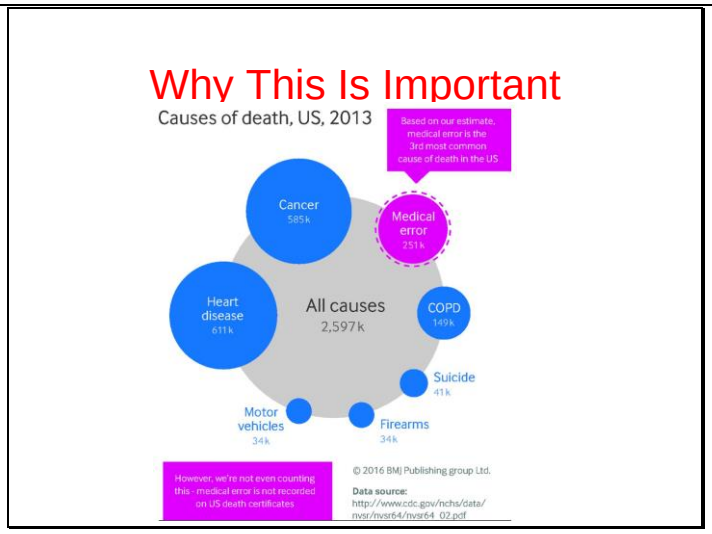
Slide 1	Doses Loading and Maintenance	
Slide 2	A Brief History of Medicine ~~~~~~ 2000 B.C. - Here, eat this root. 1000 A.D. - That root is heathen. Here, say this prayer. 1850 A.D. - That prayer is superstition. Here, drink this potion. 1940 A.D. - That potion is snake oil. Here, swallow this pill. 1985 A.D. - That pill is ineffective. Here, take this antibiotic. 2000 A.D. - That antibiotic doesn't work anymore. Here, eat this root. ~~~~~~	
Slide 3	Why This is Important The **largest** category was the 357 medication-related events which might include wrong medicines being given, incorrect labelling, **underdoses or overdoses**, and doctors' illegible handwriting. New Zealand Herald 27 Feb 2003 Page A13 Report of incidents in Waitemata District Health Board Hospitals Southern District Health Board asks grieving family for feedback after baby dies "The next day, a doctor incorrectly administered a dose of the sedative midazolam **five times higher** than he intended, to a baby already in very poor health." New Zealand Herald 9 Jun, 2020	https://www.nzherald.co.nz/nz/southern-district-health-board-asks-grieving-family-for-feedback-after-baby-dies/WEHNN3IESDDRGZCCCPDFOJBROE/

Slide 4		**Medical error—the third leading cause of death in the US** *BMJ* 2016; 353 doi: http://dx.doi.org/10.1136/bmj.i2139 (Published 03 May 2016)Cite this as: *BMJ* 2016;353:i2139
Slide 5	# Digoxin Find the answers to the following questions for a 45 year old, 60 kg woman with a serum creatinine of 0.1 mmol/L (Patient A): The target concentration of digoxin for the treatment of atrial fibrillation is 1 ng/mL. Tablets of digoxin contain 62.5 micrograms and 250 micrograms (mcg). A. What loading dose is required?	
Slide 6	# Digoxin | *Parameter*	*Value*
---	---
F (oral)	0.65
V Liters	490
CLr L/h	CLcr
CLh L/h	3 | Typical values for a 70 kg person	

Slide 7

Digoxin PK

Patient A
Age= 45 y Wt= 60 kg Sex= F Screat = 0.10 mmol/l

V = 490 L x 60/70 kg = 420 L

Slide 8

Digoxin Loading Dose

Patient A
Age= 45 y Wt= 60 kg Sex= F Screat = 0.10 mmol/l

TC = 1 mcg/L
V = 420 L

LDiv= TC x V
= 1 mcg/L x 420 L
= 420 mcg iv

LDor= LDiv / F
= 420 mcg / 0.65
= 646 mcg oral (rapid absorption rate formulation)
= 0.625 mg (2 x 250 mcg + 2 x 62.5 mcg)

Slide 9

Digoxin

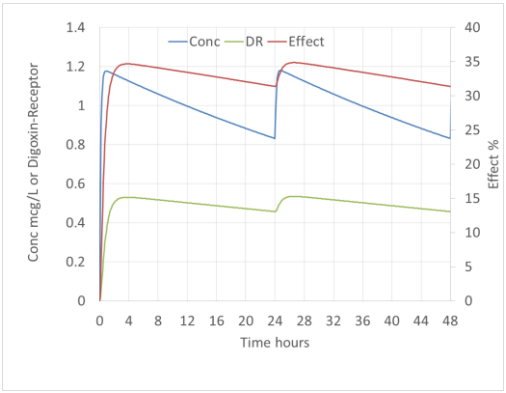
Find the answers to the following questions for a 45 year old, 60 kg woman with a serum creatinine of 0.1 mmol/L (Patient A):

The target concentration of digoxin for the treatment of atrial fibrillation is 1 ng/mL. Tablets of digoxin contain 62.5 micrograms and 250 micrograms (mcg).

A. What loading dose is required?

B. What maintenance dose is required?

Slide 10	**Creatinine Clearance Prediction** $$CL_{cr}\,(L/h) = \frac{160 - Age(y)}{250 \bullet S_{cr}\,(mmol/L)} \bullet \frac{Wt(kg)}{70} \bullet 0.9\ if\ Female$$ e.g. 60 year old, 140 Kg male with Scr 0.1 mmol/L: $$CL_{cr}\,(L/h) = \frac{160 - 60y}{250 \bullet 0.1 mmol/L} \bullet \frac{140kg}{70} = 8L/h$$	This formula is based on Bjornsson (1979). It incorporates and updates the data originally collected and published by Cockcroft & Gault. Bjornsson TD. Use of serum creatinine concentrations to determine renal function. Clin Pharmacokinet. 1979;4(3):200-22. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron. 1976;16:31-41.
Slide 11	**Digoxin PK** Patient A Age= 45 y Wt= 60 kg Sex= F Screat = 0.10 mmol/l V = 490 L x 60/70 kg = 420 L CLh = 3.0 L/h x 60/70 kg = 2.57 L/h CLr = CLcr = (160 - 45 y) / (250 x 0.1 mmol/L) x 60/70 kg x 0.9 = 3.55 L/h CLt = CLh + CLr = 2.57 + 3.55 = 6.12 L/h T1/2= 0.7 x 420 L / 6.12 L/h = 48.04 h	
Slide 12	**Digoxin Maintenance Dose** Patient A Age= 45 y Wt= 60 kg Sex= F Screat = 0.10 mmol/l TC = 1 mcg/L CLt = 6.12 L/h MDRiv= TC x CL = 1 mcg/L x 6.12 L/h = 6.12 mcg/h iv MDRor= MDRiv / F = 6.12 mcg/h / 0.65 = 9.42 mcg/h oral MD = 9.42 mcg/h x 24 h = 226 mcg every 24h = 0.25 mg once a day	

Slide 13	**Digoxin LD + MD** 	Combining a loading dose with a maintenance dose rapidly achieves plasma concentrations similar to those at steady state. The bound receptor concentration (DR) is delayed which explains why the effect of digoxin is delayed.
Slide 14	**Theophylline** Find the answers to the following questions for a 5 year old, 20 kg girl with a serum creatinine of 0.1 mmol/L (Patient B): The target concentration for theophylline for the treatment of bronchoconstriction is 10 mg/L Tablets of theophylline contain 250 mg. An elixir contains 80 mg/15 mL Hint: Adult age and renal function do not influence V or CL for theophylline A. What is the predicted volume of distribution? B. What is the predicted clearance?	
Slide 15	**Theophylline** *Parameter* / *Value* F (oral) 1 V Liters 35 CLr L/h 0 CLh L/h 2.8 Typical values for a 70 kg person	

Slide 16

Theophylline PK

Patient B
Age= 5 y Wt= 20 kg Sex= F Screat = 0.10 mmol/l

V = 35 L x 20/70 kg = 10 L

CLh = 2.8 L/h x $(20/70)^{3/4}$
= 1.1 L/h
CLr = 0 L/h
CLt = CLh + CLr
= 1.1 + 0 = 1.1 L/h

T1/2= 0.7 x 10 L / 1.1 L/h = 6.3 h

Rule of PNA predicts 1/3 of adult dose for 19 kg 5 year old child which means 1/3 of adult clearance (2.8 L/h/3 = 0.93 L/h)

Slide 17

Rules of PNA and PMA

Fraction of adult maintenance dose

Typical Weight Kg	PMA or PNA	Fraction Adult Dose	Rule of PMA+PNA Error	'true' % Adult Dose
1	25 weeks	1/300	10%	0.3
1	30 weeks	1/120	1%	0.8
3	Full Term	1/30	1%	3.3
6	3 mo	1/10	8%	9.3
7	6 mo	1/6	24%	13.4
9	1 year	1/5	3%	19.5
12	2 years	1/4	-4%	26.1
19	5 years	1/3	-11%	37.4
34	10 years	1/2	-14%	58.5
50	15 years	3/4	-3%	77.4
70	Adult	1		100.0

Weight is combined with post-natal age (PNA) and post-menstrual age (PMA) to predict the typical dose as a % of the adult dose.
The coloured areas of the table show the fraction of adult maintenance dose that would be expected for infants and children.
The fractions are based on the theoretical size and maturation model for typical drug clearance with some approximation to make the numbers easier to remember.
The 'rule of PMA+PNA' has an acceptable error for clinical dose prediction.
Although maturation is best described by a non-linear relationship it is quite well approximated by a linear function of PMA.

Slide 18

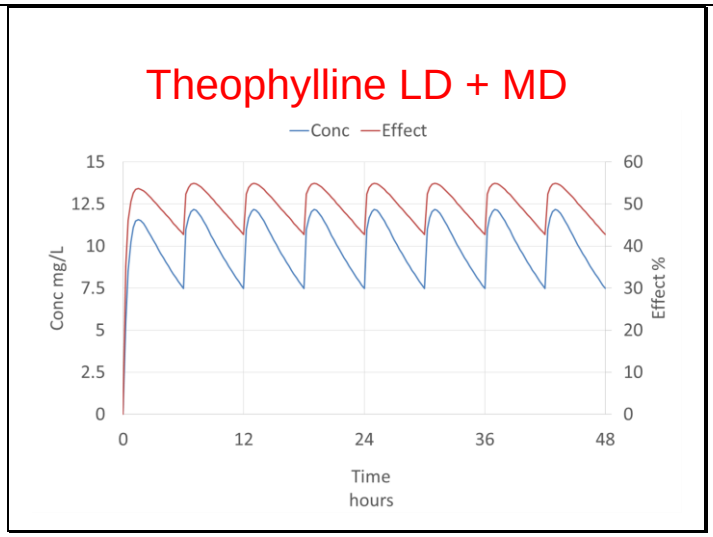
Theophylline

Find the answers to the following questions for a 5 year old, 20 kg girl with a serum creatinine of 0.1 mmol/L (Patient B):

The target concentration for theophylline for the treatment of bronchoconstriction is 10 mg/L. Tablets of theophylline contain 250 mg. An elixir contains 80 mg/15 mL.
Hint: Age and renal function do not influence V or CL for theophylline

A. What is the predicted volume of distribution?
B. What is the predicted clearance?
C. What loading dose is required?

Slide 19	**Theophylline Loading Dose** Patient B Age= 5 y Wt= 20 kg Sex= F Screat = 0.10 mmol/l TC = 10 mg/L V = 10 L LDiv= TC x V = 10 mg/L x 10 L = 100 mg iv LDor= LDiv / F = 100 mg /1.0 = 125 mg tablet (half of 250 mg tablet) = 20 mL elixir (103 mg)	
Slide 20	**Theophylline** Find the answers to the following questions for a 5 year old, 20 kg girl with a serum creatinine of 0.1 mmol/L (Patient A): The target concentration for theophylline for the treatment of bronchoconstriction is 10 mg/L. Tablets of theophylline contain 250 mg. An elixir contains 80 mg/15 mL. Hint: Age and renal function do not influence V or CL for theophylline A. What is the predicted volume of distribution? B. What is the predicted clearance? C. What loading dose is required? D. What maintenance dose is required?	
Slide 21	**Theophylline Maintenance Dose** Patient A Age= 5 y Wt= 20 kg Sex= F Screat = 0.10 mmol/l TC = 10 mg/L CLt = 1.1 L/h MDRiv= TC x CL = 10 mg/L x 1.1 L/h = 11 mg/h iv MDRor= MDRiv/F = 11 mg/h / 1.0 = 11 mg/h oral MD = 11 mg/h x 6 h = 66 mg every 6h = 10 mL 4 times a day (53 mg)	Rule of PNA predicts 1/3 of adult dose for 19 kg 5 year old child which means MDRiv=10 mg/L*0.93=9.3 mg/h = MD 55.8 mg/6h

Slide 22		If theophylline is started with a loading dose the concentration and effect are close to the steady state and this is achieved with the first dose.
Slide 23	**Cimetidine** The target concentration of cimetidine for the treatment of peptic ulceration is 1 mg/L. A. What IV loading dose is required? B. What IV infusion rate is required?	
Slide 24	**Cimetidine** *Parameter* *Value* F (oral) 0.6 V Liters 150 CLr L/h 7 x CLcr CLh L/h 10 Typical values for a 70 kg person	

Slide 25	**Cimetidine PK** Patient A Age= 45 y Wt= 60 kg Sex= F Screat = 0.10 mmol/l V = 150 L x 60/70 kg = 128.57 L CLh = 10 L/h x 60/70 kg = 8.57 L/h CLr = 7 x CLcr = 7 x (160 - 45 y) / (250 x 0.1 mmol/L) x 60/70 kg x 0.9 = 24.85 L/h CLt = CLh + CLr = 8.57 + 24.85 = 33.42 L/h T1/2= 0.7 x 128.57 L / 33.42 L/h = 2.69 h	
Slide 26	**Cimetidine Loading Dose and Infusion** Patient A Age= 45 y Wt= 60 kg Sex= F Screat = 0.10 mmol/l TC = 1.0 mg/L V = 128.57 L CL = 33.42 L/h IV Loading Dose = V x TC = 128.57 L x 1.0 mg/L = 128.57 mg IV Infusion Rate = CL x TC = 33.42 L/ h x 1.0 mg/L = 33.42 mg/h	
Slide 27	**Cimetidine** The target concentration of cimetidine for the treatment of peptic ulceration is 1 mg/L. A. What IV loading dose is required? B. What IV infusion rate is required? C. What concentration would be reached 12 hours after starting an infusion? (no loading dose)	

Slide 28	# Cimetidine 12 h Concentration Concentration can be estimated from the expected steady state concentration (1.0 mg/L) and the approximate number of half-lives (2.69 h) that the infusion has continued. At 3 h (1.0 T1/2s; 50% Css) = 0.50 mg/L At 5 h (2.0 T1/2s; 75% Css) = 0.75 mg/L At 11 h (4.0 T1/2s; 94% Css) = 0.94 mg/L At 22 h (8.0 T1/2s;100% Css) = 1.00 mg/L A more precise prediction uses an INFUSION input model: At 3 h (1.1 T1/2s; 54% Css) = 0.54 mg/L At 12 h (4.5 T1/2s; 96% Css) = 0.96 mg/L At 24 h (8.9 T1/2s;100% Css) = 1.00 mg/L	