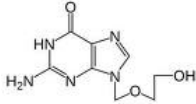


Clinical Controversies in Neuropharmacotherapy



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Objectives

- Describe a clinical scenario when IV acyclovir therapy may be warranted
- Compare and contrast the etiologies of viral meningitis and encephalitis and their associated treatments
- Understand the pharmacokinetic differences between brand and generic antiepileptic drugs (AEDs)
- List the benefits and consequences of therapeutic interchange (TE) of AEDs
- Describe a clinical scenario when TE of AEDs may be appropriate

Case Study

- HPI: 35 y/o male presents to the ED with 3 days of headache, neck stiffness, and nausea/vomiting.
- He has no PMH and is alert and oriented x 3
- Vital signs: WNL except temperature of 38.8 and 6/10 throbbing head pain
- Pertinent labs and tests: Scr=0.8, Wt= 75 kg, LP 500 WBC (90% lymphocytes), 0 RBC, 125 protein, 85 glucose
 - CSF gram stain reveals few WBCs and no organisms
 - Brain MRI shows no enhancement

Case Study

1. Is this patient a candidate for IV acyclovir therapy?
- A. Yes he appears to have a viral encephalitis
 - B. Yes he appears to have a viral meningitis
 - C. No he appears to have a fungal meningitis
 - D. No he appears to have a bacterial meningitis

Clinical Controversy #1

- Should intravenous acyclovir be initiated in *all* patients with suspected viral meningitis?

Clinical Context

- Acyclovir is an antiviral that inhibits DNA synthesis and viral replication of herpes simplex virus (HSV 1 and 2) and varicella zoster virus (VZV)
- Recommended as empirical therapy in all patients with suspected encephalitis
- Primarily renally excreted and can form crystals in urine leading to an obstructive nephropathy
- Estimated incidence of herpes simplex encephalitis (HSE): 1 in 250,000 per year
- Prevalence of HSV 2 recurrent lymphocytic meningitis is 2.2/100,000

CID 2008;47:303-27
Lancet 2001;357:1513-18

Meningitis vs. encephalitis

Meningitis

- Fever
- Headache
- Nuchal rigidity
- Photo/phonophobia
- Nausea/vomiting

Encephalitis

- Same as meningitis EXCEPT:
 - Acute mental status changes
 - Cognitive dysfunction
 - Behavioral changes
 - Seizures
 - **MRI with focal findings**

Etiology of Meningitis in Finland

Table 1 Etiology of aseptic meningitis

Etiology	Confirmed	Probable	Possible	Total, no. (%)
Enterovirus	33	5		38 (26)
HSV-2	22	2		24 (17)
VZV	8	4		12 (8)
TBEV	2	6		8 (6)
HSV-1*	3			3 (2)
Other defined agents†	4	4	2	10 (7)
Undefined agents				49 (34)

* Both HSV-1 and VZV etiologies in one patient.

† EBV (n = 2), *M pneumoniae* (n = 2), *B burgdorferii* (n = 2), adenovirus (n = 1), parainfluenzavirus (n = 1), *T gondii* (n = 1), and trimethoprim (n = 1).

HSV = herpes simplex virus; VZV = varicella zoster virus; TBEV = tick-borne encephalitis virus.

Neurology 2006;66:75-80

Etiology of Meningitis at UCH

- 302 patients received IV acyclovir from Feb 09-Feb 10
 - 46 patients with suspected aseptic meningitis or encephalitis received IV acyclovir
 - 20 cases of viral meningitis
 - 26 (others, encephalitis, etc.)
 - 20/20 of viral meningitis (100%) received IV acyclovir
 - 17/20 (85%) had viral meningitis NOS (all with negative HSV PCR)
 - 3/20 (15%) had HSV 2 meningitis

Unpublished data UCH 2009

Etiology of Encephalitis in Finland

Etiology*	n	
VZV	4	12%
HSV-1	4§	9%
TBEV	4	9%
Other agents	30	71%

* Confirmed, probable, or possible causative agent.
‡ One patient yielding positive PCR and intrathecal antibody production for both HSV-1 and VZV.

Neurology 2006;66:75-80

Evidence to Support Treatment of Viral Meningitis

- No specific guidelines exist for treatment of viral meningitis
- In Finish study about 25% of aseptic meningitis was caused by acyclovir susceptible viruses (HSV 1 and 2, VZV)
- UCH data suggest 3/15 (15%) have HSV 2 meningitis

Back to the Case

- You decide to start IV acyclovir at a dose of 750 mg IV Q 8 hours.
- On hospital day 2, the patient's serum creatinine increases to 2.3 with normal urine output.
- His CSF HSV and VZV PCRs come back negative.

Back to the Case

2. What is your next treatment decision?
- A. Discontinue IV acyclovir and start aggressive fluid resuscitation
 - B. Start maintenance IV fluids and continue IV acyclovir for 14-21 days
 - C. Start IV ganciclovir
 - D. D/C IV acyclovir and start PO acyclovir to finish a 14-21 day course

Evidence to Refute Treatment of Viral Meningitis

- Most non-focal viral meningitis will resolve without antiviral therapy
- Acyclovir induced crystalluria may lead to an obstructive nephropathy and acute renal failure
 - Usually develops 12-48 hours after therapy
 - Most often serum creatinine returns to baseline 4-9 days after drug is discontinued
- Multiple cases throughout the literature

Am J Med;1988;1067-70

Back to the Case

3. The patient wants to know if his kidney function will ever improve and when? Based on limited case reports, what do you tell him?
- A. Yes, but it may take up to several weeks before we see an improvement
 - B. No, your kidneys likely sustained permanent damage and may never improve
 - C. Yes, most patients improve about 1 week after discontinuation of the acyclovir and aggressive IV fluids
 - D. Unsure, there is not enough evidence in the literature to answer this question

Current Clinical Practice at UCH

- If pt has focal neurological findings then treatment with acyclovir should be started as soon as possible
- Most neurologists will treat HSV 2 meningitis even though there is lack of evidence
- Acyclovir is discontinued 48-72 hours after initiation once HSV PCR is negative

Clinical Controversy #2

- Can switching a patient from a brand name anti-epileptic to a generic anti-epileptic cause an increased frequency of seizures?
 - Generic to generic switching

Magnitude of the Problem

- Third most common neurological disorder
- 10% of the population will experience a seizure
- 1/100 adults have a diagnosis of epilepsy
- ~ 1 - 2 % of the population
 - 40 million worldwide
 - 2.3 million in the USA
- Estimated annual burden on society: \$12.5 billion
- Unlike many other disorders and diseases, epilepsy is an all-or-nothing problem for therapeutic success

Hauser WA et al. Epilepsy: Frequency, Causes, & Consequences. New York, NY: Demos;1991:1; Begley CE et al. The cost of epilepsy in the US. Epilepsia 2000;41:342-51.

Clinical Context

- No RCTs looking at increased seizure frequency when changing from one formulation to another
 - Claims data and retrospective analyses
 - Anecdotal evidence from patients
- FDA has set parameters for bioequivalence (BE) and therapeutic equivalence (TE)
 - Are these parameters appropriate for antiepileptic drugs? (many have "narrow therapeutic index")
- If generics are available, most pharmacies will switch patients without even notifying them

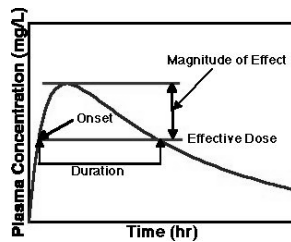
FDA Bioequivalence

- Bioequivalence (generic compared to brand) based on FDA can be presumed
 - New oral formulation must be compared with the brand product in relatively *small, single-dose* crossover studies in *young, healthy* volunteers for it to be bioequivalent
 - Established when the 90% CI of the ratio of the generic to reference compound for the AUC and C_{max} fall within 80-125%

Epilepsy Curr 200 8;8:113-17
<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation>

Pharmacokinetic Definition of Bioequivalence

- The calculated confidence interval (CI) (90%) should fall within 80-125% for the ratio of product averages (population geometric means) of the area under the serum concentration-time curve (AUC) and the maximum concentration (C_{max}) after a single dose ($AUC_{generic}/AUC_{brand}$)



<http://www.boomer.org/c/p1/index.html>

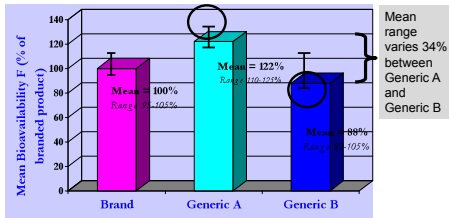
FDA Therapeutic Equivalence

- TE assumes BE and substituted product will produce the SAME clinical effect and safety profile as the original product
- TE is not directly tested by the FDA but is presumed based on tests of BE
- BE ≠ TE

Epilepsy Curr 2008;8:113-17
www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation

Generic-Generic Conversion

- Variability between products can cause patients to lose seizure control or experience adverse effects



Potential Outcomes of TE

- Changes in seizure outcomes
 - Maintained or improved seizure control*
 - No difference in seizure outcomes despite generic → generic substitution**
 - Increased seizure rate or breakthrough
 - Especially dangerous
 - Refractory patients
 - Seizure-free patients
- Adverse (side) effects
 - Either increased or decreased with substitution

*Devine ST, et al. *Curr Med Resear & Opin* 2010; 26:455-63.
**Kesselheim AS, et al. *Drugs* 2010; 70: 605-21.

Potential Outcomes of TE

- "Switchback"- Brand → Generic → Brand
 - Impact of narrow therapeutic index
 - AEDs have much higher rate of switchback compared to non-AEDs*
 - Increase in seizure frequency (case report series)**
 - 78% of generic-switched patients had breakthrough seizure within 3 months
 - May reflect population studied
 - Patient and/or physician perception (case report series)**
 - 92% switched back after breakthrough seizure
 - 96% of those regained seizure control within 3 months

*Andermann F, et al. *Epilepsia* 2007; 48:464-9.
*LeLorier J, et al. *Neurology* 2008; 70:2179-86.
**Berg M, et al. *Neurology* 2008;71:525-530.

Benefits vs. Consequences of TE Antiepileptic Drugs

- | • Benefits | • Consequences |
|---|--|
| <ul style="list-style-type: none">– Decreased drug cost compared to brand– Possible improvement in seizure rate– Possible improvement in adverse effects– Improved adherence | <ul style="list-style-type: none">– Primary Costs<ul style="list-style-type: none">• Increased healthcare utilization• Monitoring• Increased dosage• Adverse effects– Secondary Costs<ul style="list-style-type: none">• Decreased QoL• Injuries• Job insecurity• Death |

Data to Support Switching of AEDs

- Decreased cost to patient and healthcare system
- FDA contends no problems with BE testing
 - 127 BE studies in 1997 mean difference between reference and generic formulations was 3.5% for AUC and 4.3% for C_{max}

Epilepsy Curr 2008;8:113-17

Data to Refute Switching of AEDs

- Several retrospective studies show increased seizures among patients that switch AED
- Generics are not tested head to head for BE
- Decreased patient safety and QoL

Current Clinical Practice at UCH

- UCH does not carry most brand name AEDs
- Our inventory of generic AEDs changes based on multiple factors
- Patients who take a specific brand name or generic AED are allowed to take their own medication while in the hospital

American Academy of Neurology Position Statement on the Coverage of AEDs for Epilepsy

The AAN opposes generic substitution of anti-convulsant drugs for the treatment of epilepsy without the attending physician's approval. The Food and Drug Administration has allowed for significant differences between name-brand and generic drugs. This variation can be highly problematic for patients with epilepsy. Even minor differences in the composition of generic and name-brand anticonvulsant drugs for the treatment of epilepsy can result in breakthrough seizures.

- The AAN opposes all state and federal legislation that would impede the ability of physicians to determine which anticonvulsant drugs to prescribe for the treatment of patients with epilepsy.
 - The AAN opposes policies that would result in arbitrary switching among anticonvulsants. Therefore, the AAN opposes generic substitution of anticonvulsants for patients with epilepsy at the point of sale (e.g., in the pharmacy), without prior consent of the physician and the patient.

American Academy of Neurology Position Statement on the Coverage of AEDs for Epilepsy

- The AAN believes that formulary policies should recognize and should support complete physician autonomy in prescribing, and patients in accessing, the full range of anticonvulsants for epilepsy.

- The AAN believes that the use of anticonvulsant drugs in the treatment of epilepsy should be distinguished from the use of anticonvulsant drugs in treating other disorders. The AAN recognizes that different strategies may be appropriate in using anticonvulsants for the treatment of conditions other than epilepsy.

The AAN opposes prior authorization requirements by public and private formularies. Prior authorization (i.e., requiring a physician to seek approval to prescribe a drug before the drug may be dispensed) is one method formularies may utilize to limit access to anticonvulsant drugs for the treatment of epilepsy.

Neurology 2007;68:1249-50

Questions

