Slide 1	Doses Target Concentration Intervention	
Slide 2	**Problem 1 Questions 1-2** Susan is a 28 year old woman who has had epilepsy since she was 5 years old. She has been on, and off, anticonvulsant medication since that time. She has been brought to hospital by a work colleague following a generalized seizure. She is drowsy. Her mother tells you over the phone that she has been taking sodium valproate since she was 17 years old, but takes no other medicines. Sodium valproate has controlled her seizures well. When Susan wakes up she tells you that she has been very well, but has had several seizures this month. She stopped taking valproate because she thinks it makes her put on weight. . She now weighs 100 kg and is 160cm tall. BMI = 100 kg/(1.6 m x 1.6 m) = 39 kg/m2. 1. What are the reasons for measuring a serum valproate concentration ? 2. When should the sample be taken?	Q1: Many neurologists believe (for poor reasons) that plasma valproate has no predictive value for dosing. They usually use measurements just as a check on compliance. Valproate anticonvulsant effects take hours to days to appear. So it is not surprising that the effect may not be related to the concentration taken at the same time. Steady state concs (after a day) are a guide to future effectiveness. Q2: In this setting it would be most useful to take a sample immediately in order to check the dosing history. A sample should be taken in the middle of the dosing interval in order to predict clearance. Samples are often taken just before a dose – this is OK for compliance checking but less valuable for predicting future doses. Patsalos PN, Berry DJ, Bourgeois BF, Cloyd JC, Glauser TA, Johannessen SI, et al. Antiepileptic drugs--best practice guidelines for therapeutic drug monitoring: a position paper by the subcommission on therapeutic drug monitoring, ILAE Commission on Therapeutic Strategies. Epilepsia. 2008;49(7):1239-76.

Slide 3	**Problem 1 Questions 3-5** 3. Her sodium valproate concentration is 0 mg/L. What are the possible explanation(s) for this? 4. Would she benefit from anticonvulsant medication? 5. What treatment options are readily available?	Q3: Most likely cause is poor compliance. Others include sample mix up at the lab, trough conc below the limit of quantitation at the lab which may be erroneously interpreted as 0. Q4: A generalized seizure is serious health event. Anti-convulsant treatment is the first line choice. Q5: Phenytoin, carbamazepine, lamotrigine. Brain surgery for seizure control is a last resort. Smith PEM. Initial Management of Seizure in Adults. N Engl J Med. 2021;385(3):251-63.
Slide 4	**Problem 1 Question 6-7** Susan refuses to take carbamazepine because when she used it as a teenager it caused nausea. She developed a rash when she tried lamotrigine. You both agree to initiate phenytoin. 6. Should you give her a loading dose? Why/why not? 7. What route and dose would you give to Susan? Phenytoin is available in 30mg and 100mg capsules and also as an intravenous injection solution.	Q6: A loading dose is essential in order to reach the target concentration rapidly. A maintenance dose regime may take 2 weeks to reach steady state. Q7: The intravenous rate is quicker and usually preferred. IV infusion must be slow with BP and ECG monitoring. If monitoring is not possible then an oral loading dose may be used. The reliability of giving an oral loading dose has been documented here: http://www.aliem.com/trick-of-the-trade-rapid-oral-phenytoin-loading-in-the-ed/

Slide 5	**Problem 1 Answer 7 Loading Dose**
	
	Her predicted Ideal Body Weight (IBW) is 54 kg and her Fat Free Mass (FFM) is 50.6 kg. FFM may be a better predictor of fat mass ie. total weight minus FFM but IBW was used for this volume formula. Volume of phenytoin per kg is moderately higher in obese patients (lipid partition of phenytoin)
	
	Volume = 0.7 L/kg x (54 + 46 x 1.33) kg = 81 L
	
	Loading Dose = Volume x Target Concentration
	
	Loading Dose = 81 L x 10 mg/L
	= 810 mg (IV)
	= 810/ 0.95 mg (oral bioavailability 95%)
	= 852 mg (oral)
	= 8 x 100 mg capsules
		Abernethy DR, Greenblatt DJ. Phenytoin disposition in obesity. Determination of loading dose. Arch Neurol. 1985;42(5):468-71. "Phenytoin loading dose should be calculated on the basis of IBW plus the product of 1.33 times the excess weight over IBW. Very obese individuals will require large absolute loading doses of phenytoin to rapidly achieve therapeutic drug concentrations."
		IBW Males = 52 kg + 1.9 kg per inch over 5 feet height
		IBW Females = 49 kg + 1.7 kg per inch over 5 feet height
		
		Fat free mass is preferable to ideal body weight today because it separates non-fat mass from fat mass. FFM is calculated from sex, weight (kg) and height in metres (htm).
		FFM=WHSMAX*htm^2*weight/(WHS50_*htm^2+weight)
		IF (SEX="F") THEN ; female
		WHSMAX=37.99
		WHS50=35.98
		ELSE ; male
		WHSMAX=42.92
		WHS50=30.93
		ENDIF

		Janmahasatian S, Duffull SB, Ash S, Ward LC, Byrne NM, Green B. Quantification of lean bodyweight. Clin Pharmacokinet. 2005;44(10):1051-65.
Slide 6	**Problem 1 Answer 7 Maintenance Dose** Maintenance Dose Rate = Clearance x Target Concentration "Clearance" = Vmax / (Km + Conc) Assume 'functional body weight' of 70 kg for elimination Vmax= 7 mg/kg/d = 490 mg/d Km = 4 mg/L "Clearance" = 490 mg/d / (4 mg/L + 10 mg/L) = 35 L/d MDR = 35 x 10 mg/L (IV) = 350 mg/d / 0.95 = 368 mg/d (oral) = 360 mg/d (practical dose) Most people are started on a typical dose of 300 mg/d	There is no published information on the relationship between phenytoin Vmax and body composition. Based on a fat free mass of 54 kg a women with normal body composition would have about 20% fat so her total body weight if she was not obese is predicted to be 68 kg. For simplicity we might assume her 'functional body weight' is 70 kg.
Slide 7	**Problem 1 Questions 8-10** 8. How can the effectiveness of this treatment be measured? 9. What would be the value of measuring phenytoin concentration? When?	Q8: The lack of occurrence of seizures in the short term cannot be used to measure effectiveness. Measurement of drug concentration is a surrogate for effectiveness if concentrations are at the target concentration. Q9: In the acute setting after a loading dose concentrations are very valuable for dose individualization. A measurement should be made 1 hour after the end of the phenytoin infusion. Further measurements at 3 days and 7 days will indicate if concs are rising or falling towards a new steady state. This will be helpful in deciding if the maintenance dose should be decreased or increased.

Slide 8	**Problem 1 Questions 10-11** 10. You measure the serum concentration after 1 month on 360 mg/day in the middle of the dosing interval. The reported concentration is 7.5mg/L. Should the dose be increased? 11. A year later Susan sees you because she has had 2 seizures in the last month. Once again the phenytoin concentration is 7.5 mg/L. In order to achieve a plasma concentration of 15mg/L should the dose be increased to 720 mg/day?	Q 10: Many patients will have effective seizure control at concentrations between 5 and 10 mg/L. Some clinicians would not change the dose but simply wait to see what happens. Q 11: The occurrence of 2 seizures at a concentration of 7.5 mg/L means this concentration is not adequate for seizure control. A widely used acceptable range is 10-20 mg/L which suggests a practical target of 15 mg/L.
Slide 9	**Problem 1 Answer 12 Maintenance Dose** Rate Out = MDR = Vmax x Css / (Km + Css) MDR = 490 mg/d x 15 mg/L /(4 mg/L + 15 mg/L) = 386 mg/d = 386/0.95 mg/d = 407 mg/d = 400 mg/d Css = MDR *Km/(Vmax – MDR) If MDR > Vmax then steady state is not possible	
Slide 10	**Problem 2** On a dose of 400 mg/day her repeat phenytoin concentration was 12mg/L and Susan remains seizure free for 14 months. Then she re-presents to hospital with another seizure. She has a fever and when she wakes up she complains of dysuria and flank pain. She is febrile, tachycardic and her blood pressure is 80/60 [previously 110/70]; she has marked tenderness over her right kidney; her urine microscopy shows a large number of white blood cells and bacteria. Her predicted creatinine clearance is 100 mL/min. You decide to treat her with gentamicin.	

Slide 11	**Problem 2 Question 1 and 2** 1. What loading dose will you give her? The initial target concentration is 20 mg/L (peak after first dose) Volume of distribution is 0.25 L/kg in a normal size person. 2. What initial maintenance dose would you give her? The steady state target concentration is 3 mg/L (average concentration). Her creatinine clearance is 100 mL/min.	
Slide 12	**Problem 2 Answers 1 & 2** Loading Dose = Volume x Target Concentration = 0.25 L/kg x 70 kg x 20 mg/L = 17.5 L x 20 mg/L = 350 mg = 360 mg (4.5 mL of 80 mg/mL) Maintenance Dose Rate= Clearance x Target Concentration = [100 mL/min * 60/1000] x 3 mg/L = 6 L/h x 3 mg/L = 18 mg/h Maintenance Dose = 18 mg/h x 24 h = 432 mg per day = 400 mg per day (5 mL of 80 mg/mL)	Gentamicin is hydrophilic and does not distribute into fat cells as well as into non-fat tissues. The volume of distribution when body composition is normal is 0.25 L/kg. Susan's 'functional body weight' can be used to predict her volume of distribution. Creatinine clearance is a direct prediction of gentamicin clearance that is based on total body weight. It accounts for differences in body composition.
Slide 13	**Problem 2 Question 3** 2. Should you measure a gentamicin concentration? If so, when?	Because of unpredictable differences between people it is advisable to measure concentrations and predict the individual clearance of gentamicin. Recommended times are 1 h after the start of the first infusion dose (to allow distribution to tissues) and 8 h after the first dose (when concentration is still measurable).

Slide 14	**Problem 2 Question 3** 3b. The concentration ½ h after a ½ h infusion of 400 mg is 18 mg/L. The concentration 8 h after the start of the infusion is 1.1mg/L. What is the volume and clearance? The volume is 400 mg / (18 mg/L) or about 20 L The half-life is about 2 hours (18 -> 9 -> 4.5->2.25 -> 1.125) Recall that half-life=0.7 x volume/clearance so we can calculate clearance: Clearance = 0.7 x volume/half-life = 0.7 x 20 L / 2 h = 7 L/h MDR = 7 L/h x 3 mg/L = 21 mg/h = 504 mg per day = 480 mg (6 mL of 80 mg/mL)	3b: Half-life can be calculated more precisely from C(t2)=C(t1)*exp(-k*deltat) C(t2)/C(t1)=exp(-k*(t2-t1)) ln(C(t2)/C(t1))=-k*(t2-t1) k=ln(C(t1)/C(t2))/(t2-t1) = ln(18/1.1)/(8-1) = 0.399 h-1 half-life= 0.7/k = 1.75 h clearance= 0.7 x volume/half-life = volume x k = 20 L x 0.399 = 7.98 L/h = 8 L/h Maintenance dose rate = clearance x target = 8 L/h x 3 mg/L = 24 mg/h Maintenance dose = 24 mg/h x 24 h =576 mg per day = 560 mg per day (7 mL of 80 mg/mL)
Slide 15	**Problem 2 Question 4** 4. Susan remained on a dose of 400 mg/day. She has another seizure and blood tests are repeated. Her albumin has fallen to 20g/L [normal 40g/L] and the phenytoin concentration is 5mg/L. Why has the phenytoin concentration fallen? What changes should be made to her dose? Phenytoin is extensively bound to plasma proteins (mainly albumin). Without any change in unbound clearance a fall in albumin conc from 40 g/L to 20 g/L would be expected to have no effect on unbound concentration. But total concentration is expected to be halved. In this case the total concentration of 5 mg/L corresponds to 10 mg/L with normal albumin. This is expected to be effective. The occurrence of a further seizure could be due to another cause e.g. intercurrent illness. The measured concentration of 5 mg/L is not a justification by itself to increase the dose.	