	7.1 mg/kg/dose	10 mg/kg/dose
amlodipine	2.5 mg/d	0.04 mg/kg/day	0.1 mg/kg/d
furosemide	20–40 mg/d	0.29–0.57 mg/kg/d	2 mg/kg/d

Adult mg/kg doses are calculated for a 70 kg adult. They are less than the recommended pediatric mg/kg doses.

TABLE 3. Ratios of Liver and Kidneys Weights to Total Body Weight at Different ages[20]

Age	Liver	Kidneys
1	4%	0.70%
2	3.6%	0.74%
5	3.0%	0.66%
18	2.4%	0.42%

One pill can kill has been adopted by the US DEA as public safety messaging regarding the hazards of illicit counterfeit pills.[26] The DEA documented that 6 out of 10 fentanyl-laced fake prescription pills contain a potentially lethal dose of fentanyl.[27] This is an appropriate use of this slogan.

CONCLUSION

The one pill can kill construct is a pediatric toxicology myth. Adherence to it may result in needless referral to emergency departments, prolonged emergency department observation and inappropriate hospital admissions. A more accurate construct is that one pill of anything other than opioids will not kill anybody[10] with the caveat being that we are referring to regulated pharmaceuticals.

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