Post Stroke epilepsy Management

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Reader in Clinical Neurology & Honorary Consultant

BASP Trainees Weekend, March 2012
Summary

• Diagnosis
• Starting AEDs
• Stopping AEDs
• Education & Information
  – Diagnosis - of epilepsy, of electroclinical syndrome
  – Consequences & Comorbidities (medical, psychosocial, SUDEP, treatment related…..)
  – Specific – pregnancy, LD, employment…..
Summary

- Diagnosis
- Starting AEDs
- Stopping AEDs
- Education & Information
  - Diagnosis - of epilepsy, of electroclinical syndrome
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  - Specific – pregnancy, LD, employment…..

1. NICE CG20, Dx and management of the epilepsies; 2004&2012 update
Diagnosis:

1. Was it a seizure?
2. What type of seizure?

<table>
<thead>
<tr>
<th>Duration</th>
<th>Self limiting</th>
<th>Continuous (status)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cause</td>
<td>Acute Provoked</td>
<td>Unprovoked</td>
</tr>
<tr>
<td>Onset &amp; spread</td>
<td>Generalized</td>
<td>Focal</td>
</tr>
</tbody>
</table>

3. Is it epilepsy?
4. What is the cause?
5. What impairment is it causing?

All inform treatment decisions

Engel, Epilepsia 2001; ILAE taskforce diagnostic scheme
Berg, Epilepsia 2010: ILAE taskforce Classification
Diagnosis:

1. Was it a seizure?
   • Very broad differential Dx
   • Dx based primarily on history/witness accounts
   • Witness accounts varied reliability\(^1\)
   • MRI & EEG\(^2\) little utility

Should be by Epilepsy Specialist\(^3\)

(1 clinic/week epilepsy; Epilepsy training/CPD)

3. NICE CG20, Dx and management of the epilepsies; 2004&2012 update
Acute provoked Sz vs epilepsy

• <7-14 days of acute brain insult

<table>
<thead>
<tr>
<th>Study (all first CVA)</th>
<th>%</th>
<th>Acute</th>
<th>-1y</th>
<th>-5y</th>
<th>-10y</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>n535, Population</td>
<td>6 (1w)</td>
<td>3</td>
<td>7.4</td>
<td>8.9</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>n675, Population</td>
<td>2(24h)</td>
<td>5.7</td>
<td>11.5</td>
<td></td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>n1897, Hospital</td>
<td>4.8 (2w)</td>
<td>3.8</td>
<td></td>
<td></td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>n581, Hospital</td>
<td>2.4 (1w)</td>
<td>3.1</td>
<td>5.5(3y)</td>
<td></td>
<td>4</td>
<td></td>
</tr>
</tbody>
</table>

Increased risk with blood, cortical, ant. circulation
Early Sz do increase risk late sz, ~ 21-57%
70-90% initial late sz have recurrence/develop epilepsy

Acute Provoked sz:
No indication long term AEDs

• No evidence of benefit
  – One failed trial post stroke\(^1\)
  – Few studies of AED post TBI, SAH, Craniotomy
  – 43-79% won’t have late sz anyway

• Good evidence of potential harm
  – 3-30% unacceptable side effects
  – 1-5% risk idiosyncratic reaction
  – Drug interactions
  – Long term risks – bone health\(^1\); CVS Risk\(^2\)?

Epilepsy Rx principles

• Diagnosis should not be in doubt
  – Detailed explanation

• General Advice
  – Driving; Occupation; Pregnancy & Contraception; Alcohol, sleep, drugs…..

• Is it appropriate to treat at all?

**Risks of not treating vs risks of treating IN THE INDIVIDUAL**

– Frequency, seizure type, other lifestyle issues,
– AED Treatment, likely several years
– Joint Decision;
– Most people will achieve good control at little personal cost
Starting AEDs (i)

Risk of seizure recurrence

- First unprovoked
  ~50% will be seizure free at 2y \( oRx \)
  Early Rx no long term influence \(^1,2\)

- First acute provoked sz
  Status epilepticus at onset 46% vs 13% \(^3\)

70-90% late sz post stroke will recur

Starting AEDs (ii)

Consequences/risks of seizures

- psychosocial consequences
  - Driving, employment, education, independence, recreation……..

- SUDEP\(^1\) / increased mortality
  - GTCS, Live/sleep alone;
  - 1:50 (failed surgery) - >1:8,000 (GP) person years

- Injury\(^2\)

- Intractability ?

- Brain damage?

2. Kwon, *Epilepsia* 2010
• Seizure cessation not guaranteed
  – 1st AED - 58% Idiopathic; 43% symptomatic
  – Post Stroke – 70% seizure free

• idiosyncratic reactions 1/1,000-50,000

• dose related side effects 3-30%

• pregnancy/contraception

• Long term risks
  – Bone Health
  – Memory/balance (PHT, ? Other drugs)

1. Kwan, Epilepsia 2001
Choice of AED

- Individualized to seizure, syndrome, age, gender, comorbidity, co-medication, preferences
- Try alternative first line if initial not tolerated/effective

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<th>Adjunctive</th>
<th>Others</th>
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<td>GTCS</td>
<td>CBZ, LTG, OXC, VPA</td>
<td>CLB, LTG, LEV, TOP</td>
<td></td>
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<tr>
<td>AS</td>
<td>ETX, VPA</td>
<td>LTG</td>
<td></td>
</tr>
<tr>
<td>MyS</td>
<td>VPA</td>
<td>LEV</td>
<td>CLB, CLN, ZON</td>
</tr>
<tr>
<td>Focal (+/- GTCS)</td>
<td>CBZ, LTG, OXC, VPA</td>
<td>CLB, GBP, OXC, TOP</td>
<td>ESL, LCS, LEV, PGB, PHT, PB, ZON</td>
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CBZ – offer slow release
Avoid changing formulations

NICE CG20 2012 update
First Line AEDs

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CBZ – offer slow release
Avoid changing formulations

NICE CG20 2012 update
When first drug fails:

- Ineffective (n=113)
- Intolerable Side Effects (n=69)
- Idiosyncratic Reaction (n=29)
- Others (n=37)

% Patients

- Seizure-free
- Uncontrolled

Failed 2 drugs ~5% ever seizure free

Kwan and Brodie N Engl J Med 2000
Medical Management
Refractory epilepsy

• Refer to specialist/tertiary service

• Review
  – Diagnosis (Is it epilepsy; Seizure syndrome)
  – Precipitants (Sleep; Alcohol; Recreational drugs…)
  – Compliance & Drug history

• Management principles: Have a plan!
  – Set realistic goals and time course
  – Balance risks vs benefits on individual basis
  – Withdraw unhelpful AEDs
  – Maintain “backbone” of best so far
  – Serial trials add-on Rx to minimum effective/maximum tolerated
# Choice of AED

**“old”**

- Acetazolamide 1988
- Carbamazapine 1965
- Clobazam 1979
- Clonazepam 1974
- Ethosuximide 1955
- Phenobarbital 1932
- Phenytoin 1958
- Primidone 1952
- Sodium Valproate 1973

**“new”**

- Vigabatrin 1989
- Lamotrigine 1991
- Gabapentin 1993
- Piracetam 1993
- Topiramate 1995
- Tiagabine 1998
- Fosphenytoin 1999
- Oxcarbazepine 2000
- Levetiracetam 2000
- Pregabalin 2004
- Zonisamide 2005
- Rufinamide 2007
- Eslicarbazepine 2009
- Retigabine 2011

## 23 DRUGS

- 23 mono-therapy options
- 253 2-drug combinations
- 1771 3-drug combinations
Set and agree realistic goals

Each change in AED:

- **seizure freedom** - 1-5%
- **50% reduction in frequency** 30-50%
  
  - severity
  - context
    
    personality & mood
    occupation & expectations
    Lifestyle

- Tolerability

Gilliam et al, *Neurology* 2004
Which AED: what is your goal?

Adapted from Marson et al., Epilepsia, 1997, 38, 859-880
Wilby, HTA 2005.
Therapeutic drug monitoring

- To confirm toxicity
- To detect non-compliance
- Adjustment phenytoin dose
- Management pharmacokinetic interactions
- Specific clinical conditions (e.g. Status, organ failure, ? Pregnancy)

There is no need for “routine” drug monitoring
Stopping AEDs

- Seizure freedom
- Lack of effect
- Intolerable side effects
- Pregnancy

Discuss & Balance:
- Seizure recurrence (risk, consequences, failure to regain control)
- Psychosocial consequences of stopping
- Risks of ongoing treatment

- 2 years
- Are they really?
Risk factors for seizure recurrence

- age > 16 years
- seizures only on awakening
- > 1 AED
- seizures on AED treatment
- 1º or 2º GTCS
- myoclonic seizures
- (abnormal EEG)

PSE 2y Recurrence rate
>16y, øMyS
18-49% On Rx
35-76% Off Rx

Conclusions

• Diagnosis of seizures/epilepsy, and management should be under supervision of specialist
• Multidisciplinary approach, education & shared decision making
• Starting, changing and stopping AEDS
  – Risks of seizure recurrence
  – Potential consequences of seizures
  – Risks and consequences of treatment
• Choice of AED – individualized, NICE guidance
• Monotherapy for most, trials serial add on if required
• Post stroke ~70% achieve seizure freedom
• Refractory patients (Failed >2 Rx) – refer to tertiary centre
Declaration

I have received:

– Hospitality from all major AED manufacturers
– Invited talks for UCB Pharma, Janssen-Cilag, Sanofi-Synthelabo
– Unrestricted Research Grants from UCB Pharma, Johnson&Johnson & Pfizer
Percentage of Patients Seizure-free

Outcome & etiology

Stephen, Kwan, Brodie. Epilepsia 2001
## Established Status Epilepticus

Published clinical data in SE

<table>
<thead>
<tr>
<th>Drug</th>
<th>N (RCT)</th>
<th>N Refract</th>
<th>% Efficacy (mean)</th>
<th>AE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenobarbitone</td>
<td>139 (18)</td>
<td>0</td>
<td>61-94 (80)</td>
<td>Rare ↓BP</td>
</tr>
<tr>
<td>Phenytoin(Fos)</td>
<td>315(315)</td>
<td>0</td>
<td>43-100 (70)</td>
<td>↓BP12-30%, Rash</td>
</tr>
<tr>
<td>Valproate</td>
<td>499 (125)</td>
<td>172</td>
<td>63-95 (79)</td>
<td>Rare NH4, Liver</td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>498 (0)</td>
<td>215</td>
<td>45-100 (70)</td>
<td>None serious</td>
</tr>
<tr>
<td>Lacosamide</td>
<td>52 (0)</td>
<td>34</td>
<td>43-100 (47)</td>
<td>None serious</td>
</tr>
</tbody>
</table>

VPA and LEV : additional 400+ each safety/other studies

*LEV, VPA, LCS not licensed for SE

HC Review for ESETT, Data Feb 2011
Generic prescribing of AEDs

- Recommendations based on “bioequivalence”
  
  BUT

  Bioequivalence
  DOES NOT EQUAL
  Therapeutic equivalence

- Considerable variation in bioequivalence for slow release preparations: Use branded prescriptions

- Individual patients on any drug should be maintained on the same formulation

http://www.epilepsy.org.uk/info/drugs_change.html
http://www.nhsdirect.nhs.uk/articles/article.aspx?ArticleId=1003
NAPC Year book, 1999, Cock H
Trials in post stroke seizure

• Feasibility issues
  – DB RCT 3m Rx with LEV, started 2-7d post CVA, 12m f/u; 1st endpoint: Late first seizure
  – High Risk group (13% risk, estimated reduce to 5% on LEV), 200/arm
  – est 155 available pts/year/each of 2 centres
  – 18 months – 16 recruited, terminated.
    31/500 actually eligible
    50% Eligible refused (SE, burden)

van Tuijl, Seizure 2011