IV formulations of antiepileptic drugs

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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
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

Physical properties of a drug for IV formulation

- **Solubility**
  - Problem for some AEDs (eg carbamazepine)
  - Solubility depends on intrinsic chemistry, pH of environment, pKₐ
  \[ S_{sol} = S_{HA}(1 + 10^{pH-pK_a}) \]
  - Phenobarbital: pKₐ 7.9, target pH 9, intrinsic solubility 7mg/mL
  - Amobarbital: pKₐ 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 intrinsic solubility (0.02 mg/mL)

- **pH**
  - Ionisation of a compound depends on pH.
  - Some compounds have different forms soluble at different pH
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

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.
Examples of AED accumulation

Chlormethiazole used in status Epilepticus

Pentobarbital used in status epilepticus

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
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

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
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

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

- 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 no response)

**In-hospital IV therapy in early SE**
- Lorazepam vs diazepam
- Lorazepam vs placebo
- Lorazepam vs diazepam/phenytoin
- Lorazepam vs phenobarbital
- Lorazepam vs phenytoin
- Midazolam vs lorazepam
- Midazolam vs diazepam
- Diazepam vs placebo

- **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)

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
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, arrhythmia 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


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


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

<table>
<thead>
<tr>
<th>Table 2: Summary of pharmacokinetic parameters.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parameter</td>
</tr>
<tr>
<td>$K_e$ (h⁻¹)</td>
</tr>
<tr>
<td>$t_1/2$ (h)</td>
</tr>
<tr>
<td>$V_F$ (L)</td>
</tr>
<tr>
<td>$V_d$ (L/kg)</td>
</tr>
<tr>
<td>CL (L/h)</td>
</tr>
<tr>
<td>CL (L/h/kg)</td>
</tr>
</tbody>
</table>

$V_d$: volume of distribution; $K_e$: elimination rate constant; CL: clearance; $t_1/2$: half-life; kg: body weight in kilograms.
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)
  - Cmax
  - 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>
<thead>
<tr>
<th>System organ class/preferred term</th>
<th>Placebo (n = 12)</th>
<th>2000 mg (n = 6)</th>
<th>4000 mg (n = 6)</th>
<th>5000 mg (n = 6)</th>
<th>10,000 mg (n = 6)</th>
<th>All levetiracetam doses (n = 36)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any drug-related adverse events</td>
<td>1 (8.3)</td>
<td>4 (66.7)</td>
<td>5 (83.3)</td>
<td>6 (100)</td>
<td>5 (83.3)</td>
<td>29 (80.6)</td>
</tr>
<tr>
<td>Nervous system</td>
<td>1 (8.3)</td>
<td>3 (50)</td>
<td>4 (66.7)</td>
<td>6 (100)</td>
<td>5 (83.3)</td>
<td>27 (75)</td>
</tr>
<tr>
<td>Balance disorder</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (16.7)</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>0</td>
<td>2 (33.3)</td>
<td>1 (16.7)</td>
<td>5 (83.3)</td>
<td>4 (66.7)</td>
<td>10 (28)</td>
</tr>
<tr>
<td>Diarrhea persistent</td>
<td>0</td>
<td>3 (50)</td>
<td>1 (16.7)</td>
<td>1 (16.7)</td>
<td>2 (33.3)</td>
<td>7 (19.4)</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>1 (8.3)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Headache</td>
<td>0</td>
<td>0</td>
<td>1 (16.7)</td>
<td>0</td>
<td>1 (16.7)</td>
<td>3 (8.3)</td>
</tr>
<tr>
<td>Somnolence</td>
<td>0</td>
<td>1 (16.7)</td>
<td>2 (33.3)</td>
<td>2 (33.3)</td>
<td>3 (50)</td>
<td>12 (33.3)</td>
</tr>
<tr>
<td>Eye, blurred vision</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>GI disorder</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>0</td>
<td>0</td>
<td>1 (16.7)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (16.7)</td>
<td>1 (2.8)</td>
</tr>
<tr>
<td>General disorders</td>
<td>0</td>
<td>1 (16.7)</td>
<td>2 (33.3)</td>
<td>0</td>
<td>0</td>
<td>5 (13.9)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>0</td>
<td>1 (16.7)</td>
<td>2 (33.3)</td>
<td>0</td>
<td>0</td>
<td>4 (11.1)</td>
</tr>
<tr>
<td>Feeling drunk</td>
<td>0</td>
<td>0</td>
<td>1 (16.7)</td>
<td>0</td>
<td>0</td>
<td>1 (2.8)</td>
</tr>
<tr>
<td>Thirst</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (16.7)</td>
<td>1 (2.8)</td>
</tr>
</tbody>
</table>


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

<table>
<thead>
<tr>
<th>System organ class and preferred term</th>
<th>All treatment emergent AEs no. (%)</th>
<th>Drug-related AEs a (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nervous system disorders</td>
<td>1 (4)</td>
<td>0</td>
</tr>
<tr>
<td>Disturbance in attention</td>
<td>1 (4)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>5 (20)</td>
<td>0</td>
</tr>
<tr>
<td>Headache</td>
<td>1 (4)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Eye disorders</td>
<td>1 (4)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Vision blurred</td>
<td>1 (4)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Ear and labyrinth disorders</td>
<td>1 (4)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Rectal and urinary disorders</td>
<td>1 (4)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Urticaria</td>
<td>1 (4)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>General disorders</td>
<td>1 (4)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>and administration-site conditions</td>
<td>1 (4)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Auteuria</td>
<td>1 (4)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Nausea</td>
<td>1 (4)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>1 (4)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1 (4)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Diuretic blood pressure decreased</td>
<td>1 (4)</td>
<td>1 (4)</td>
</tr>
</tbody>
</table>

*aDescribed by the investigator as possibly, probably, or highly probably related to study drug.

High dose IV Levetiracetam for acute seizure exacerbations

- IV LEV in 9 children (aet 3mn-3.7yrs) with acute repetitive seizures
- 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)**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Weight (kg)</th>
<th>LEV max dose (mg/kg/day)</th>
<th>LEV max dose (mg/day)</th>
<th>LEV max level (mmol/L)</th>
<th>Seizure frequency before IV-LEV (acute exacerbation)</th>
<th>Resolution of SE within</th>
<th>Seizure frequency on high dose IV-LEV</th>
<th>Overall effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>13</td>
<td>3,300</td>
<td>254</td>
<td>82</td>
<td>100/day</td>
<td>Yes</td>
<td>10-15/day</td>
<td>Refractory SE</td>
</tr>
<tr>
<td>2</td>
<td>11.5</td>
<td>3,000</td>
<td>272</td>
<td>45</td>
<td>4-5/month</td>
<td>Yes</td>
<td>3-4/day</td>
<td>98% seizure reduction</td>
</tr>
<tr>
<td>3</td>
<td>11.5</td>
<td>3,000</td>
<td>169</td>
<td>35</td>
<td>2-3/mo</td>
<td>Yes</td>
<td>None</td>
<td>Seizure-free</td>
</tr>
<tr>
<td>4</td>
<td>10.5</td>
<td>3,000</td>
<td>286</td>
<td>108</td>
<td>40/day</td>
<td>Yes</td>
<td>None</td>
<td>Seizure-free</td>
</tr>
<tr>
<td>5</td>
<td>8</td>
<td>2,000</td>
<td>150</td>
<td>44</td>
<td>6/day</td>
<td>Yes</td>
<td>1-2/mo</td>
<td>&gt;90% seizure reduction</td>
</tr>
<tr>
<td>6</td>
<td>8</td>
<td>2,000</td>
<td>235</td>
<td>94</td>
<td>22/day</td>
<td>Yes</td>
<td>2-3/mo</td>
<td>&gt;90% seizure reduction</td>
</tr>
<tr>
<td>7</td>
<td>12.5</td>
<td>3,000</td>
<td>230</td>
<td>156</td>
<td>31/day</td>
<td>Yes</td>
<td>None</td>
<td>Seizure-free</td>
</tr>
<tr>
<td>8</td>
<td>10</td>
<td>2,000</td>
<td>200</td>
<td>31/day</td>
<td>6/day</td>
<td>Yes</td>
<td>None</td>
<td>Seizure-free</td>
</tr>
<tr>
<td>9</td>
<td>12</td>
<td>3,000</td>
<td>275</td>
<td>54</td>
<td>7-15/day</td>
<td>Yes</td>
<td>7-15/day</td>
<td>No change compared to baseline, resolution of clusters</td>
</tr>
</tbody>
</table>

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

**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.
3rd London Innsbruck Colloquium on Acute Seizures and Status Epilepticus
Oxford UK : 7th - 9th April 2011

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