New drugs – necessity for therapeutic drug monitoring

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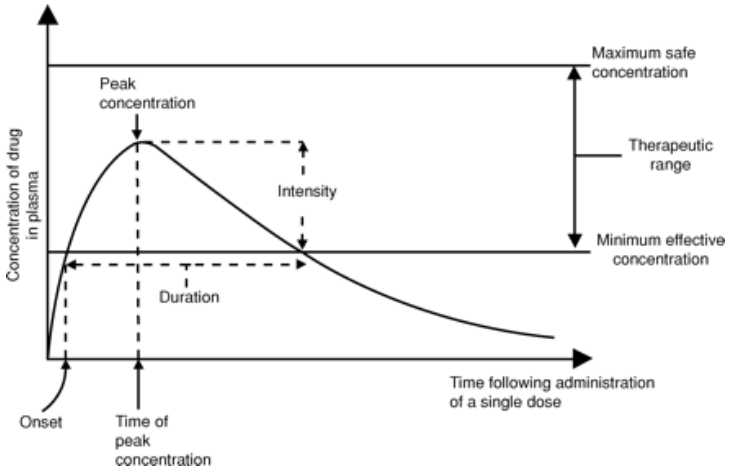
Drugs suitable for TDM

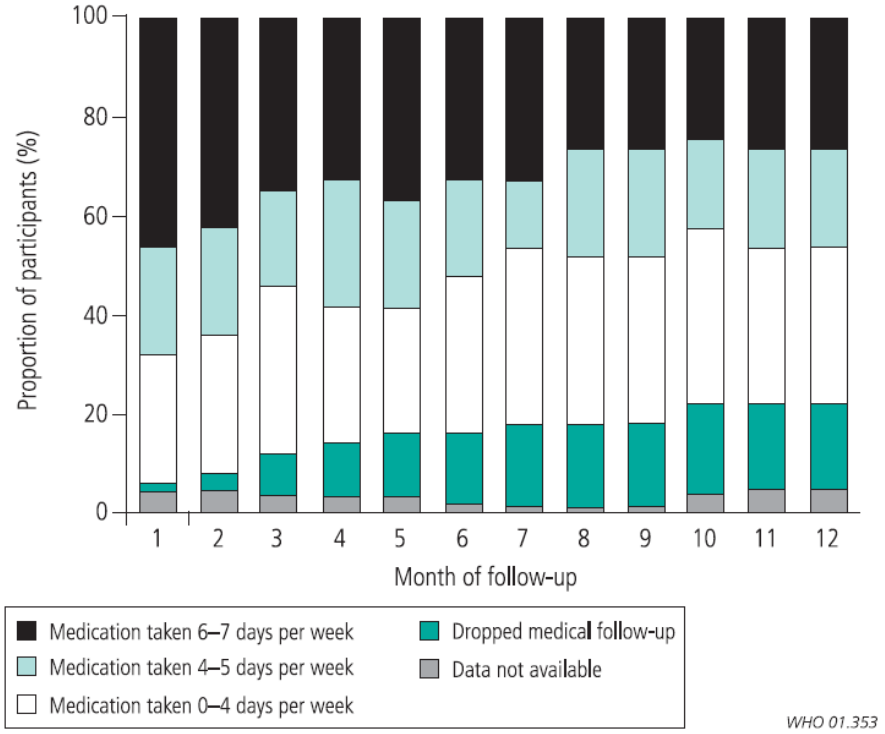
- Narrow therapeutic range
- Clear relationship between plasma or blood concentration and effect and/or toxicity
- Pharmacological effect clinically not well determinable
- Examples
  - theophylline
  - digoxin
  - lithium
  - immunosuppressants, e.g. cyclosporin, tacrolimus
  - aminoglycosides, vancomycin, daptomycin
  - antimycotics
  - antiepileptics



TDM - indications

- Therapy control - calculation of individual kinetics
- Dose adjustment
- Insufficient success of drug therapy despite therapeutic dose
- Toxicity despite therapeutic dose
- Possible drug interactions
- Control of compliance

Compliance with antihypertensive treatment



Bulletin of the World Health Organization 2002;80:33-39

TDM – assessment of the plasma concentrations

Reference range
- Thresholds of effect and toxicity in the population

Therapeutic range
- Dose or concentration range which is effective and safe for individual patients

Measurement of the drug concentration in body fluids
- serum
- plasma
- blood
- saliva

AND

Correlation and interpretation in connection with the clinical picture of the patient

Pharmacological properties of antiepileptics

Substance	Protein binding (%)	Half-life (h)	Q_0	Maintenance dose (mg/kg/d)	Reference range	
Carbamazepine	72-76	20	>0.9	9	4-12 mg/mL	16-48 μmol/L
Clonazepam	80	30	>0.9	0.15	Not established	Not established
Ethosuximide	0	40	0.8	30	50-100 mg/mL	350-700 μmol/L
Gabapentin	0	5	0.1	10-30	Not established	Not established
Lamotrigine	56	24	0.9	4-8	1-4 mg/mL	12-55 μmol/L
Levetiracetam	10	7	0.7	15-40	Not established	Not established
Oxcarbazepine	40 (MHD)	10 (MHD)	>0.9	8-20	15-35 mg/L	50-110 μmol/L
Phenobarbital	60	80	>0.9	2-3	15-40 mg/mL	60-160 μmol/L
Phenytoin	90	20-30	>0.9	6	10-20 mg/mL	40-80 μmol/L
Topiramate	15	21	0.8	3-6	Not established	Not established
Valproate	90	15	>0.9	15-20	50-100 mg/mL	300-600 μmol/L

Perampanel

Pharmacology

•Blocks ionotropic AMPA-glutamate receptors non-competitively

Indication

•Add-on treatment for partial seizures

Dosage

•4 mg to 12 mg/day in the evening – titration

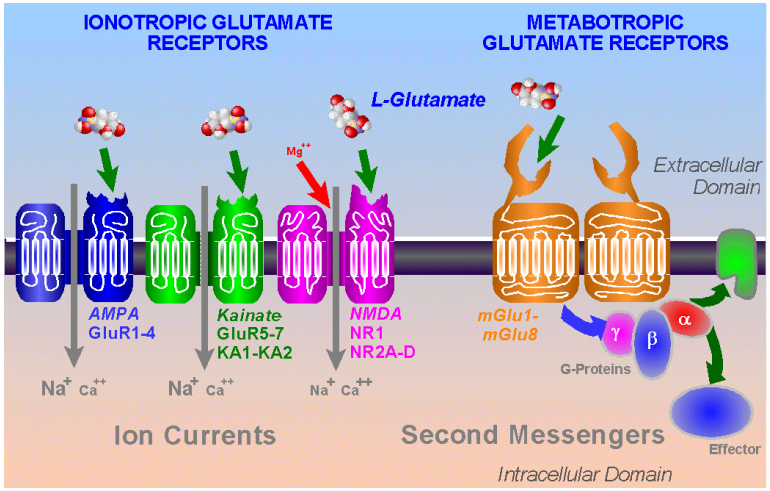
Pharmacokinetics

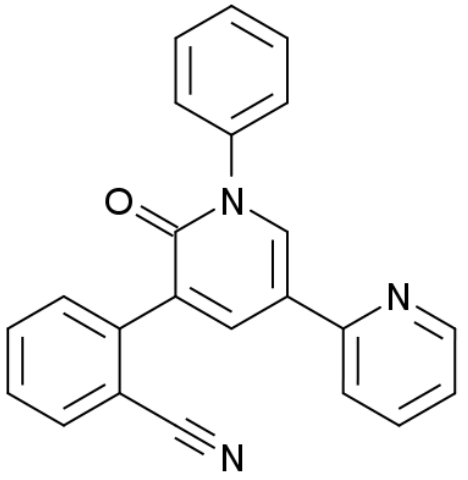
•Bioavailability ≈100%, protein binding 95%, V_d ≈40L, half-life ≈100h

•Multiple ring hydroxylations by CYP3A4

•Glucuronidation and renal (30%) and biliary (70%) elimination

•Interactions with CYP inhibitors and inducers





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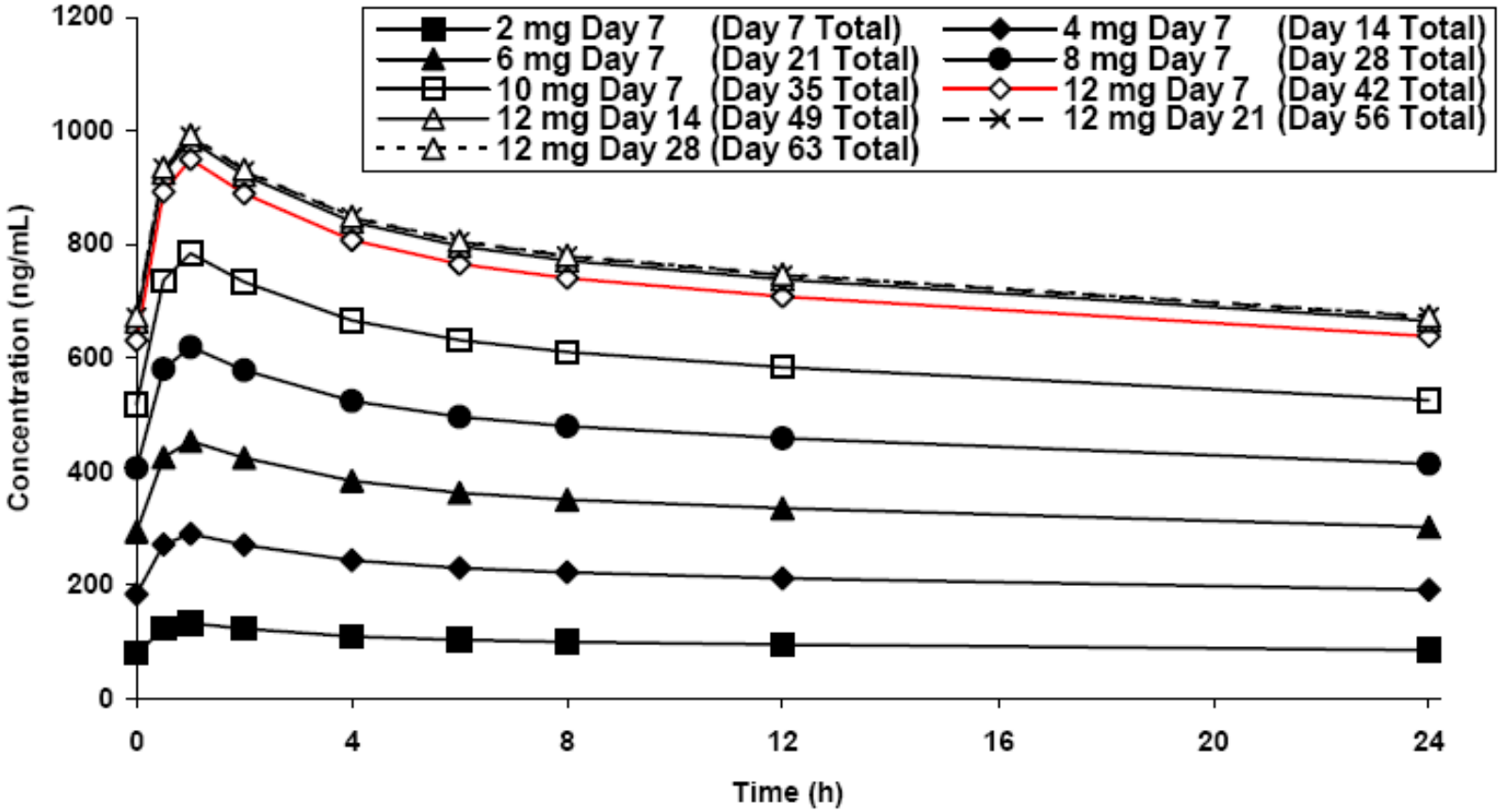
Perampanel – dose-dependent pharmacokinetics



- Kinetics is dose-dependent
- Changes in the EEG associated with perampanel are also dose-dependent

Perampanel – effect and safety

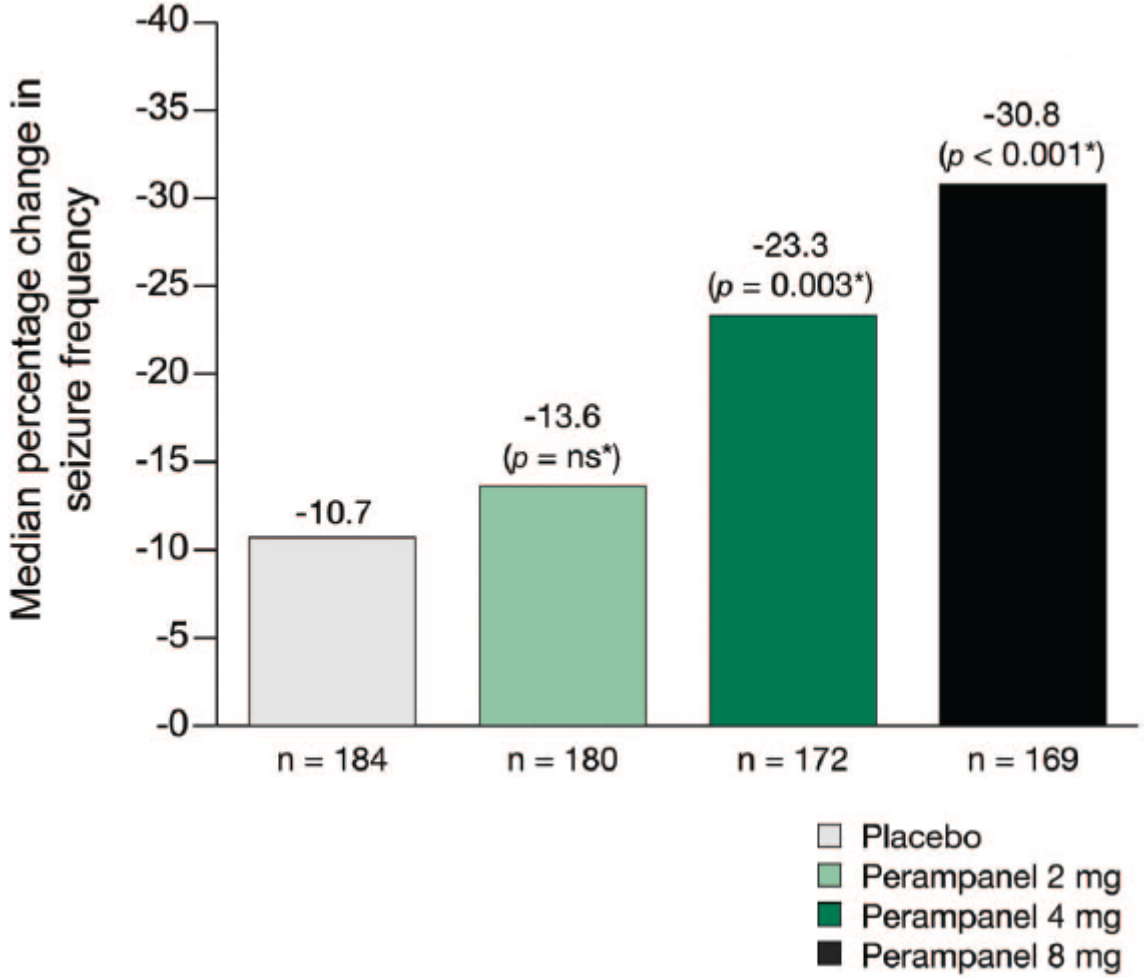
- Double-blind, placebo-controlled trial
- 706 Patients treated with 1-3 antiepeliptics and with ≥1 seizure per week
- Add-on treatment with perampanel 2, 4, and 8 mg/day or placebo following a 6-week baseline phase
- Treatment for 13 weeks
- Primary endpoints: median percent change in seizure frequency and 50% responder rate

		Perampanel		
	Placebo (n = 195)	2 mg/day (n = 190)	4 mg/day (n = 172)	8 mg/day (n = 169)
Mean age (SD), y	33.4 (12.6)	33.9 (13.6)	33.6 (12.2)	34.6 (12.9)
Female gender, n (%)	90 (48.6)	95 (52.9)	84 (48.8)	92 (54.4)
Race, n (%)				
Asian, non-Chinese	34 (18.4)	35 (19.4)	37 (21.5)	28 (16.6)
Chinese	31 (16.8)	25 (13.9)	29 (16.9)	25 (14.8)
Caucasian	119 (64.3)	119 (66.1)	105 (61.0)	116 (68.6)
Other	1 (<1)	1 (<1)	1 (<1)	0
Mean BMI (SD), kg/m^2	23.9 (4.7)	23.5 (4.6)[a]	24.5 (4.7)	24.4 (4.9)
Mean time since epilepsy diagnosis (SD), mo	209.9 (128.1)	232.4 (145.2)	236.9 (145.3)[b]	239.4 (142.9)[c]
Seizure type, n (%)				
Simple partial without motor signs	52 (28.1)	53 (29.4)	48 (27.9)	57 (33.7)
Simple partial with motor signs	55 (29.7)	53 (29.4)	54 (31.4)	51 (30.2)
Complex partial	155 (83.8)	153 (85.0)	147 (85.5)	138 (81.7)
Complex partial with secondary generalization	136 (73.5)	115 (63.9)	119 (69.2)	117 (69.2)
Seizure frequency per 28 days during the prerandomization phase, median (min, max)[d]	9.3 (3.3, 569.1)	10.1 (3.2, 429.6)	10.0 (2.9, 4503.9)	10.9 (3.4, 723.2)
No. concomitant AEDs at baseline, n (%)				
1	28 (15.1)	30 (16.7)	19 (11.0)	27 (16.0)
2	90 (48.6)	80 (44.4)	88 (51.2)	82 (48.5)
3	67 (36.2)	70 (38.9)	65 (37.8)	60 (35.5)
Perampanel inducing AED[e]	106 (57.3)	105 (58.3)	93 (54.1)	93 (55.0)
Most common concomitant AEDs[f]				
Valproic acid	77 (41.6)	80 (44.4)	75 (43.6)	63 (37.3)
Lamotrigine	57 (30.8)	56 (31.1)	68 (39.5)	66 (39.1)
Carbamazepine	64 (34.6)	58 (32.2)	56 (32.6)	53 (31.4)
Levetiracetam	44 (23.8)	48 (26.7)	45 (26.2)	45 (26.6)
Topiramate	51 (27.6)	38 (21.1)	40 (23.3)	40 (23.7)
Oxcarbazepine	36 (19.5)	35 (19.4)	25 (14.5)	34 (20.1)
Clobazam	16 (8.6)	17 (9.4)	20 (11.6)	17 (10.1)

Neurology 2012;78:1408–1415

Perampanel – effect on seizure frequency

- Clear dose-dependent effect is visible
- Since pharmacokinetics is also dose-dependent, it can be assumed that effect is dependent on plasma and target concentration
- Formal proof for this assumption is lacking, however



Neurology 2012;78:1408–1415

Perampanel – adverse events

	Patients, n (%)			
	Placebo (n = 185)	2 mg/day (n = 180)	4 mg/day (n = 172)	8 mg/day (n = 169)
AnyTEAE	101 (54.6)	111 (61.7)	111 (64.5)	121 (71.6)
Any treatment-related TEAE	59 (31.9)	67 (37.2)	77 (44.8)	96 (56.8)
Any TEAE leading to discontinuation[a]	7 (3.8)	12 (6.7)	5 (2.9)	12 (7.1)
Any TEAE leading to dose reduction/ interruption	6 (3.2)	3 (1.7)	12 (7.0)	29 (17.2)
Any serious TEAE	9 (4.9)	6 (3.3)	6 (3.5)	6 (3.6)
TEAEs in ≥5% (any treatment group)				
Dizziness	18 (9.7)	18 (10.0)	28 (16.3)	45 (26.6)
Somnolence	12 (6.5)	22 (12.2)	16 (9.3)	27 (16.0)
Headache	16 (8.6)	16 (8.9)	19 (11.0)	18 (10.7)
Fatigue	5 (2.7)	8 (4.4)	13 (7.6)	9 (5.3)
Upper respiratory tract infection	5 (2.7)	11 (6.1)	6 (3.5)	3 (1.8)
Nasopharyngitis	3 (1.6)	7 (3.9)	9 (5.2)	3 (1.8)
Gait disturbance	2 (1.1)	1 (<1)	2 (1.2)	9 (5.3)

Abbreviation: TEAE = treatment-emergent adverse event.
[a] Study/treatment discontinuation.

Neurology 2012;78:1408–1415

TDM for perampanel

Problematic drug

- Clinical effect difficult to establish for individual patients
- Long half-life, drug interactions, high protein binding

Reference range

- So far not established
- Large clinical study assessing free and total plasma concentrations and therapeutic effect and toxicity
- Population pharmacokinetic analysis

Therapeutic range

- Has to be established for every patient treated
- TDM helpful in certain situations

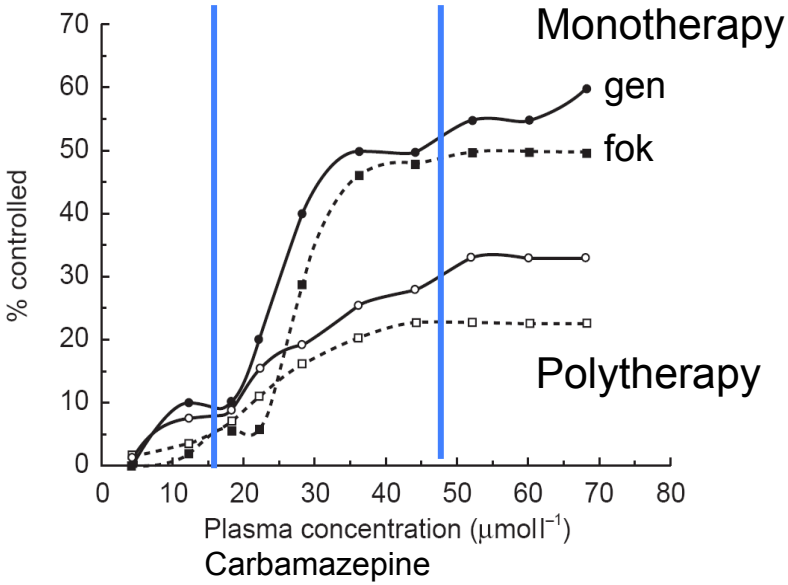
Determination of reference range

Conventional determination

- *Lower threshold*: proofed efficacy
- *Upper threshold:* starting toxicity
- *Consequence*: thresholds not well defined, overlap

Newer methods

- Cumulative percentage of patients as a function of plasma concentration who have no seizure during 1 year



Br J Clin Pharmacol 2001;52:11s-20s

Determination of reference range - phenytoin

Relationship between kinetics and dynamics

- Best established pk-pd relationship for all antiepileptics

Determination of effect threshold (Buchthal, 1960)

- 80 patients with at least 1 grand-mal seizure per week treated with phenobarbital and/or phenytoin
- 6 of 24 patients with phenytoin <10mg/L (25%) were seizure-free
- 21 of 27 patients with serum phenytoin >10 mg/L (77%) were seizure-free

Determination of toxicity threshold (Kutt, 1964)

- Nystagmus in all patients with serum phenytoin >20 mg/L
- Ataxia starting in patients with serum phenytoin >30mg/L (Lund, 1974)
- Ataxia in all patients with serum phenytoin >40 mg/L

Aminoglycosides - pharmacology

Kinetics

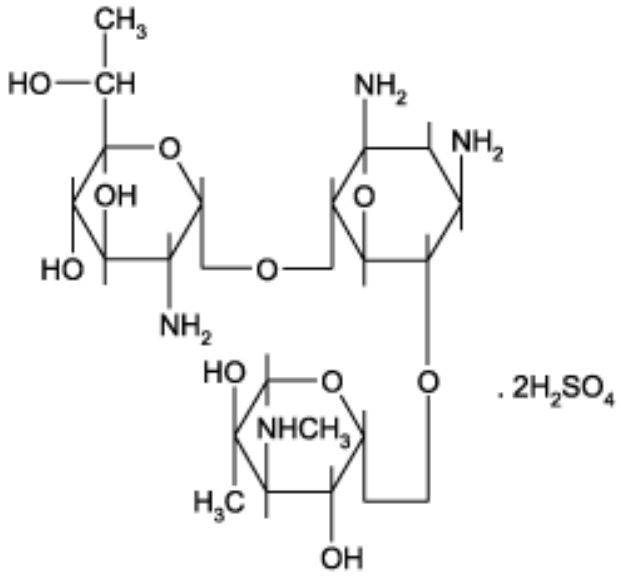
- Low oral bioavailability
- V_d 0.3 L/kg, bad tissue penetration
- Renal elimination, half-life 2-3 h

Administration

- Intravenously during 30 min
- Peak: 30 min after stop of infusion

Tretament regimens

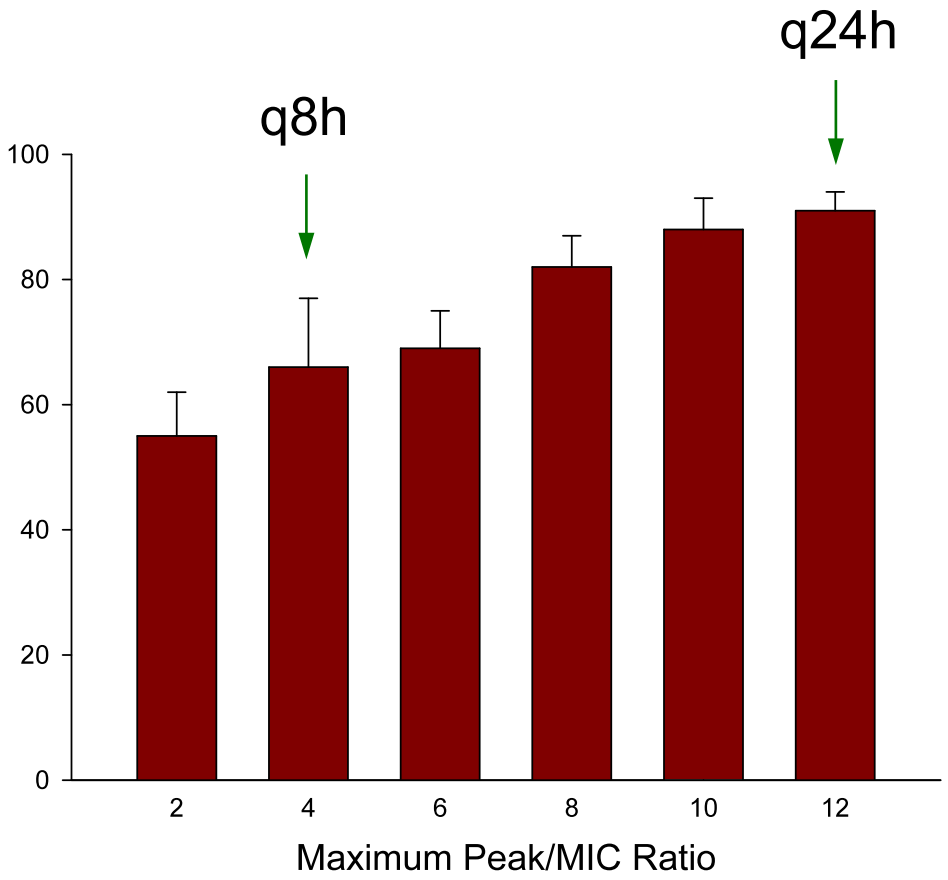
- 3 times daily
- Once daily



Gentamycin

Aminoglycosides - principles of therapy

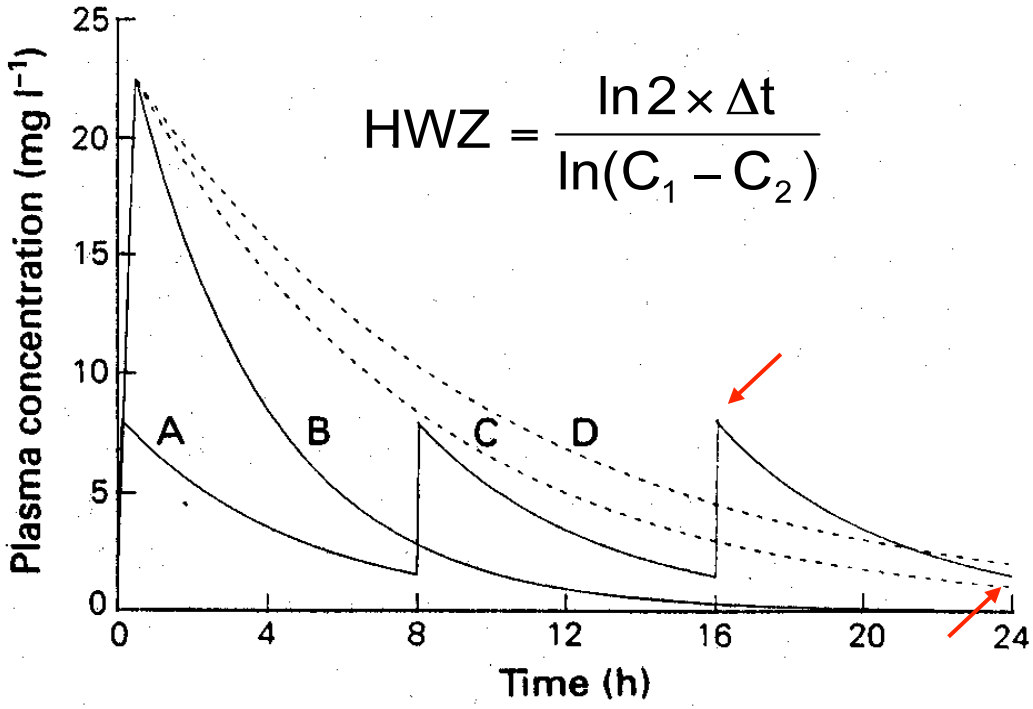
- Effect correlates with peak-concentration
- Toxicity correlates with total exposure (sum of all AUCs)
- Maximal effect at constant toxicity with high peaks and maintained AUC
- Once daily may be bether than three times daily



J Infect Dis 1987;155:93-9

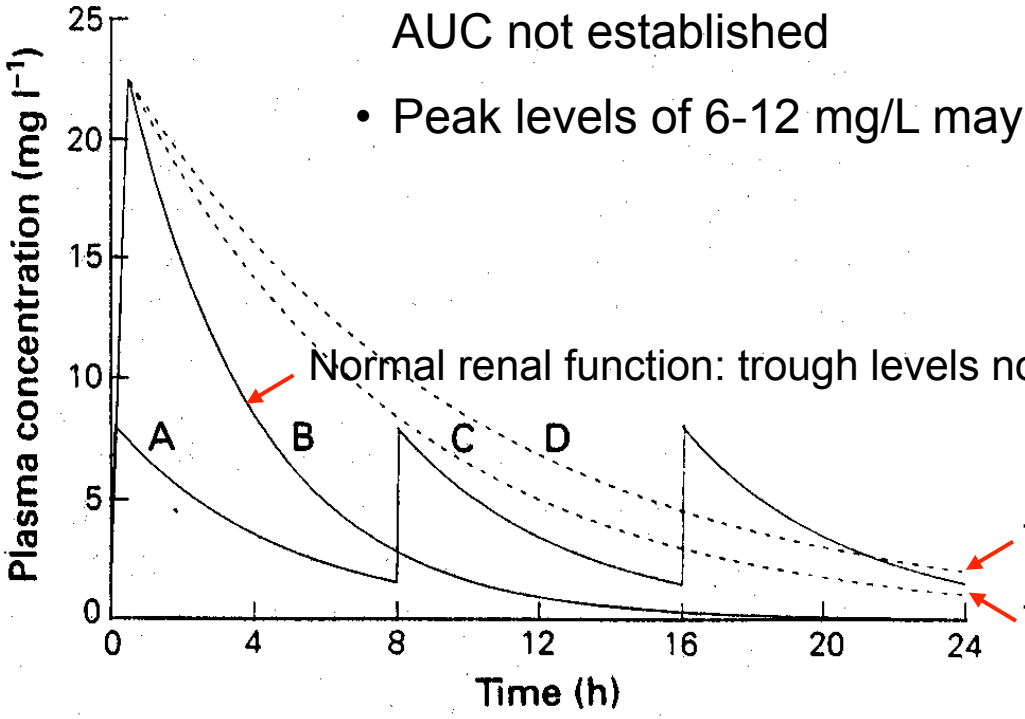
Aminoglycoside monitoring 3 times daily administration

- Determination of peak and trough levels
- Established thresholds for peak (6 – 12 mg/L) and trough levels (<2 mg/L)
- Adjust dose or application time
- Monitoring recommended
  - Impaired renal function
  - Duration of therapy >3 days



Administration once daily

- Dose: 5 mg/kg for gentamycin, netilmycin, tobramycin; 15 mg/kg amikacin
- Normal renal function: trough levels <<2 mg/L → conventional TDM is not sensitive enough
- Trough levels of 1 mg/L or 2 mg/L are wrong; correlation with AUC not established
- Peak levels of 6-12 mg/L may be too low



Dose adjustment via estimation of AUC

Principle

- Achieve the same AUC as with 3 times daily administration

Procedure

- Determine the serum concentration approximately 2 and 6 hours after stop of infusion (note exact time points)
- Calculate C_{max}, AUC, V_d and half-life
- Adjust dose according to C_{max} and AUC

Assumptions

- Linear kinetics
- AUC can be estimated by two serum concentrations

Br J Clin Pharmacol 1995;39:605-9

Dose adjustment for once daily tobramycin using the AUC method

Patient	NN	DOB
date of PK sampling		
Aminoglycoside	Tobra	

AUC calculator (v2010-01mh)				*date*	*2010-03-31*
	input variables		***output***		
tmax (=end of infusion)	0.5	h	t/2=	5.3	h
c1	14.8	mg/L	ke=	0.130	
t1(after start of infusion)	2	h	cmax	18.0	mg/L
c2	8.8	mg/L	c24h	0.8	mg/L
t2(after start of infusion)	6	h	AUC(tmax-24h)	132	mg/L*h
body weight	80	kg	Vd	0.42	L/kg
AUC(0-24h) target	100		**AUC(0-24h)**	**140**	**mg/L*h**
dose current	600	mg/24h	**dose new**	**427**	**mg/24h**
AUC target (Genta, Tobra)	*70-100*				
AUC target (Amikacin)	*200-240*	*Amikacin (2-3x Genta)*			

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Conclusions

- To establish TDM for new drugs labor intensive and complicated
  - Reliable quantification
  - Reference range and therapeutic range
- TDM procedures are not static, they may change with alterations in drug application (aminoglycosides) and new clinical studies (digoxin)
- Good collaboration between clinical chemists, clinical pharmacologists and clinicians is absolutely mandatory