Are We Safely Dosing Medications in Obese Children?

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Target Objectives

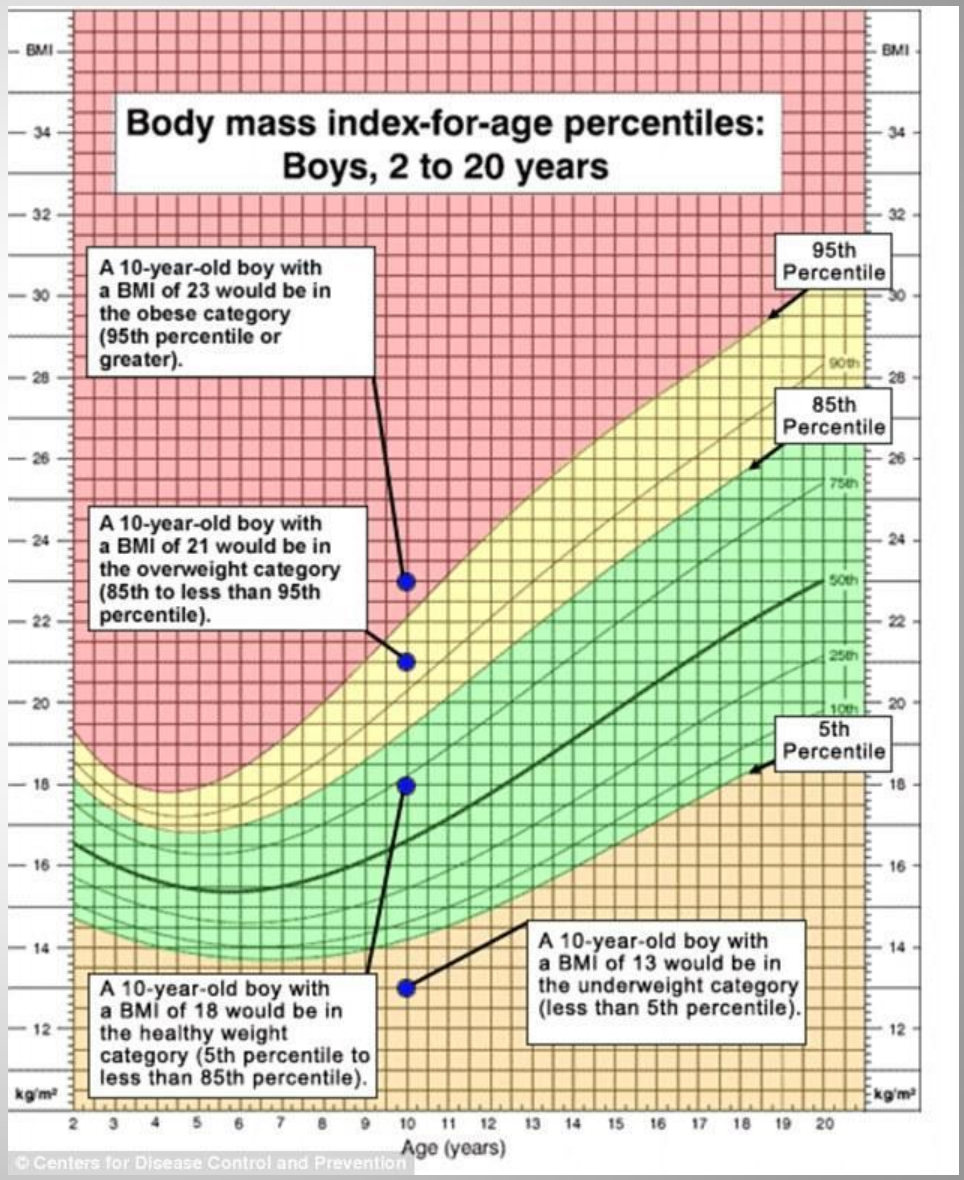
- Review the basics of pharmacokinetic principles
- Describe evidence based practices for safe drug dosing in the obese pediatric population
- Identify anesthetic implications for drug administration in the obese pediatric population

Why We Should Care?

34% percent of children in the United States are obese or overweight

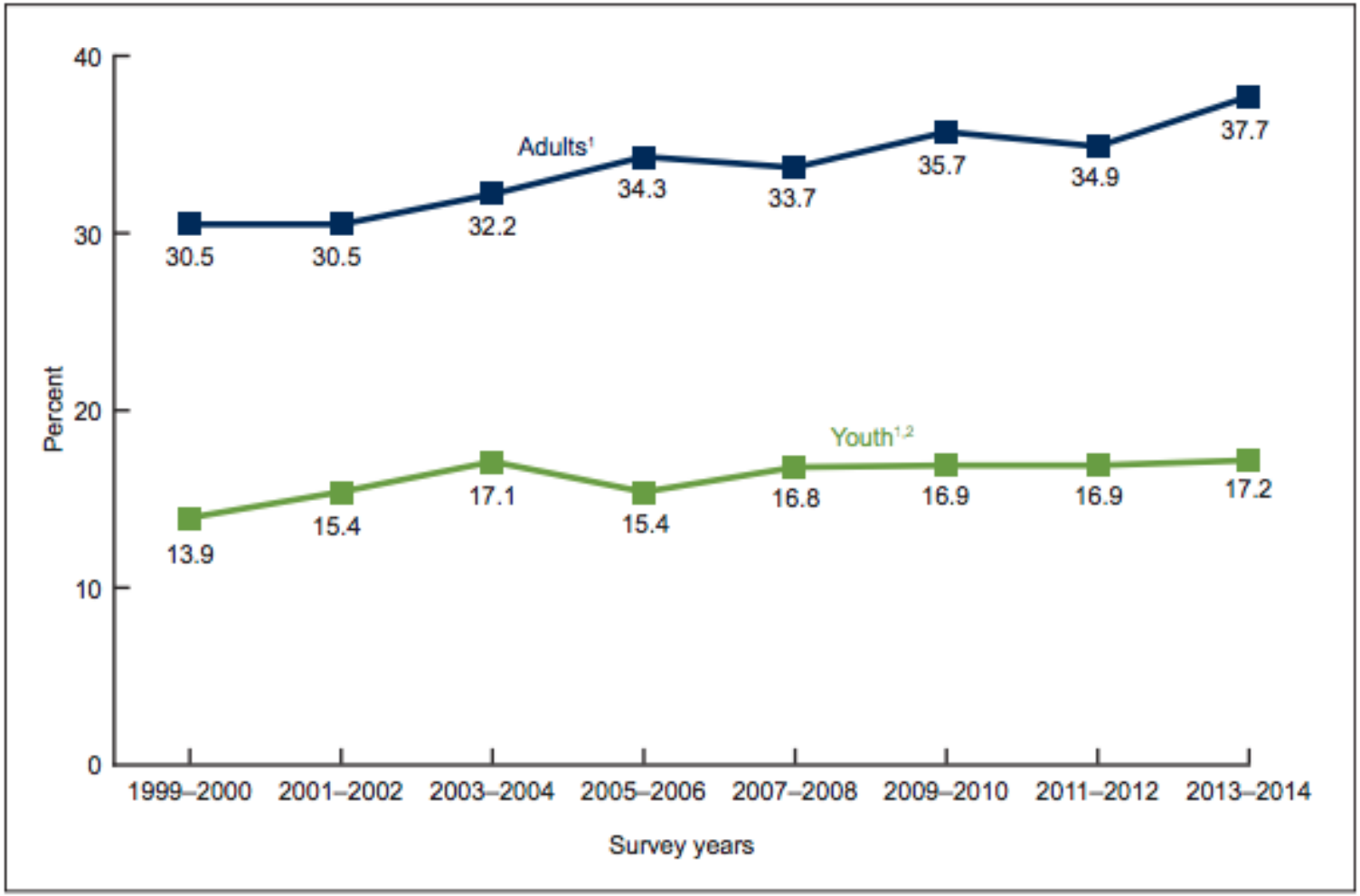
of those 34%, as of 2014 data, 17.2% are obese

***CDC defines overweight as a BMI at or above the 85th percentile and below the 95th percentile and obesity as a BMI at or above the 95th percentile**



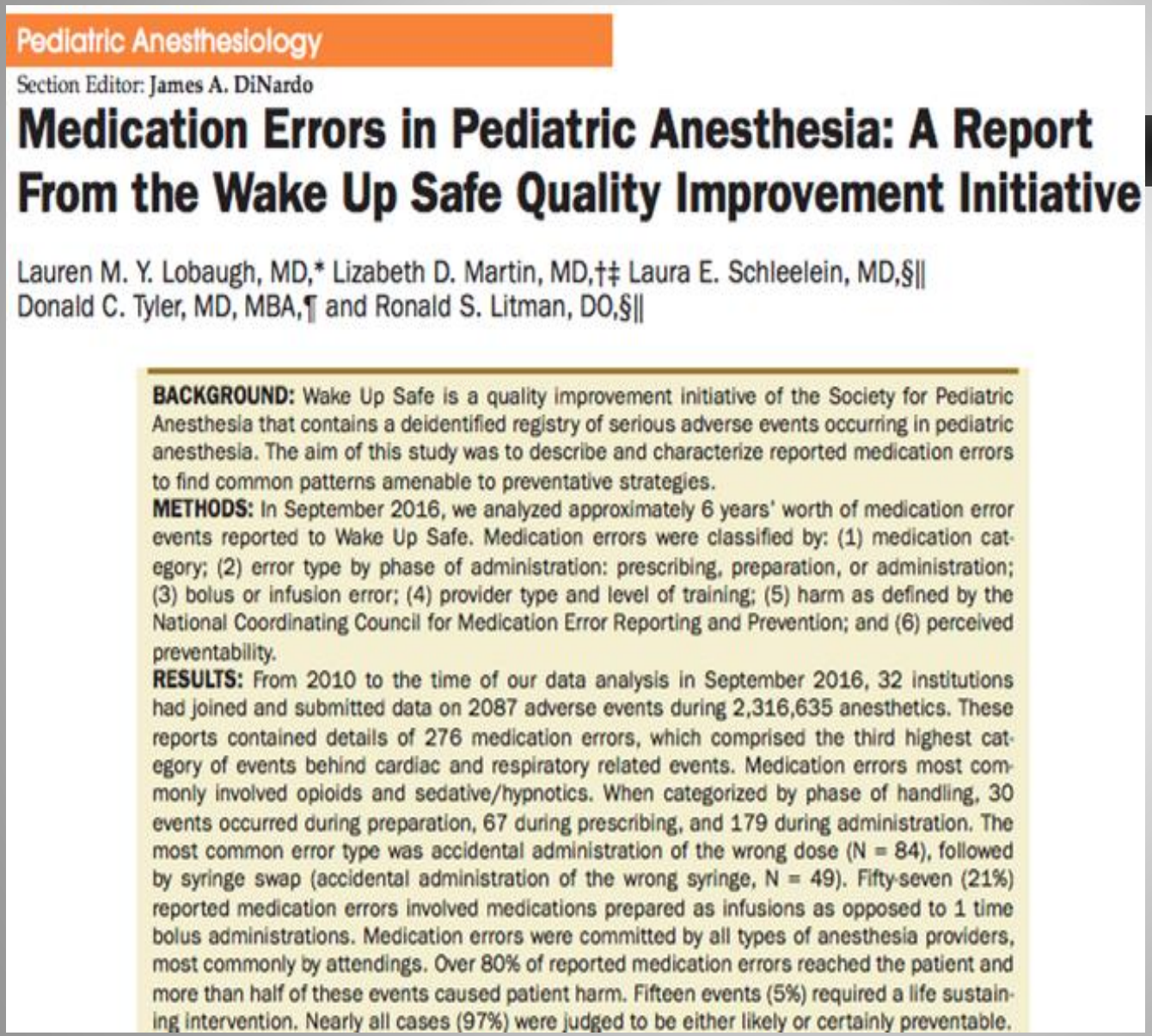
Trends In Obesity Prevalence

Figure 5. Trends in obesity prevalence among adults aged 20 and over (age-adjusted) and youth aged 2–19 years: United States, 1999–2000 through 2013–2014



[1]Significant increasing linear trend from 1999–2000 through 2013–2014.
[2]Test for linear trend for 2003–2004 through 2013–2014 not significant ($p > 0.05$).
NOTE: All adult estimates are age-adjusted by the direct method to the 2000 U.S. census population using the age groups 20–39, 40–59, and 60 and over.
SOURCE: CDC/NCHS, National Health and Nutrition Examination Survey.

Wake Up Safe Quality Improvement Initiative



Pediatric Anesthesiology

Section Editor: James A. DiNardo

Medication Errors in Pediatric Anesthesia: A Report From the Wake Up Safe Quality Improvement Initiative

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Donald C. Tyler, MD, MBA,¶ and Ronald S. Litman, DO,§‖

BACKGROUND: Wake Up Safe is a quality improvement initiative of the Society for Pediatric Anesthesia that contains a deidentified registry of serious adverse events occurring in pediatric anesthesia. The aim of this study was to describe and characterize reported medication errors to find common patterns amenable to preventative strategies.

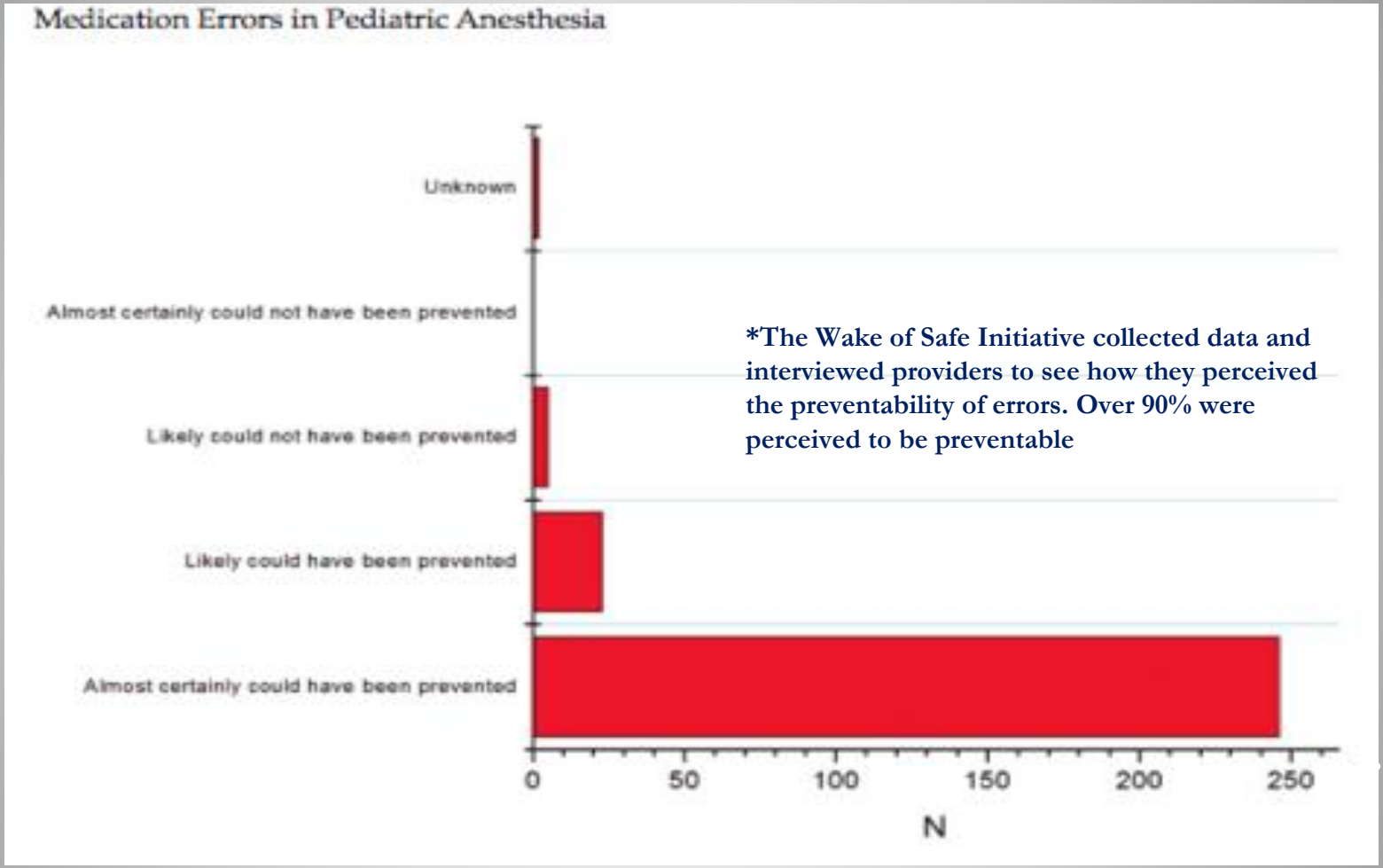
METHODS: In September 2016, we analyzed approximately 6 years' worth of medication error events reported to Wake Up Safe. Medication errors were classified by: (1) medication category; (2) error type by phase of administration: prescribing, preparation, or administration; (3) bolus or infusion error; (4) provider type and level of training; (5) harm as defined by the National Coordinating Council for Medication Error Reporting and Prevention; and (6) perceived preventability.

RESULTS: From 2010 to the time of our data analysis in September 2016, 32 institutions had joined and submitted data on 2087 adverse events during 2,316,635 anesthetics. These reports contained details of 276 medication errors, which comprised the third highest category of events behind cardiac and respiratory related events. Medication errors most commonly involved opioids and sedative/hypnotics. When categorized by phase of handling, 30 events occurred during preparation, 67 during prescribing, and 179 during administration. The most common error type was accidental administration of the wrong dose (N = 84), followed by syringe swap (accidental administration of the wrong syringe, N = 49). Fifty-seven (21%) reported medication errors involved medications prepared as infusions as opposed to 1 time bolus administrations. Medication errors were committed by all types of anesthesia providers, most commonly by attendings. Over 80% of reported medication errors reached the patient and more than half of these events caused patient harm. Fifteen events (5%) required a life sustaining intervention. Nearly all cases (97%) were judged to be either likely or certainly preventable.

***Medication errors ranked 3rd out of 17 reportable adverse events behind respiratory and cardiovascular events.**

***The most common medication error was wrong dose. Either underdosing or overdosing**

Distribution of Perceived Preventability

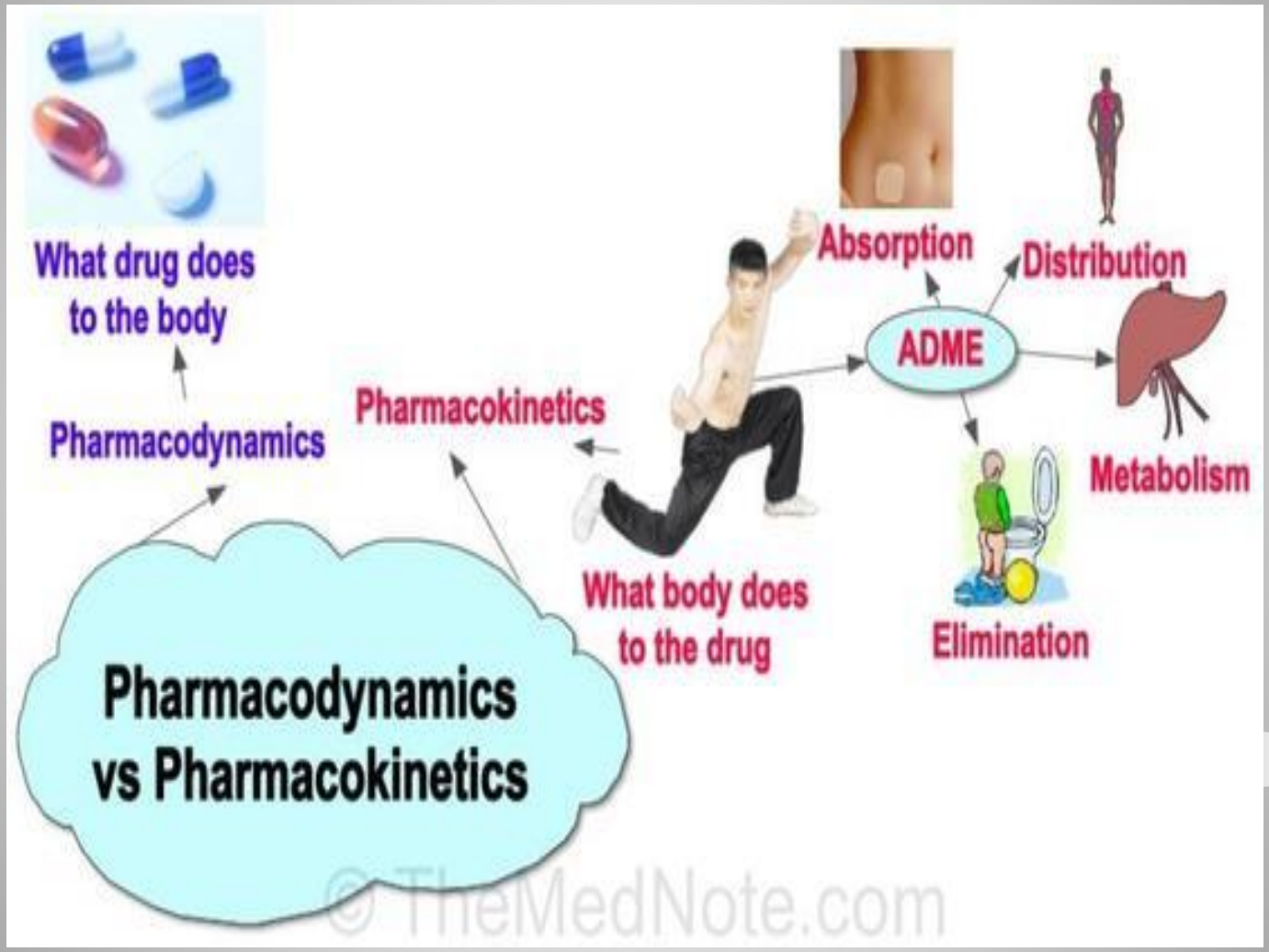


***The Wake of Safe Initiative collected data and interviewed providers to see how they perceived the preventability of errors. Over 90% were perceived to be preventable**

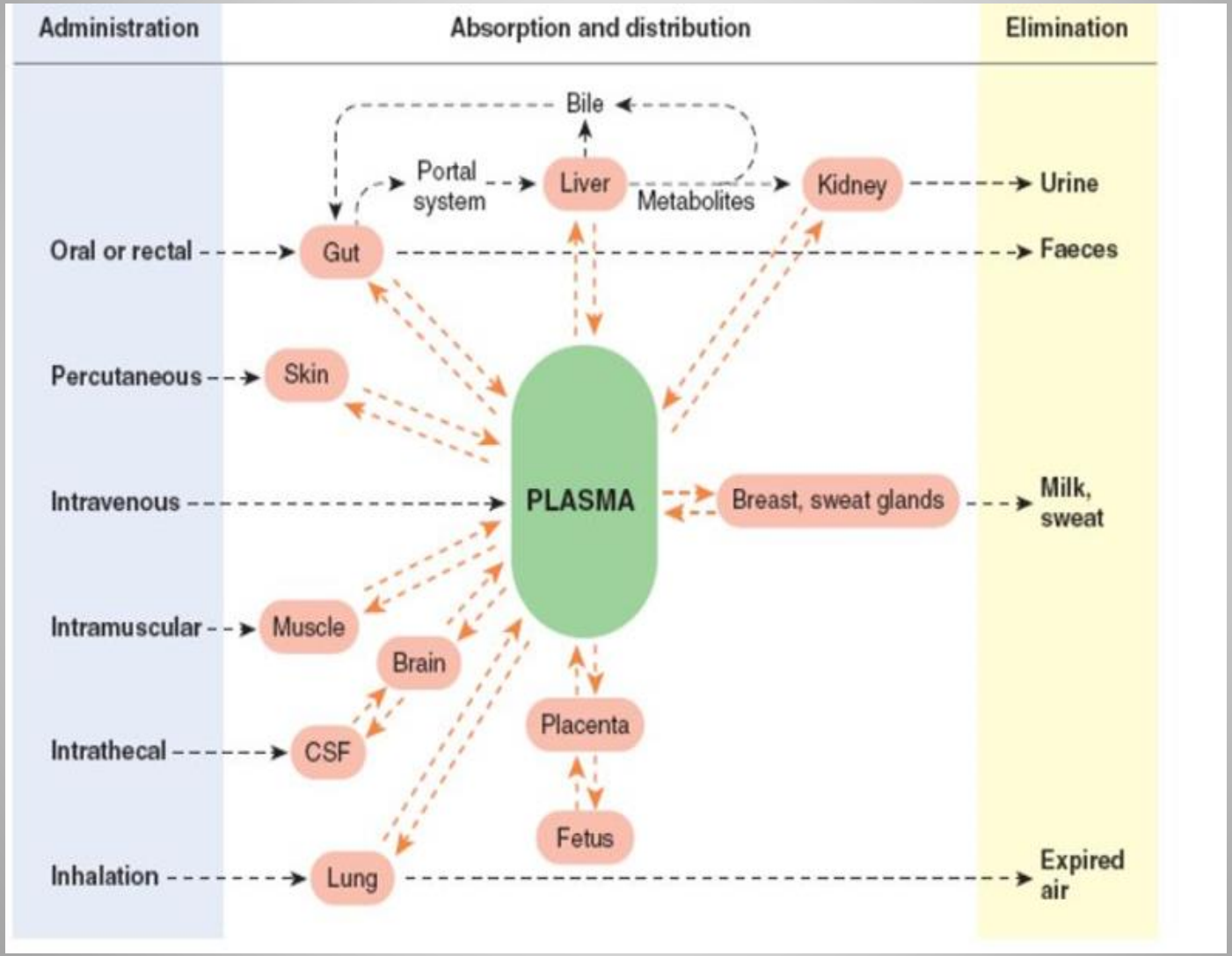
Most errors were either found to be due to a failure of execution or a failure of intention

A failure of intention is "you make a plan, but your plan was faulty…"

Pharmacology – The Basics



Pharmacokinetics



Question

The ionized portion of the drug confers pharmacologic activity? True or False?

Influence of pK_a and pH

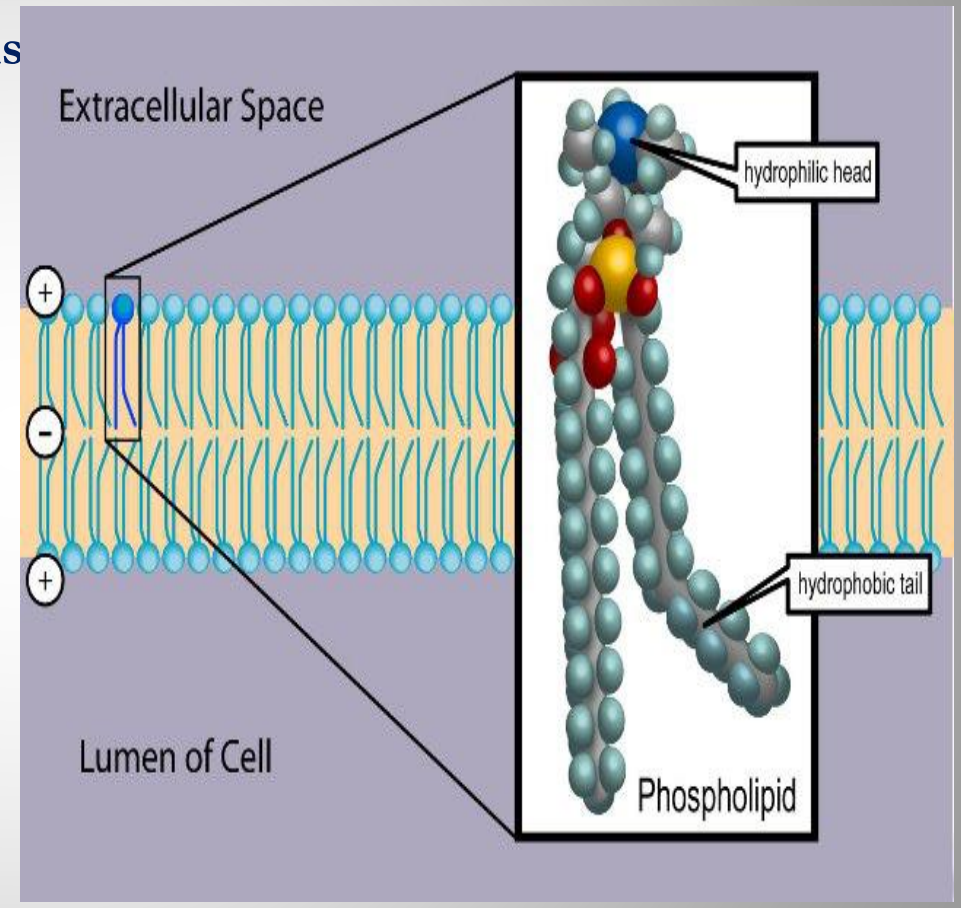
pK_a is the pH at which half the drug is in its ionized form

* ionized = water soluble

* nonionized = lipid soluble

Nonionized molecules are lipid soluble and diffuse across cell membranes

Ionized molecules are unable to penetrate lipid cell membranes because of low lipid solubility. Why?



Question

A patient has a pH of 7.3. You administer an acidic drug to this patient with a pKa of 4.5. What degree of ionization would you expect?

Is it >50% ionized or <50% ionized?

Question

A patient has a pH of 7.3. You administer an acidic drug to this patient with a pKa of 8.1. What degree of ionization would you expect?

Is it >50% ionized or <50% ionized?

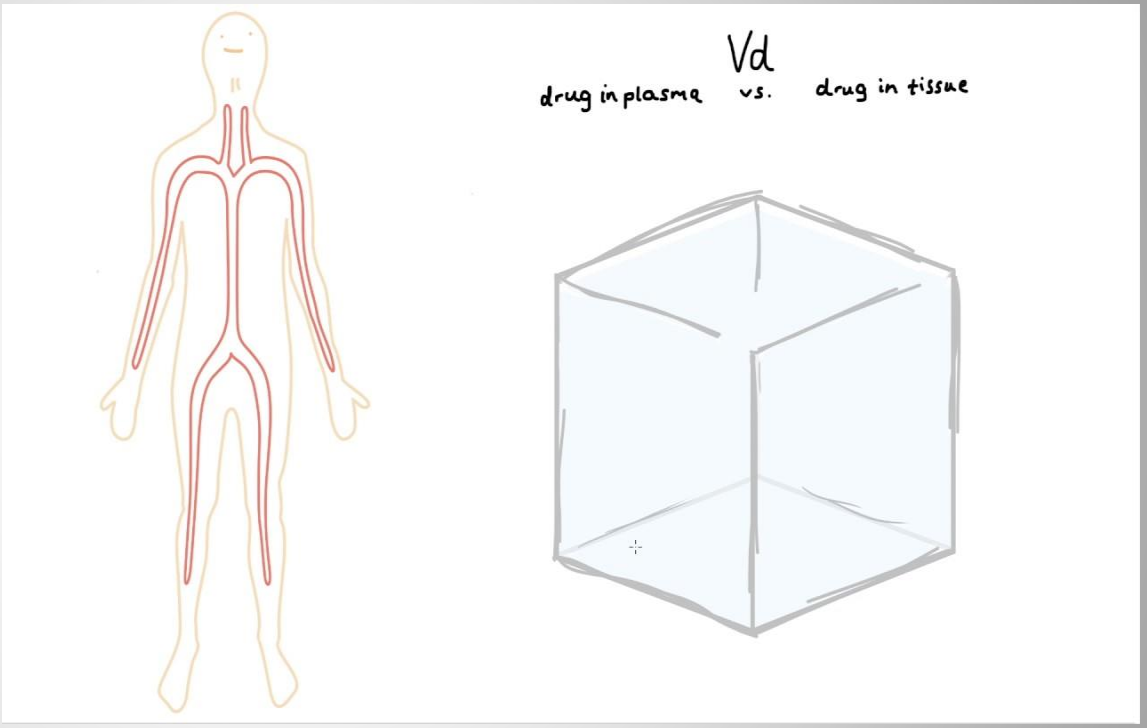
Volume of Distribution (Vd)

Vd describes the relationship between the drug's plasma concentration and tissue concentration.

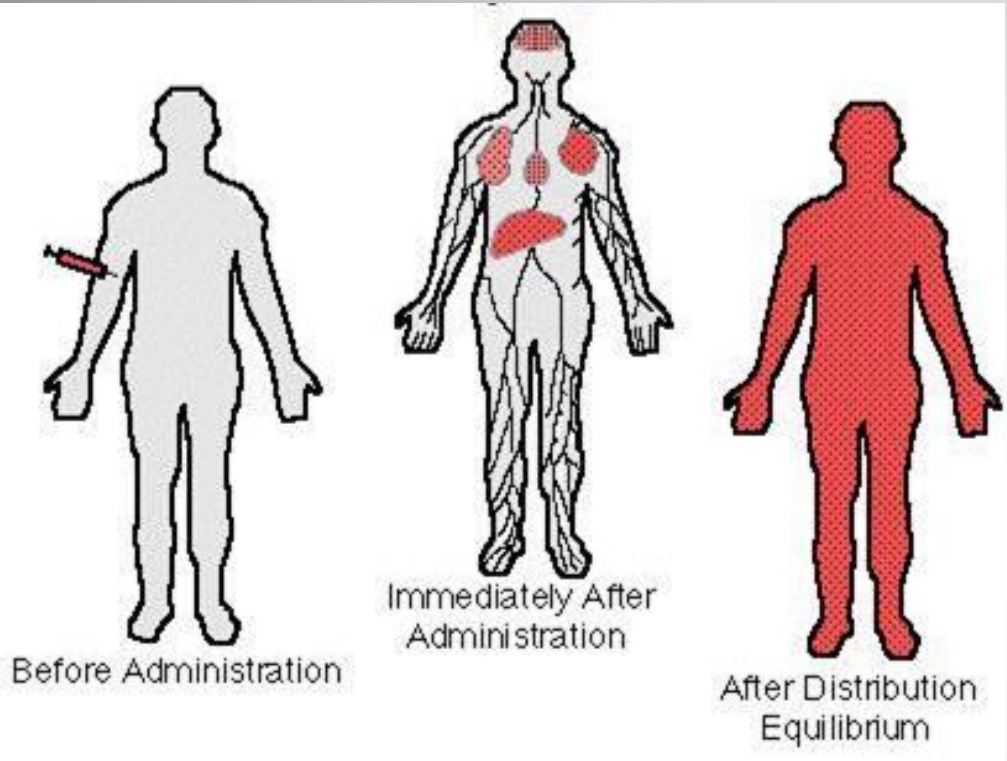
It is a theoretical measure of how a drug distributes throughout the body.

A drug with a Vd that exceeds total body water is assumed to be lipophilic. Why?

A drug with a Vd less than total body water is assumed to be hydrophilic. Why?

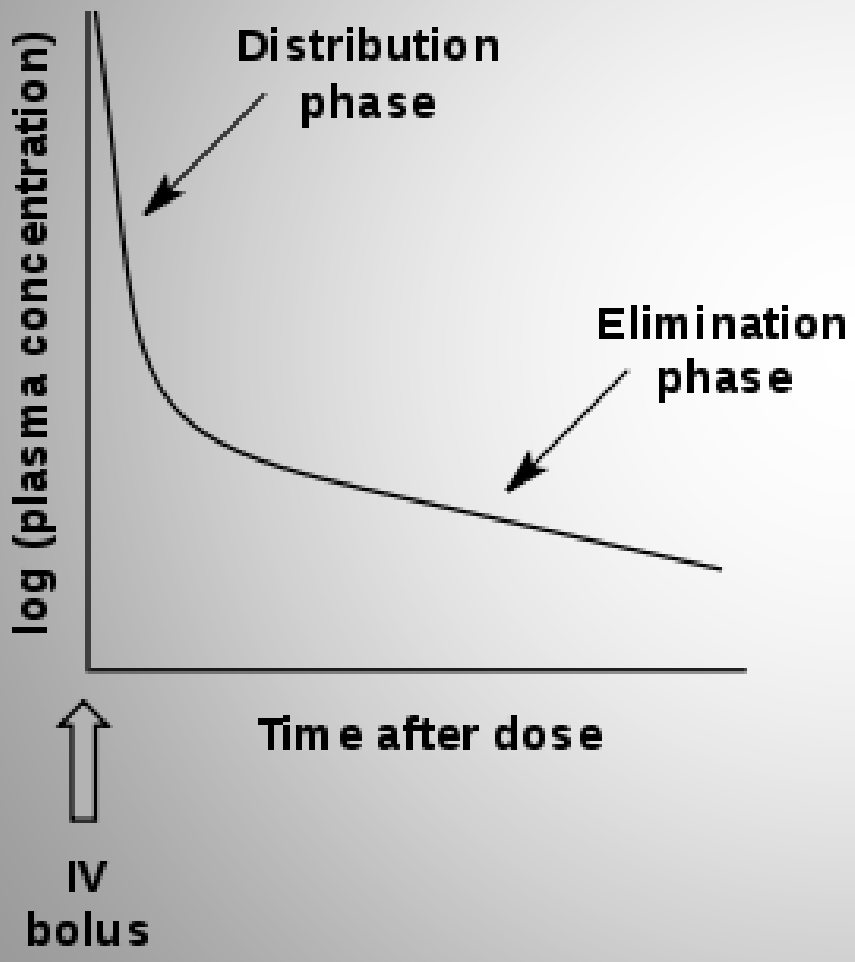


Vd



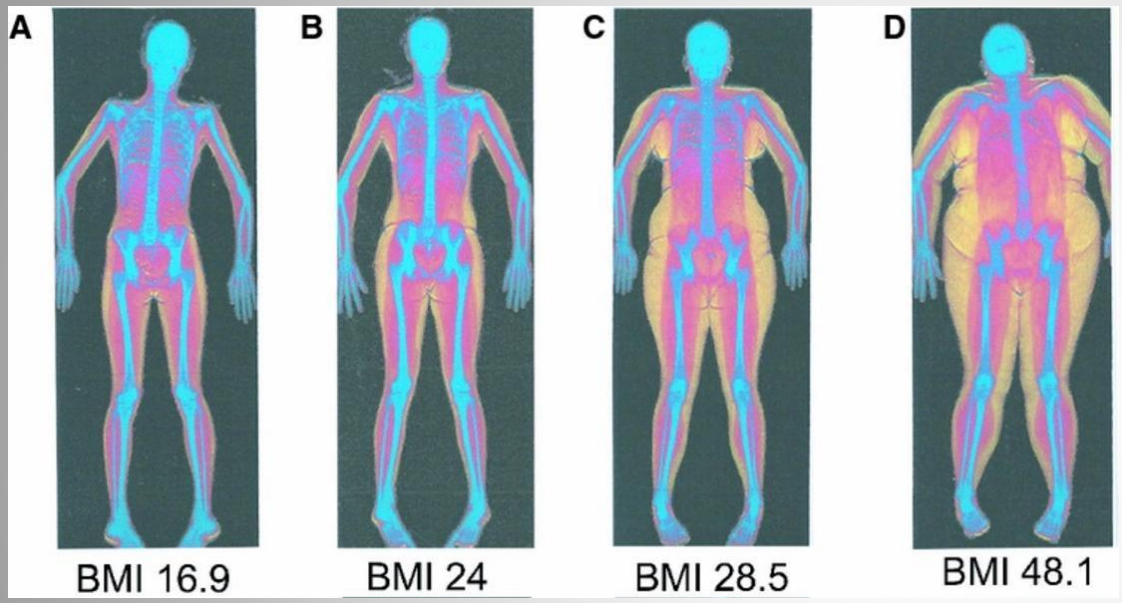
Tissue Group	Composition	Body Mass (%)	Cardiac Output (%)
Vessel-rich	Brain, heart, liver, kidney, endocrine glands	10	75
Muscle	Muscle, skin	50	19
Fat	Fat	20	6
Vessel-poor	Bone, ligament, cartilage	20	0

*** In obese patients there is more accumulation of lipophilic drugs in the fat and it takes longer for the drug to be eliminated.**



- Steep alpha phase: Initial dispersal of drug from central compartment
- Beta phase: A logarithmic plot of the slower elimination
- (Elimination half-life)
- Plasma half-life is directly proportional to volume of distribution, inversely proportional to overall rate of clearance

How Body Composition Affects Distribution



Obese individuals possess a higher body proportion of fat = larger Vd for lipophilic meds due to distribution of drugs into the adipose tissue.

Vd of hydrophilic medications will be altered (increased or decreased) due to increased lean body mass and increased blood volume.

Pathophysiological Changes in Obesity that May Affect Pharmacokinetics

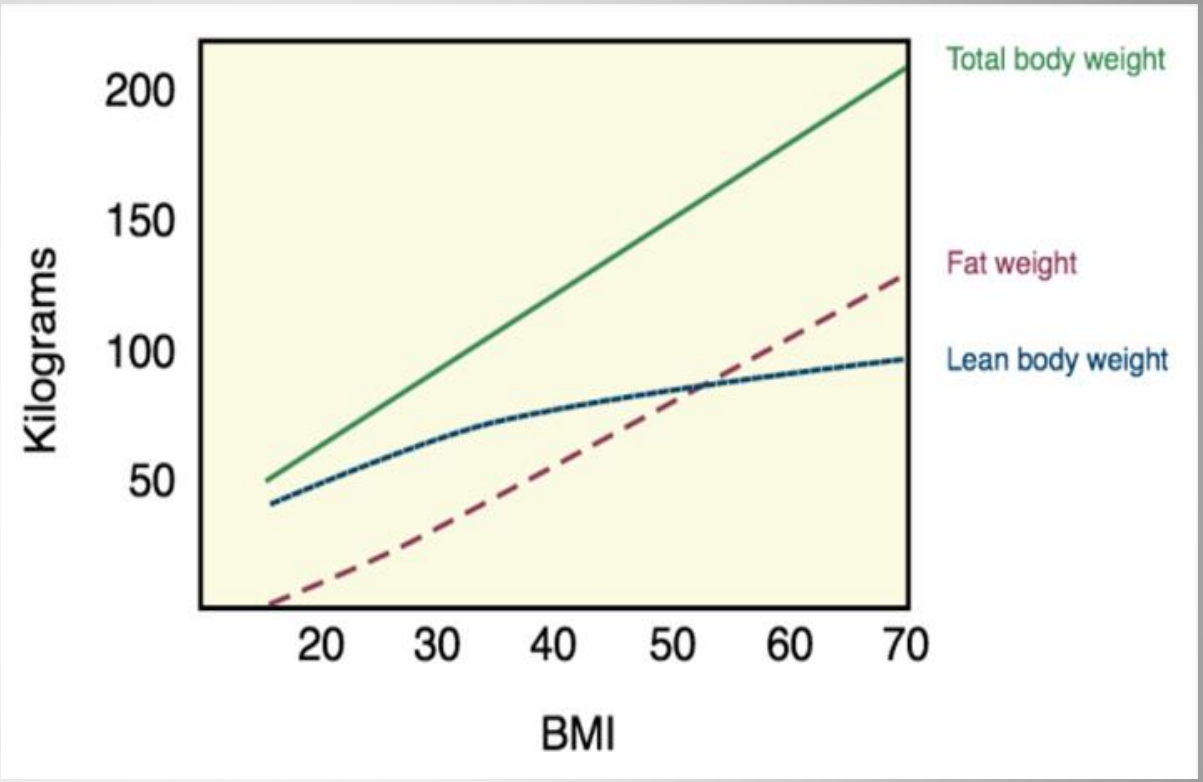
- Increased blood volume ⇨ requires a higher dose to achieve a given plasma concentration
- Increased CO ⇨ faster drug delivery to the vessel rich group
- Altered plasma protein binding ⇨ altered free fractions available
- Lipid solubility of the drug ⇨ large fat mass greatly increases Vd for lipophilic drugs
- Fat mass and muscle mass increase ⇨ plasma volume is also larger

Simplifying Weight Calculations

Total Body Weight: (TBW)

Ideal Body Weight: (IBW)
IBW= BMI_{50} x height in m^2
(Based on age specific 50th percentile on CDC Growth Chart)

*Lean Body Weight: (LBW)
LBW= IBW x 1.3



In 2017, the Pediatric Pharmacy Advocacy Group published recommendations for dosing drugs in Obese children…

Reiteration of the vital importance of proper dosing to ensure safe practices in this population.

Improper dosage of medications is the most commonly reported errors in treating children!

Article Citation:
Kelly L. Matson, Evan R. Horton, and Amanda C. Capino (*2017*) Medication Dosage in Overweight and Obese Children. The Journal of Pediatric Pharmacology and Therapeutics: January-February 2017, Vol. 22, No. 1, pp. 81-83.

https://doi.org/10.5863/1551-6776-22.1.81

POSITION STATEMENTS

Medication Dosage in Overweight and Obese Children

Kelly L. Matson, PharmD; Evan R. Horton, PharmD; Amanda C. Capino, PharmD; on behalf of the Advocacy Committee for the Pediatric Pharmacy Advocacy Group

University of Rhode Island College of Pharmacy, Kingston, RI (KM); UMass Memorial Children's Medical Center, Worcester, MA (KM); Pharmacy Practice, Massachusetts College of Pharmacy and Health Sciences, Worcester, MA (EH); Baystate Children's Hospital, Springfield, MA (EH); Pharmacy Practice, University of Mississippi School of Pharmacy, Jackson, MS (AC)

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Approximately 31.8% of U.S. children ages 2 to 19 years are considered overweight or obese. This creates significant challenges to dosing medications that are primarily weight based (mg/kg) and in predicting pharmacokinetics parameters in pediatric patients. Obese individuals generally have a larger volume of distribution for lipophilic medications. Conversely, the Vd of hydrophilic medications may be increased or decreased due to increased lean body mass, blood volume, and decrease percentage of total body water. They may also experience decreased hepatic clearance secondary to fatty infiltrates of the liver. Hence, obesity may affect loading dose, dosage interval, plasma half-life, and time to reach steady-state concentration for various medications. Weight-based dosing is also a cause for potential medication errors. This position statement of the Pediatric Pharmacy Advocacy Group recommends that weight-based dosing should be used in patients ages < 18 years who are < 40 kg; weight-based dosing should be used in patients ≥ 40 kg, unless, unless the recommended adult dose for the specific indication is exceeded; clinicians should use pharmacokinetic analysis for adjusting medications in overweight/obese children; and research efforts continue to evaluate dosing of medications in obese/overweight children.

Keywords: drug dosage calculations, drug therapy, obese, overweight, pediatrics, pharmacokinetics, therapeutic drug monitoring

Pediatric Pharmacy Advocacy Group

1. Weight based dosing should be used in patients ages < 18 years of age who are < 40kg

1. Children > 40kg, weight based dosing should be used, unless the patient's dose or dose per day exceeds the recommended adult dose for the specific indication

1. Variable recommendations for dosing different medications may lead to inconsistencies for dosing practices, leaving children at risk for overdosing or underdosing, especially in the obese population

Should Propofol induction be based on TBW, LBW, or IBW?

Pediatric Anesthesia

Explore this journal

Original Article

Population pharmacokinetic–pharmacodynamic modeling and dosing simulation of propofol maintenance anesthesia in severely obese adolescents

Vidya Chidambaran ✉, Raja Venkatasubramanian, Senthilkumar Sadhasivam, Hope Esslinger, Shareen Cox, Jeroen Diepstraten, Tsuyoshi Fukuda, Thomas Inge, Catherijne A.J. Knibbe, Alexander A. Vinks

First published: 13 May 2015 Full publication history

DOI: 10.1111/pan.12684 View/save citation

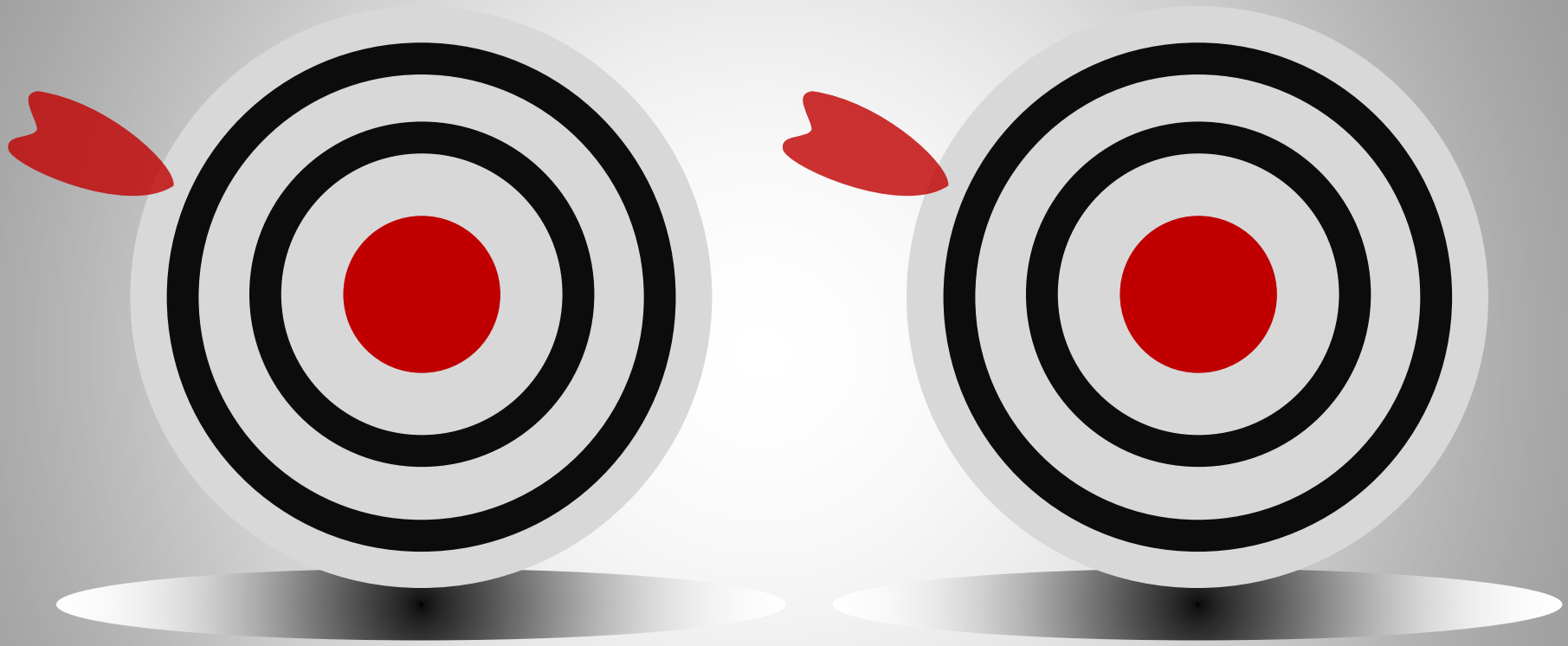
What we already know: Total body weight is predictive of Propofol Vd, but effect.

What this article adds: First study to describe PK/PD of Propofol in SO adolescents.

A prospective PK/PD study was conducted in 26 SO adolescents ages 9-18, undergoing surgery with intravenous Propofol anesthesia clinically titrated by providers blinded to BIS.

This study concluded that maintenance dosing for Propofol should be based on *Total Body Weight* and maintains an adequate level of anesthesia as shown through BIS monitoring

Propofol Dosing Recommendation



Induction:

LBW

Maintenance:

TBW

Pediatric Anesthesia

Pediatric Anesthesia ISSN 1155-5645

ORIGINAL ARTICLE

A retrospective description of anesthetic medication dosing in overweight and obese children

Constance N. Burke[1], Terri Voepel-Lewis[1], Deborah Wagner[1], Irwin Lau[2], Andrew Baldock[3], Shobha Malviya[1] & Olubukola Nafiu[1]

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OW children have a greater risk of being over or underdosed

Keywords
pediatric; anesthesiology; medication dosing; overweight; obese

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Section Editor: Jerrold Lerman

Accepted 2 March 2014

doi:10.1111/pan.12396

Summary

Introduction: Pediatric obesity is a major health concern in the United States and as many as 34% of those who require general anesthesia are overweight or obese (OW). The lack of data and recommendations for dosing medications in obese children leaves significant gaps in the understanding of correct dosing in the clinical setting.

Objective: To determine whether OW children were more likely to receive doses of medications outside the recommended range.

Methods: Following IRB approval, patient medical records were queried to identify children 2 through 17 years who underwent noncardiac surgeries and received at least one medication of interest. Children with hepatic disease, renal disease, neurological impairment, sleep-disordered breathing, or missing height or weight measurements were excluded. Children were stratified into weight categories based on age and gender percentiles as per CDC guidelines.

Retrospective study from 2006-2011, ages 2 to 17

Noncardiac procedures

Reviewed dosing of midazolam, cis, neostigmine, and succinylcholine

***OW children received a dose of morphine that exceeded safe range**

***Reversal agents were under dosed leaving OW children are risk of respiratory compromise**

Fentanyl Dosing Recommendation

Loading Dose:

LBW

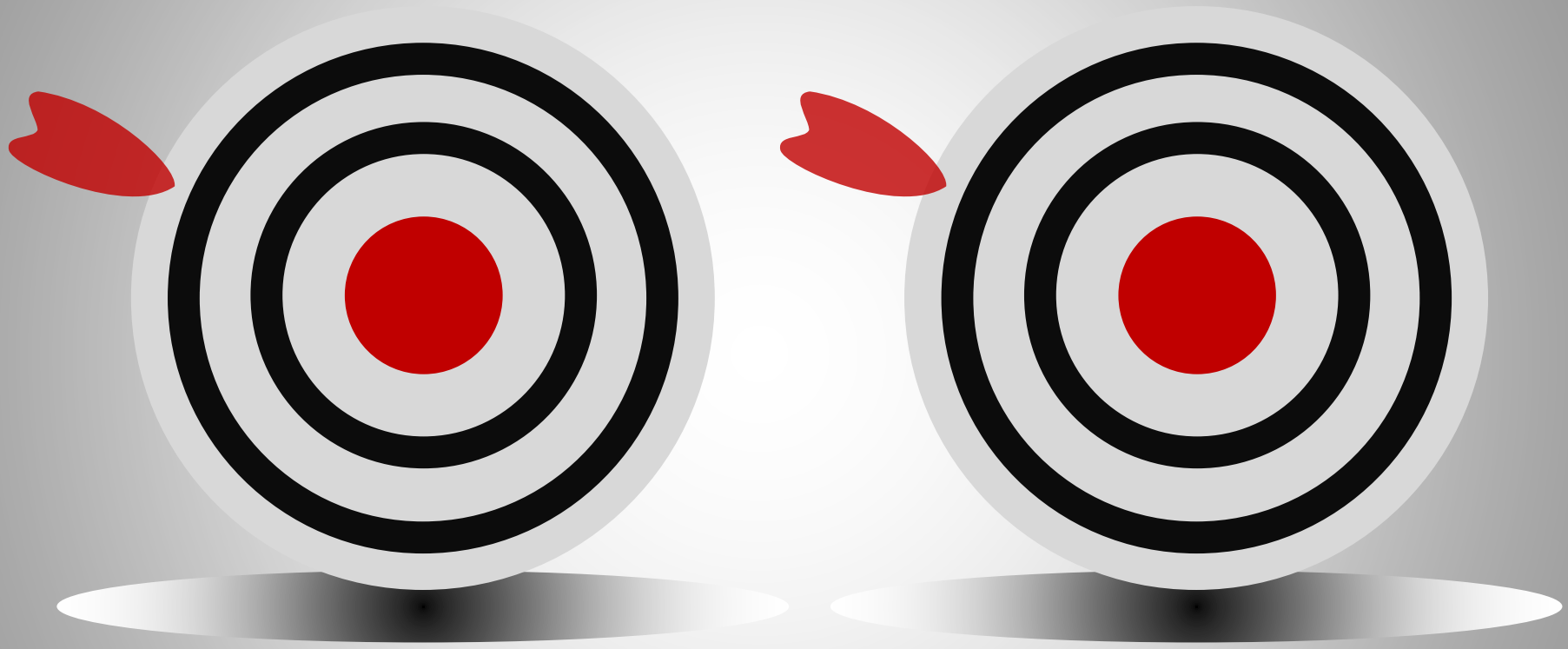
Maintenance:

IBW

&

Individual Response

Midazolam & Morphine
Dosing Recommendation



Loading Dose:

IBW

Maintenance:

IBW

&

Individual Response

Succinylcholine Dosing Recommendation

Induction:

TBW

*Under dosing muscle relaxants may lead to suboptimal intubating conditions

Rocuronium & Vecuronium Dosing Recommendation

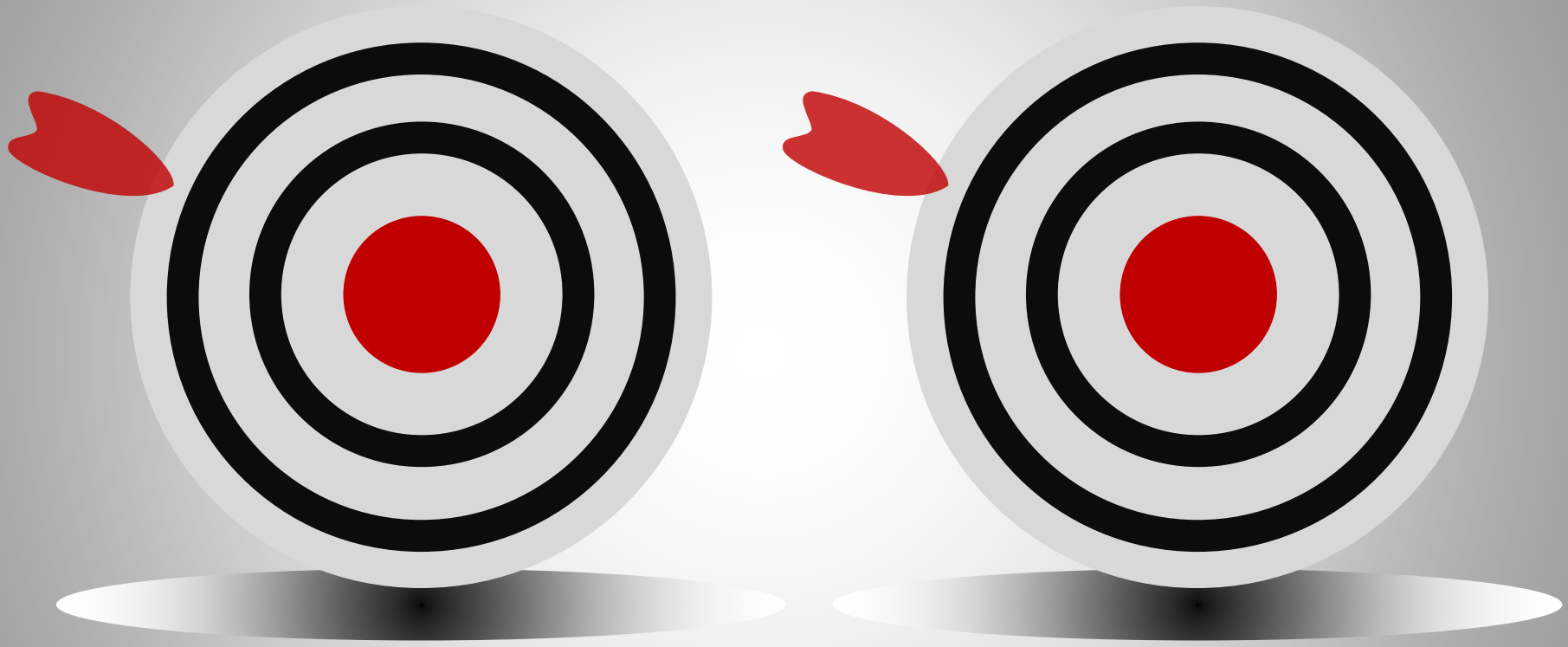
Induction:

IBW

Maintenance:

LBW

Cisatracurium Dosing Recommendation



Induction:

TBW

Maintenance:

TBW

Dexmedetomidine Dosing Recommendation

Loading Dose:

TBW

Maintenance:

TBW

Neostigmine Dosing Recommendation

Reversal Dose:

TBW

*To ensure full recovery give dose based on TBW. Delayed full recovery may be seen in obese patients

Match the drug with the appropriate drug-dose calculation method for an
obese patient using the following weights.

A. Lean Body Weight **B.** Ideal Body Weight **C.** Total Body Weight

Succinylcholine
Rocuronium
Propofol Induction

Succinylcholine	Total body weight
Rocuronium	Ideal body weight
Propofol induction	Lean body weight

Drug	Induction Dose	Maintenance Dose
Propofol	LBW	TBW
Fentanyl	LBW	IBW & Individual Response
Midazolam	IBW	IBW & Individual Response
Morphine	IBW	IBW & Individual Response
Succinylcholine	TBW	
Rocuronium	IBW	LBW
Vecuronium	IBW	LBW
Cisatracurium	TBW	TBW
Dexmedetomidine	TBW	TBW
	Reversal Dose	
Neostigmine	TBW	

A safe guide to remember.: The Pediatric Pharmacy Advocacy Group supports:

- Use **IBW** for *induction* of **hydrophilic** drugs and **LBW** for *maintenance* doses
- For **lipophilic** drugs the Pediatric Pharmacy Advocacy Group supports the use of **TBW**

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Any Questions?