IV formulations of antiepileptic drugs

Epilepsy Society of Thailand, July 22nd 2010
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- **Introduction**
- **Pharmacological and pharmacokinetic aspects**
  - **Solubility and pH**
  - **Speed of action**
  - **Problems of accumulation in IV therapy**
- **Indications for IV AED therapy**
  - **IV AED therapy in acute seizures**
  - **IV AED therapy in status epilepticus**
  - **IV AEDs as temporary replacement for oral therapy**

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Introduction

- Most AEDs are given in oral formulations in chronic therapy
- IV formulations needed though in specific situations
- Physical characteristics of the drug influence whether an IV formulation is possible
- Pharmacokinetics of IV formulations very different from those of oral preparations. Thus, drug handling/side effects/characteristics differ in IV and oral preparations
- Pharmacodynamic properties of a drug (efficacy etc) however will not vary at equivalent doses

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Physical properties of a drug for IV formulation

- **Solubility**
  - Problem for some AEDs (eg carbamazepine)
  - Solubility depends on intrinsic chemistry, pH of environment, pK_a

    $S_{tot} = S_{HA}(1 + 10(pH-pK_a))$, eg:
    - Phenobarbital: pK_a 7.9, target pH 9, intrinsic solubility 7mg/mL
    - Amobarbital: pK_a 7.9, target pH 9, intrinsic solubility 1.2mg/mL
    - Therefore, phenobarbital can be made into soluble formulation but not amobarbital
  - Co-solvency – enhance the solubility of non-polar substances usually by containing hydrogen and non-hydrogen bonds. An example is propylene glycol to dissolve phenytoin which has very low instrinsic solubility (0.02 mg/mL)
- **pH**
  - Ionisation of a compound depends on pH.
  - Some compounds have different forms soluble at different pH

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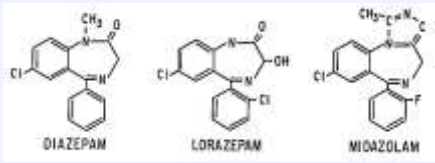
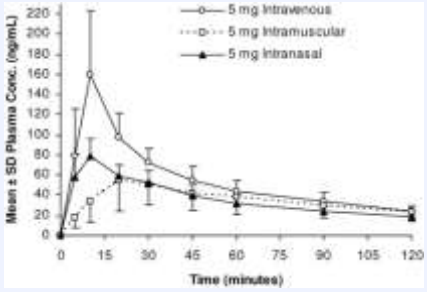
Solubility properties can be utilised in IV formulations for epilepsy

- **Midazolam**
- **The only water soluble benzodiazepine – but low aqueous solubility and must be buffered at pH 3 to go into solution**
- **Solubility increased by cyclodextrin complexation**
- **Water soluble for IM injection. However, in circulation, the pH change results in a change in configuration – closure of the diazepine ring – and conferring lipid solubility so rapid entry into the brain**
- **This is an useful property**
- **The drug Can thus be given as IV, IM, IN or buccal formulation**





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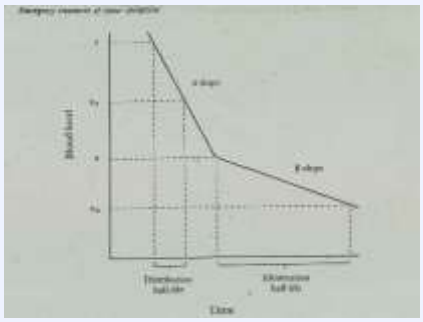
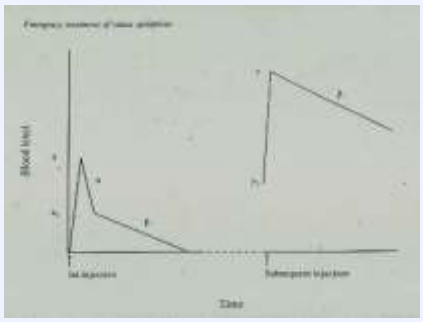
Principles of IV Pharmacokinetics – danger of drug accumulation

Fat soluble drugs with long half lives (eg barbiturates) have high affinities for fat, large volumes of distribution and relatively low hepatic clearances → tissue accumulation.





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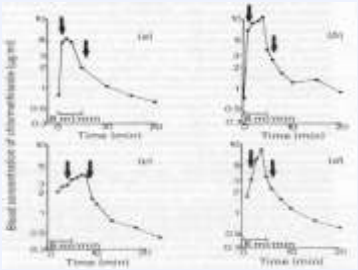
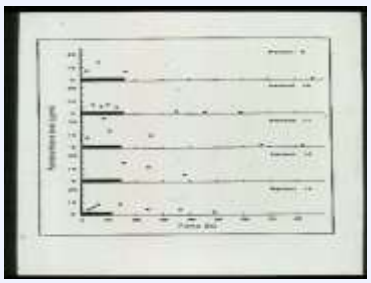
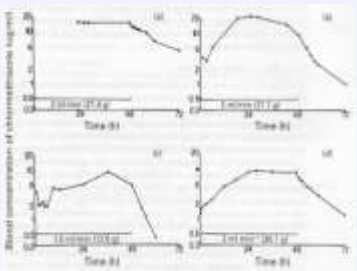
Examples of AED accumulation

Chlormethiazole used in status Epilepticus



Pentobarbital used in status epilepticus





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Key feature of IV AED usage: Speed of action

- **The risks of IV therapy are only worth taking if rapid speed of action is required**
- **Lipid soluble drugs are not well absorbed by IM injection**
  - Only two commonly used AEDs are absorbed rapidly IM: midazolam phenobarbital
- **Other methods such as rectal, intranasal and buccal instillation are alternatives to IM/IV**
- **For very lipid soluble drugs, the rate of infusion is important**
  eg Diazepam – max rate is 5mg/min
- **For less lipid soluble drugs, the rate of infusion is unimportant**
  eg Lorazepam

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Indications for IV formulations

- **Acute emergency therapy for a seizure**
  Usual therapy → Benzodiazepines
- **Status epilepticus**
  Usual therapy → Benzodiazepines, phenytoin, phenobarbital, valproate, levetiracetam and anaesthetic drugs
- **When oral therapy has to be temporarily discontinued**
  Drugs with an IV formulation include: valproate, levetiracetam, lacosamide, phenytoin, phenobarbital

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Acute emergency therapy for a seizure

- **Key points**
  - **Short seizures do not carry risk of brain damage**
  - **Drug treatment is not usually needed to terminate a normal seizures**
  - **Prophylaxis is possible in repetitive seizures / seizure clusters**
  - **A prolonged seizure carries the risk of evolving to status epilepticus and status epilepticus carries risks of brain damage**

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Key points in emergency drug treatment of seizures

- Drug treatment needed therefore only for long convulsive seizures (>5 mins or longer than the habitual seizure for any individual), or where seizures are likely to be repetitive
- Drugs needed which act RAPIDLY – so conventional oral therapy or intramuscular therapy ineffective
- Difference if in-hospital or out-of-hospital – due to the risk of drug induced cardio-respiratory collapse
- Careful observation of any person given emergency therapy is vital
- As well as drug therapy, general and first aid measures important

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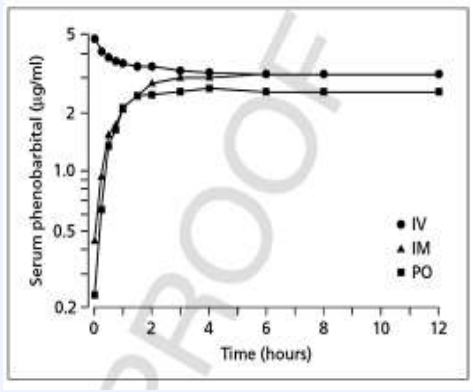
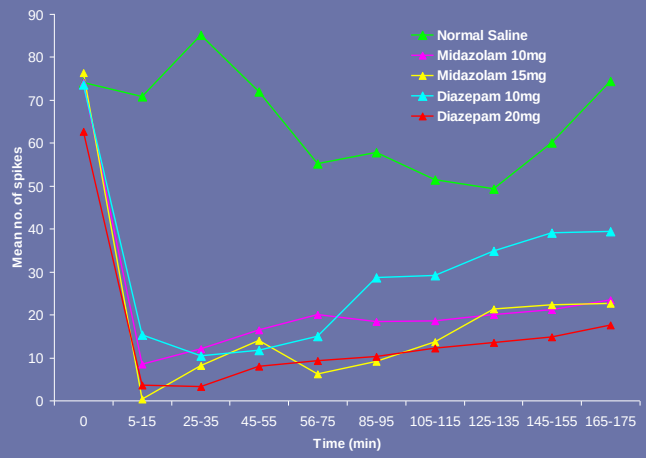
Rapidity of onset of action

- Rapid drug action is a fundamental requirement
- Most drugs are too slowly active by oral or IM injection and so require to be given by IV injection
- Only midazolam of the currently available AEDs is absorbed fast enough by IM route
- Diazepam (in solution not by suppository) and other drugs can be given rectally



Rapidity of action - IM midazolam compared to IV diazepam and placebo



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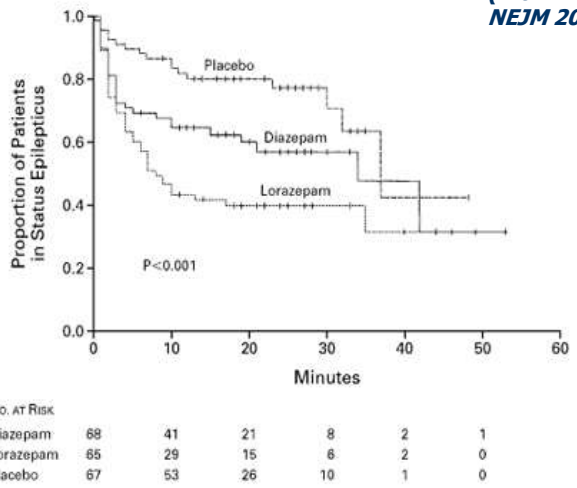
Acute IV treatment of prolonged seizures

- **Lorazepam 4 mg (IV bolus; rate not critical), can be repeated after 10 mins if no response**
- **Diazepam 10-20mgs (IV bolus; not more than 5mg/min; can be repeated after 10 mins if not response)**
- **In-hospital IV therapy in early SE**
  - **Lorazepam vs diazepam – 3 RCTs (n=289)**
  - **Lorazepam vs placebo – 1 RCT (n=137)**
  - **Lorazepam vs diazepam/phenytoin – 1 RCT (n=192)**
  - **Lorazepam vs phenobarbital – 1 RCT (n=188)**
  - **Lorazepam vs phenytoin – 1 RCT (n=198)**
  - **Midazolam vs lorazepam – 1 RCT (n=27)**
  - **Midazolam vs diazepam – 1 RCT (n=40)**
  - **Diazepam vs placebo – 1 RCT (n=139)**
- **Conclusions (10 RCTs):**
  1. **DZP and LZP are better than placebo**
  2. **LZP is better than phenytoin**
  3. **LZP may be better than DZP (2 out of 3 measures)**

RCT of Lorazepam, diazepam and placebo

- **IV emergency treatment: Study from San Francisco; 205 adult patients randomised to lorazepam 2mg, diazepam 5mg or placebo'**

(From : Alldredge et al NEJM 2001 345: 631)



No. at Risk						
Diazepam	68	41	21	8	2	1
Lorazepam	65	29	15	6	2	0
Placebo	67	53	26	10	1	0

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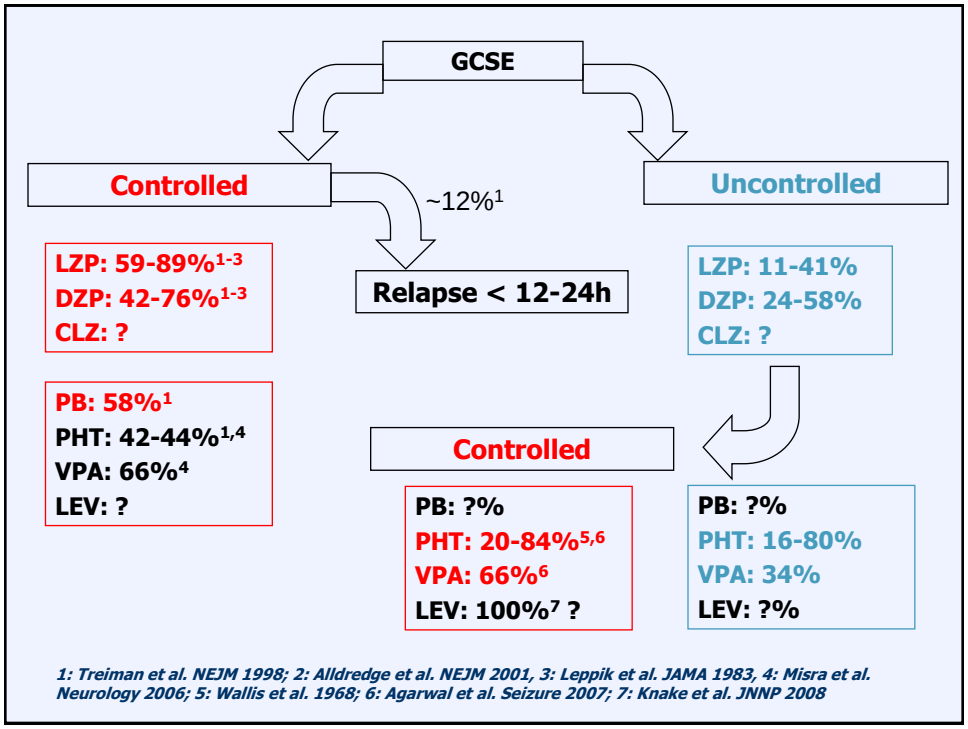
Stage 2 – established SE: post-BZD AED therapy

- **RCTs in established SE:**
  - **Diazepam/phenytoin vs phenobarbital - 2 RCTs (n=222)**
  - **Phenytoin vs phenobarbital - 1 RCT (n= 186)**
  - **Diazepam/phenytoin vs phenytoin - 1 RCT (n= 196)**

- **Conclusions (4 RCTs):**
  1. **No significant differences**
  2. **trend to favour DZP/PHT over PB**
  3. **trend to favour PB over PHT**



1: Treiman et al. NEJM 1998; 2: Alldredge et al. NEJM 2001, 3: Leppik et al. JAMA 1983, 4: Misra et al. Neurology 2006; 5: Wallis et al. 1968; 6: Agarwal et al. Seizure 2007; 7: Knake et al. JNNP 2008

New drugs in treatment at the stage of established TCSE – Valproate

- 20 published studies (7 prospective)
- 533 children and adults
- One randomised controlled study showed valproate to be superior to phenytoin
- >75% seizure control within 20 minutes of valproate infusion
- Dose 15-45mg/kg
- Cardiovascular toxicity much less than with phenytoin or phenobarbital (hypotension, arrythmia etc)
- Theoretical risk of valproate encephalopathy, hyperammonaemia, acute coagulation defects etc.
- Further clinical experience required, but valproate has the promise to become the drug of choice in established SE

IV valproate compared to oral valproate

- **Pharmacokinetics well studied**
  - Bioequivalence with similar pharmacokinetic parameters

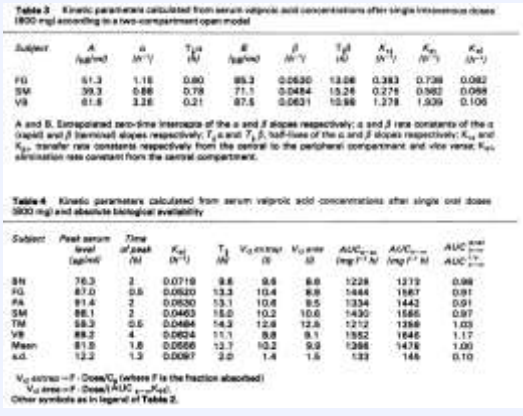


Table 3 Kinetic parameters calculated from serum valproic acid concentrations after single intravenous doses (800 mg) according to a two-compartment open model

Subject	A (μg/ml)	α (h⁻¹)	$T_{1/2}\alpha$ (h)	B (μg/ml)	β (h⁻¹)	$T_{1/2}\beta$ (h)	K_{12} (h⁻¹)	K_{21} (h⁻¹)	K_{el} (h⁻¹)
FG	61.3	1.16	0.60	85.3	0.0630	13.08	0.383	0.738	0.082
SM	39.3	0.88	0.78	71.1	0.0484	15.26	0.275	0.582	0.068
VB	61.8	3.28	0.21	87.5	0.0631	10.98	1.278	1.939	0.106

A and B, Extrapolated zero-time intercepts of the α and β slopes respectively; α and β rate constants of the α (rapid) and β (terminal) slopes respectively; $T_{1/2}\alpha$ and $T_{1/2}\beta$, half-lives of the α and β slopes respectively; K_{12} and K_{21}, transfer rate constants respectively from the central to the peripheral compartment and vice versa; K_{el}, elimination rate constant from the central compartment.

Table 4 Kinetic parameters calculated from serum valproic acid concentrations after single oral doses (800 mg) and absolute biological availability

Subject	Peak serum level (μg/ml)	Time of peak (h)	K_{el} (h⁻¹)	$T_{1/2}$ (h)	$V_{d\,extrap}$ (l)	$V_{d\,area}$ (l)	$AUC_{0-\infty}$ (mg l⁻¹ h)	$AUC'_{0-\infty}$ (mg l⁻¹ h)	$\frac{AUC^{oral}_{0-\infty}}{AUC^{i.v.}_{0-\infty}}$
SN	76.3	2	0.0719	9.6	9.6	9.6	1228	1213	0.99
FG	87.0	0.5	0.0520	13.3	10.4	9.9	1464	1467	0.91
FA	91.4	2	0.0530	13.1	10.6	9.5	1334	1442	0.91
SM	88.1	2	0.0463	15.0	10.2	10.6	1430	1585	0.97
TM	88.3	0.5	0.0484	14.3	12.8	12.6	1212	1398	1.03
VB	89.2	4	0.0624	11.1	8.8	8.1	1552	1646	1.17
Mean	81.9	1.8	0.0566	12.7	10.2	9.9	1396	1478	1.00
s.d.	12.2	1.3	0.0097	3.0	1.4	1.5	133	146	0.10

$V_{d\,extrap} = F \cdot Dose/C_0$ (where F is the fraction absorbed)
$V_{d\,area} = F \cdot Dose/(AUC_{0-\infty} \cdot K_{el})$
Other symbols as in legend of Table 2.

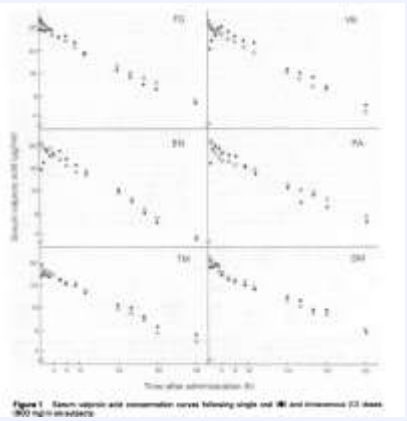


Figure 1 Serum valproic acid concentration curves following single oral (●) and intravenous (○) doses (800 mg) in six subjects

(From: Perucca et al: Br. J. clin. Pharmac. (1978), 5, 313-318)

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New drugs in treatment at the stage of established TCSE – Valproate

- **Study in Thai children** ***(Visudtibhan et al Brain and Development 2010 in press; doi doi:10.1016/j.braindev.2010.04.003)***

11 children (age 1-15 years) – pharmacokinetics studied at dose of 15-20 mg/kg

Table 2
Summary of pharmacokinetic parameters.

	K_e (h-1)	$t_{½}$ (h)	V_d (L)	V_d/kg (L/kg)	CL (L/h)	CL/kg (L/h/kg)
Median	0.07	9.51	6.97	0.20	0.69	0.02
Minimum	0.03	4.39	2.38	0.15	0.16	0.01
Maximum	0.16	24.23	19.37	0.53	2.10	0.05

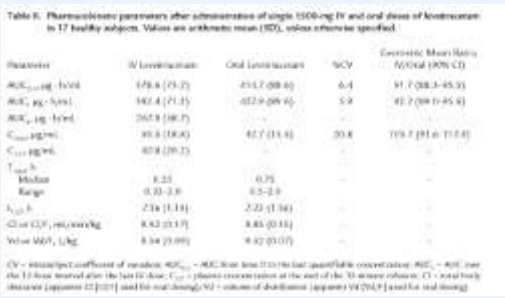
V_d, volume of distribution; K_e, elimination rate constant; CL, clearance; $t_{1/2}$, half-life; kg, body weight in kilogram.

New drugs in treatment at the stage of established TCSE – levetiracetam (currently an unlicensed indication)

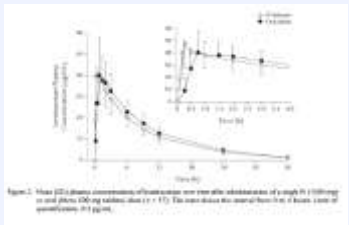
- Intravenous formulation now licensed for replacement therapy,
- Pharmacokinetics established (Stockis et al 2007)
  - Cmax and AUC equivalent to oral
  - Bioequivalence
  - Safety and tolerability equivalent
- Commonest side effects dizziness and somnolence
- Dose 30mg/kg/day dose (equiv 1500mg IV adults)
- Case reports and small open series show excellent efficacy
- 20 abstracts presented at London colloquium presenting efficacy data in 128 patients with SE
  - Efficacy in TCSE, NCSE, CPSE, focal SE, myoclonic SE symptomatic, idiopathic, de novo SE, SE in chronic ep, children, adults, acute brain injury, tumours
  - Dose 500-2000mg IV bolus (9000mg/day in one report)
  - No effect on cardiovascular or respiratory function
  - No adverse effects at infusion site
- Very promising profile – now need for an RCT SE

IV antiepileptic drugs – given as replacement for oral therapy: example of levetiracetam

- Bioequivalence established (Stockis et al 2007; Ramael 2006)
  - Area under curve (AUC)
  - C_{max}
  - Half life (plasma)
  - Plasma clearance
  - Volume of distribution ($Vol_{d)}$



  - IV and oral Kinetics



(From: Ramael et al: Clinical Therapeutics 28:734-743 2006)

IV antiepileptic drugs – Levetiracetam IV tolerability

- **IV levetiracetam at 2000-4000mg given over 5 and 15 mins compared to placebo:**

TABLE 2. *Number (percentage) of subjects with study drug-related, treatment-emergent adverse events, intent-to-treat population*

	Levetiracetam intravenous infusion							
		15 min			5 min			
System organ class/ preferred term	Placebo (n = 12)	2,000 mg (n = 6)	3,000 mg (n = 6)	4,000 mg (n = 6)	1,500 mg (n = 6)	2,000 mg (n = 6)	2,500 mg (n = 6)	All levetiracetam doses (n = 36)
Any drug-related adverse events	1 (8.3)	4 (66.7)	5 (83.3)	6 (100)	5 (83.3)	3 (50)	6 (100)	29 (80.6)
Nervous system	1 (8.3)	3 (50)	4 (66.7)	6 (100)	5 (83.3)	3 (50)	6 (100)	27 (75)
Balance disorder	0	0	0	0	1 (16.7)	0	0	1 (2.8)
Dizziness	0	2 (33.3)	1 (16.7)	5 (83.3)	4 (66.7)	2 (33.3)	5 (83.3)	19 (52.8)
Dizziness postural	0	0	3 (50)	1 (16.7)	1 (16.7)	2 (33.3)	0	7 (19.4)
Dysgeusia	1 (8.3)	0	0	0	0	0	0	0
Headache	0	0	0	1 (16.7)	0	1 (16.7)	1 (16.7)	3 (8.3)
Somnolence	0	1 (16.7)	1 (16.7)	2 (33.3)	2 (33.3)	3 (50)	3 (50)	12 (33.3)
Eye, blurred vision	0	0	0	0	0	0	1 (16.7)	1 (2.8)
GI disorders	0	0	0	1 (16.7)	0	1 (16.7)	0	2 (5.6)
Dry mouth	0	0	0	0	0	1 (16.7)	0	1 (2.8)
Nausea	0	0	0	1 (16.7)	0	0	0	1 (2.8)
Vomiting	0	0	0	1 (16.7)	0	0	0	1 (2.8)
General disorders	0	1 (16.7)	2 (33.3)	0	0	1 (16.7)	1 (16.7)	5 (13.9)
Fatigue	0	1 (16.7)	2 (33.3)	0	0	0	1 (16.7)	4 (11.1)
Feeling drunk	0	0	1 (16.7)	0	0	0	0	1 (2.8)
Thirst	0	0	0	0	0	1 (16.7)	0	1 (2.8)

GI, gastrointestinal.

(Ramael et al: Epilepsia, 47(7):1128–1135, 2006)

IV Levetiracetam given for 4 days as replacement therapy

- **IV levetiracetam in 24 patients (19 – 4000mg/day; 4 – 3000mg/day and 2 – 2000mg/day : infusions over 15 min, bd) replaced same dose oral therapy**
- **Well tolerated with similar blood levels**

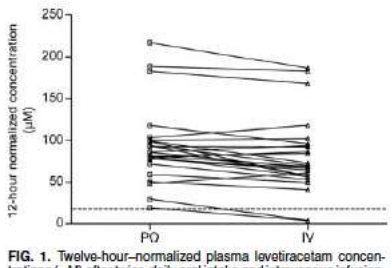


FIG. 1. Twelve-hour–normalized plasma levetiracetam concentrations (μM) after twice-daily oral intake and intravenous infusion. *Dotted horizontal line*, The lower quantification limit of the assay method (17.6 μM).

TABLE 2. *Number of subjects with at least one treatment-emergent adverse event (AE), intent-to-treat population*

System organ class and preferred term	All treatment-emergent AEs no. (%)	Drug-related AEs[a] no. (%)
Nervous system disorders		
Disturbance in attention	1 (4)	0
Dizziness	1 (4)	1 (4)
Headache	5 (20)	0
Eye disorders		
Vision blurred	1 (4)	1 (4)
Ear and labyrinth disorders		
Ear pain	1 (4)	1 (4)
Renal and urinary disorders		
Dysuria	1(4)	1 (4)
General disorders and administration-site conditions		
Asthenia	1 (4)	0
Fatigue	3 (12)	0
Investigations		
Diastolic blood pressure decreased	1 (4)	1 (4)

[a]Described by the investigator as possibly, probably, or highly probably related to study drug.

Baulac et al: ***Epilepsia, 48(3):589–592, 2007***

High dose IV Levetiracetam for acute seizure exacerbations

- **IV LEV in 9 children (aet 3mn-3.7yrs) with acute repetitive seizuress**
- **Hospitalised – dose of >150mg/kg/day (mean dose 228mg/day/day)**
- **In 8 of the 9 patients seizures ceased**
- **Well tolerated with no complications**

Table 1. Effects of high-dose intravenous levetiracetam (IV-LEV)

Pt	Weight	LEV max dose (mg/day)	LEV max dose (mg/kg/day)	LEV max level (trough)	Seizure frequency baseline	Seizure frequency before IV-LEV (acute exacerbation)	Resolution of SE/clusters	Seizure frequency on high dose IV-LEV	Overall effect
1	13 kg	3,300	254	82	100/day	Refractory SE	Yes	10–15/day	Refractory SE resolved, >80% seizure reduction
2	11 kg	3,000	272	45	4–5/month	15/day	Yes	1/week	>90% seizure reduction
3	11.8 kg	2,000	169	35	2–3/week	6–7/day	Yes	3–5/day	90% seizure reduction
4	10.5 kg	3,000	286	108	40/day	>1,000/day (40–50/hour)	Yes	None	Seizure-free
5	8 kg	1,200	150	44	6/day	11/day	Yes	1–2/day	>50% seizure reduction
6	8 kg	1,800	225	94	22/day	100–400/day (6–16/hour)	Yes	2/month	>90% seizure reduction
7	12.7 kg	2,800	220	156	3/day	>400/day (>20/hour)	Yes	None	Seizure-free
8	10 kg	2,000	200	N/A	3/day	6/day	No	30/day	Seizures worse
9	12 kg	3,300	275	54	7–15/day	40/day	Yes	7–15/day	No change compared to baseline, but resolution of clusters

LEV, levetiracetam; N/A, not applicable; SE status epilepticus.

Depositario-Cabacar et al: ***Epilepsia, 51(3):1319-1322, 2010***

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Summary

- **Key pharmacological properties are solubility and pH**
- **Key pharmacokinetic properties are rate of action and risk of accumulation**
- **Indications for IV therapy are:**
  - **Acute seizures and acute repetitive seizures – traditionally BZDs**
  - **Status epilepticus – traditionally BZDs, PHT, PB**
  - **Temporary replacement therapy – many drugs**
- **Newer IV therapies for SE are all off-label, and include VPA and LEV**
- **IV LEV pharmacology and pharmacokinetics have been well studies and recently published.**

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3rd London Innsbruck Colloquium on Acute Seizures and Status Epilepticus

Oxford UK : 7th - 9th April 2011

For further information:

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