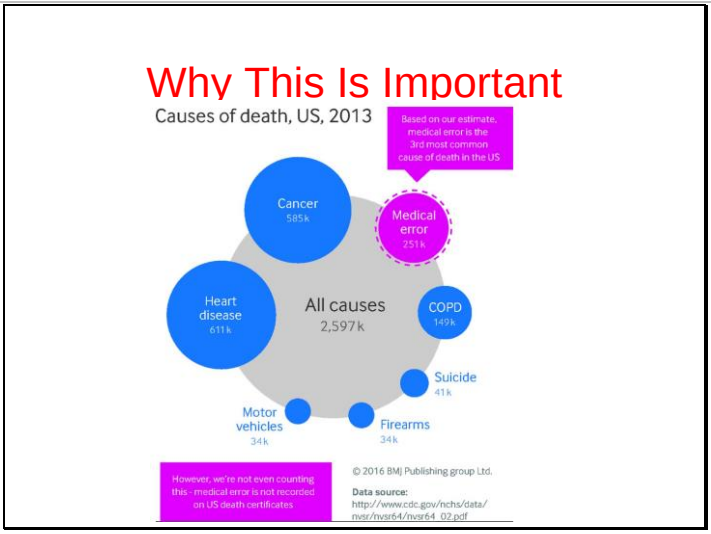
Slide 1	# Theophylline Loading and Maintenance	
Slide 2	## A Brief History of Medicine ~~~~~~ 2000 B.C. - Here, eat this root. 1000 A.D. - That root is heathen. Here, say this prayer. 1850 A.D. - That prayer is superstition. Here, drink this potion. 1940 A.D. - That potion is snake oil. Here, swallow 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	

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	# 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 6	# 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 7

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 8

Theophylline PK

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

$V = 35\ L \times 20/70\ kg = 10\ L$

$CLh = 2.8\ L/h \times (20/70)^{3/4}$
$= 1.1\ L/h$

Rule of PNA = 0.93 L/h (14% too small)
Linear per kg = 0.8 L/h (27% too small)

$CLr = 0\ L/h$
$CLt = CLh + CLr$
$= 1.1 + 0 = 1.1\ L/h$

$T1/2 = 0.7 \times 10\ L / 1.1\ L/h = 6.3\ h$

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)
Linear per kg scaling of clearance (2.8 L/h*20/70=0.8 L/h) is 27% lower than expected from allometric theory and actual dose practice in children.

Slide 9

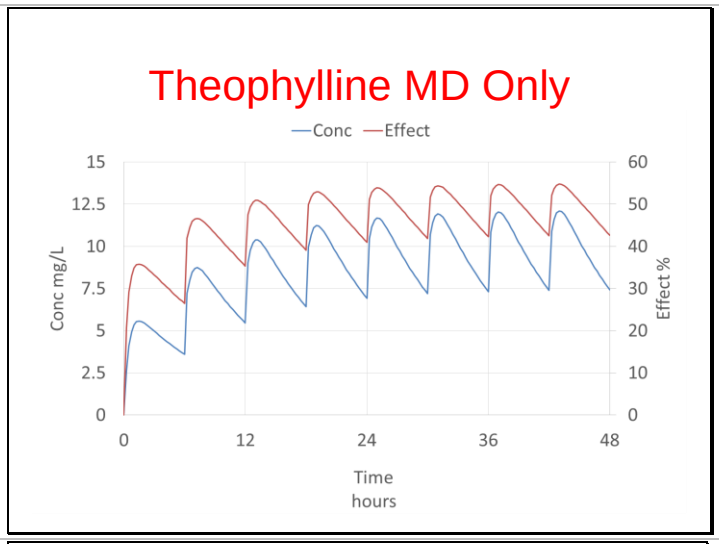
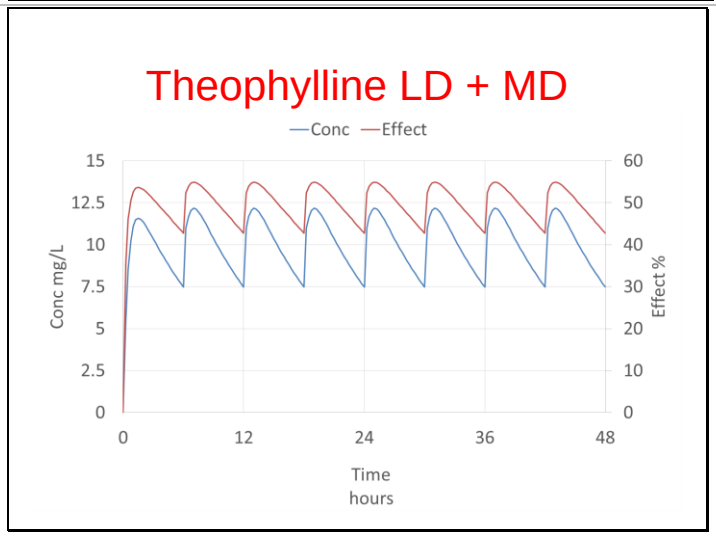
Theophylline

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 10	**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 = 100 mg oral (rapid absorption rate formulation)	
Slide 11	**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 12	**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/6 h)	Elixir has 80 mg/15 mL. 10 ml=80*10/15=53 mg 5 mL is standard teaspoon so 10 mL is a convenient amount to administer.

Slide 13		If theophylline is started with the first dose the same as subsequent maintenance doses it takes over 24 hours to approach steady state concentration and effect.
Slide 14		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.