

Pharmacotherapeutic Management of Peripheral Neuropathy

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Overview

- Etiology and Pathogenesis
- Tricyclic Antidepressants
- SSRIs, SNRIs
- Drug Interactions (iso-enzyme metabolism)
- Anti-convulsants
- Anti-arrhythmic
- Topicals

NEUROPATHIC PAIN



Neuropathic pain arises as result of a primary lesion or dysfunction of the nervous system which leads to the loss of the capacity to conduct information. The nervous system is in a sense short-circuited and action potential generation becomes out of control.

1. Gallagher RM. Primary care and pain medicine. *Med Clin N Am.* 1999;83(3):555-583
2. Semenchuk M. Adjuvant analgesic for management of neuropathic pain. *Pharmacy Newswatch.* Biezer JL ed. Park-Davis. 1999;(6) no 1.

NEUROPATHIC PAIN Definitions

- Presumed site of injury
 - peripheral (polyneuropathies-diabetes, HIV, drug- induce, idiopathic), phantom/stump, traumatic mononeuropathies
 - central (spinal cord injury, stroke)
 - mixed (postherpetic neuralgia, sympathetically maintained pain syndromes)

SEVERAL ETIOLOGIES SIMILAR CLINICAL MANIFESTATIONS

- Spontaneous pain (paroxysmal or constant)
 - burning, shooting, lancinating
- Paresthesias
 - abnormal nonpainful sensations that may be spontaneous or evoked (tingling)
- Dysesthesias
 - abnormal pain sensations that may be spontaneous or evoked (unpleasant tingling)
- Hyperalgesia
 - exaggerated painful response to a normally noxious stimulus
- Allodynia
 - painful response to a normally non-noxious stimulus (light touch--burning)
- Localized hyperhidrosis, altered skin temperature, trophic changes to skin
- Later stages-hyporeflexia, weakness

NEUROPATHIC PAIN

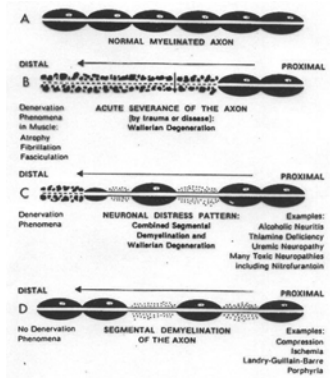
Abnormal "wiring"

- ✓ connections, neurotransmitters, and receptors
- ✓ Single pharmacologic approach often not as effective as multiple approaches

NEUROPATHIC PAIN AND PHARMACOLOGY

- Tricyclic Antidepressants-enhancement of inhibitory pathway
- Anticonvulsants-sodium channel blockade
- Antiarrhythmics/Anesthetics-sodium channel blockade
- Clonidine-decrease sympathetic tone
- Capsaicin-substance P depletion
- Ketamine/Amantadine-NMDA receptor blockade
- Baclofen-enhance inhibitory blockade

Effects on Nerve Axon



Pathogenesis related to DM

- Poorly controlled hyperglycemia.
- Accumulation of sorbitol in nerve cells.
- Decrease in nerve free myoinositol and decreased activity of nerve sodium-potassium adenosine triphosphate.
- Increased nonenzymatic peripheral nerve glycosylation.
- Nerve hypoxia.

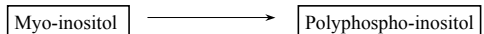
Other Causes-1

- Diseases
 - A.I.D.S.
 - Herpes Simplex Virus
 - Syphilis
 - Sclerotic/Connective Tissue Disorders
- Back/Tissue Injury
- Iatrogenic Causes

Differential Diagnosis

- Organic Peripheral Neuropathy
- B-12
- Porphyria
- Heavy Metal poisoning
- Collagen Disease
- Cancer
- Lymphoma
- Diabetes

Pathogenesis-Biochemistry



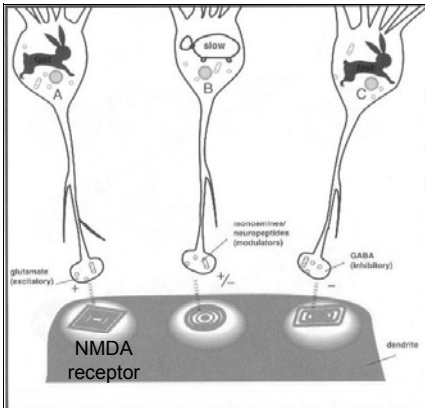
A sodium dependent active transport system maintains the cellular concentration of myoinositol at a concentration of 30-90 times that of plasma.

transport of $\text{Na}^+/\text{K}^+/\text{Ca}^{++}$ nerve conduction

INSULIN DEFICIENCY AND HYPERGLYCEMIA DECREASE THE MYOINOSITOL, RESULTING IN DECREASED NERVE CONDUCTION VELOCITY.

Reference: Calissa PT, Jaber LA

Neurotransmitter Signals



TCA's Mechanism of Action

TCA's block the central neuronal re-uptake of 5-HT and NE.

Antidepressant Pharmacology

	Dose [mg]	Amine Effects Sedation		Anticholinergic
3* Amino TCA				
Amitriptyline [Elavil]	25-300	NE > 5HT	3	3
Clomipramine [Anafranil]	25-300	5HT	2	3
Doxepin [Sinequan] 25-300	NE > 5HT	3	2	
Imipramine [Tofranil]	25-300	NE > 5HT	2	2
Trimipramine [Surmontil]	25-300	NE > 5HT	3	3
2* Amino TCA				
Amoxapine [Asenden]	50-600	NE	1	1
Desipramine [Norpramin]	25-300	NE	0.5	1
Maprotiline [Ludomil]	25-225	NE	2	2
Protriptyline [Vivactil]	10-60	NE	0.5	2
Nortriptyline [Pamelor]	25-250	NE	1	1
Serotonin Reuptake Inhibitors				
Fluoxetine [Prozac] 5-80	5HT	0.5	0	
Fluvoxamine [Luvox]	50-300	5HT	0.5	0
Paroxetine [Paxil] 10-50	5HT	0.5	0.5	
Citalopram [Celexa] 10-60	5HT	0.5	0	
Sertraline [Zoloft] 50-200	5HT	0.5	0	
Escitalopram [Lexapro]	10-20	5HT	0.5	0
Atypical Antidepressants				
Duloxetine [Cymbalta]	40-60	5HT > NE	0	0.5
Venlafaxine [Effexor]	25-375	5HT > NE	0	0.5
Bupropion [Wellbutrin]	100-450	NE, DA	0	0
Nefazodone [Serzone]	100-600	5HT > NE	3	0
Trazodone [Desyrel] 50-600	5HT > NE	3	0	
Mirtazapine [Remeron]	15-45	NE [?]	3	0

TCA Antidepressants

- Protein Binding - 90 %
- extremely lipophilic
- metabolism:
 - first pass
 - active metabolites
 - N-demethylation
 - glucuronidated
 - eliminated
- ie. imipramine > 2-OH imipramine > desipramine > 2-desmethyl desipramine

PREGNANCY: TCA of choice = desipramine

SE/Problems of TCAs

- adverse behavior effects
- anticholinergic
- seizures (highest w/ maprotiline)
- autonomic side effects
- cardiac side effects
- lag time = 3-5 days
- troublesome SEs (addressed by SSRIs)
- narrow therapeutic index

Clinical Considerations (TCA's)

- Combination w/ thyroid replacement.
- May ppt mania or hypomania in patients predisposed

Terminology

- Inducer
- Inhibitor
- Substrate
- Do two inducers result in 200% induction?
- What is Genetic Polymorphism?

SSRIs

- Most Important P450 Enzymes:
 - 1A2
 - 2C family
 - 2D6
 - 3A3
 - 3A4

Nemeroff CB et al., Newer Antidepressants and the Cytochrome P450 System, Am J Psychiatry 153:3, March 1996, p.311-320

SOME IMPORTANT RELATIONSHIPS BETWEEN DRUGS AND CYTOCHROME P-450 (CYP) ENZYMES

CYP	Drug Substrates	Inhibitors	Inducers
1A2	caffeine, clomipramine, theophylline	cimetidine fluvoxamine ticlopidine fluoroquinolones	omeprazole tobacco
2C9	diclofenac, ibuprofen, piroxicam, losartan, tolbutamide, warfarin	fluconazole fluvastatin zafirlukast	rifampin
2C19	omeprazole, lansoprazole, diazepam, (S)-mephenytoin, neflnavir	cimetidine fluvoxamine	rifampin
2D6	CNS-active agents: amitriptyline, desipramine, imipramine, paroxetine, haloperidol, thioridazine Antiarrhythmic agents: mexiletine, propafenone Beta-blockers: propranolol, metoprolol, timolol Narcotics: codeine, dextromethorphan, hydrocodone	cimetidine fluoxetine paroxetine quinidine amiodarone ritonavir	barbiturates carbamazepine phenytoin rifampin troglitazone
3A4	Calcium channel blockers: diltiazem, felodipine, nimodipine, nifedipine, nisoldipine, nitrendipine, verapamil Immunosuppressive agents: cyclosporine A, tacrolimus Steroids: budesonide, cortisol, 17 β -estradiol, progesterone, testosterone Macrolide antibiotics: clarithromycin, erythromycin, troleandomycin Chemotherapeutic agents: cyclophosphamide, tamoxifen, vincristine, vinblastine, ifosfamide Nonsedating antihistamines: astemizole, terfenadine Benzodiazepines: alprazolam, midazolam, triazolam Opioids: alfentanil, fentanyl, sufentanil HMG-CoA Reductase Inhibitors: lovastatin, simvastatin, atorvastatin, cerivastatin HIV protease inhibitors: indinavir, neflnavir, ritonavir, saquinavir, amprenavir Others: cisapride, quinidine, sildenafil	amiodarone clarithromycin erythromycin fluconazole grapefruit juice itraconazole ketoconazole mibefradil ritonavir indinavir troleandomycin	

HIV Patients and P450

- Variability in Activity of Hepatic CYP3A4 in Patients Infected with HIV
 - Erythromycin breath test (ERMBT)
 - variability in HIV+ patients may be greater than in controls
 - concomitant therapy of inducers and inhibitors effect clearance for CYP3A4 substrates.

Slain D, Pakyz A, Israel D, Monroe S, Polk R. Pharmacotherapy 2000;20(8):898-907

Are SSRI's Effective for PN?

- Paroxetine: Sindrup SH, Gram LF, Brosen K, Aaes-Jorgensen T, Gram LF. The selective serotonin reuptake inhibitor paroxetine is effective in the treatment of diabetic neuropathy symptoms. Pain 1990;42:135-44.
- Venlafaxine / Nafazodone????
 - Galer BS, 1995.
 - Songer DA, Schultz H, 1992.
 - Lang E, Hord AH, Denson D
- Mirtazapine (Remeron)???
- *Reboxetine

Venlafaxine (Effexor)

- M/A: inhibition of NE and 5-HT as with ?
- active metabolites
- lacks antiACh, adrenergic and histaminergic activity, although may cause somnolence, dry mouth and sweating
- weak inhibitor of cytochrome P450
- dose: up to 375mg/day (split bid-tid)

Newest Agents

- Duloxetine (Cymbalta)
 - Available as 20, 30, 60mg enteric coated, caplets
 - Dose: 40-60mg per day, qd-bid
 - Do not crush, chew, cut
 - Metabolism (CYP450):
 - 1A2 (weak), 2D6 substrate
 - Moderate 2D6 inhibitor

Newest Agents

- Mirtazapine (Remeron)-Chemically unrelated to SSRIs, TCAs, MAOIs
- Analog of Mianserin
- M/A:
 - Blocks presynaptic alpha2 adrenergic receptors (net effect incr. NE release)
 - Blocks postsynaptic 5-HT2 and 5-HT3 receptors (net effect, enhances serotonin release)
- Metabolism: Hepatic P450
 - 1A2, 3A4, 2C9, 2D6/inhibits 1A2, 2D6,3A4
- May also have anxiolytic and sedative effect

Inhibition of Cytochrome P450 in Vitro by SSRIs

SSRI	K _i (mcgM)
Fluvoxamine	8.2
Sertraline	0.7
Fluoxetine	0.6
Norfluoxetine	0.43
Paroxetine	0.15 *****
Quinidine	0.03

Tramadol HCl

- M/A: blocks reuptake of 5-HT, NE mild opiate agonist activity
- DOSE: start low, go slow, to maximum of 400mg/day
- DI: SSRIs, 5-HT syndrome, seizures
- SE: N/V, GI upset, bloating, syncope, constipation
- ADDICTION POTENTIAL: ???

Tramadol (Ultram®)

Recent Data Addressing Clinician Concerns

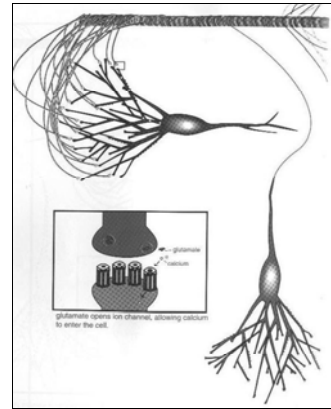
- Cicero TJ, Adams EH. et al. A postmarketing surveillance program to monitor ultram (tramadol hcl) abuse in the united states. Drug and Alcohol Dependence 57 (1999) 7-22.
- Petrone D, Kamin M, Olson W. Slowing the titration rate of tramadol hcl reduces the incidence of discontinuation due to nausea and/or vomiting: a double-blind randomized trial. Journal of Clinical Pharmacy and Therapeutics (1999) 24, 115-123.
- Gassa C, Derby L, Vasilakis-Scaramozza C, Jick H. Incidence of first-time idiopathic seizures in users of tramadol. Pharmacotherapy 2000;20 (6):629-634.

Anti-convulsants in PN

- Carbamazepine
 - Oxcarbazepine (Trileptal®)
- Phenytoin
- Valproate
- Gabapentin (Neurontin®)
- Topiramate (Topamax®)

Carbamazepine in PN

- increase actions of GABA (open Cl⁻ channels)
- decrease actions of excitatory amino acids (glutamate)
- increase action of adenosine
- **modify ionic conductance's !!!**



Carbamazepine in PN

- T_{1/2} reduced in children-higher metabolic rate
- T_{1/2} longer in neonates and elderly
- Get levels:
- Pt experience pain despite their range (ie. compliance, rapid metabolism)
- Pt appears toxic
- Dosage adjustment required (loss of pain control)
- Pregnancy or change in condition

Carbamazepine

- 1200mg/day, divided TID, QID
- initiate @ 200mg PO BID, inc. 200mg each week
- therapeutic range: 4-12 mcg/mL
- SE: sedation, nystagmus, syncope, blurred vision, ataxia
- bone marrow suppression: aplastic anemia, agranulocytosis (warn pt of s/s of infection, fever, bleeding, echymosis)
- **metabolite may be responsible for toxicity, even if patient is subtherapeutic**

Phenytoin

- 300mg-400mg PO qd to BID (MM kin)
- highly protein bound, effected by displacement and hypoalbuminemia
- SE: drowsiness, ataxia, nystagmus, SJS, lupus, hepatitis, gingival hyperplasia

General Considerations

Autoinduction
carbamazepine
phenytoin

Plasma Protein Displacement
phenytoin
valproate
carbamazepine

Gabapentin

- FDA Approved Indication:
refractory partial seizures
- dose: 900-1800mg (300-3600mg/d) TID
- No protein binding
- SE: generally well tolerated, somnolence, syncope, ataxia

Gabapentin Literature

- ↑ 100 case reports reviewed
- Morello et al. - Randomized Double-blind Study Comparing the efficacy of gabapentin with Amitriptyline on Diabetic peripheral Neuropathy. AIM. 9/13/99.
- Fudin and Audette - Letter to the Editor. AIM. 4/10/2000.
- Dallocchio, Buffa, et al. - Gabapentin vs. amitriptyline in painful diabetic neuropathy: an open-label pilot study. J Pain Symptom Manage 2000;20:280-285.

Post Herpetic Neuralgia

- Efficacy-safety study
- Multi-center, randomized, double-blind, placebo controlled, parallel design
- 229 subject from US sites
- Up to 3600mg, and higher!
- Measures: Likert scale, SF-MPQ, SF-36
- Results: sig reduction in pain scores

JAMA, December 2, 1998--Vol 280, No 21

Antiarrhythmic Agents

- Lidocaine
- Mexiletine:
 - Kastrup et al. Pain 1987.
 - Dejgard et al. Lancet 1988.
 - Strack et al. Diabetes Care 1992.

My Recommendations

1. TCA's (amitriptyline)- first line???
2. Elderly (frail) patients TCA vs. SNRIs
3. Tramadol (Ultram®)
4. Gabapentin (Neurontin®)
5. Topiramate (Topamax®)
Oxcarbazepine (Trileptal®)
6. Tiagabine (Gabitril®)
7. Anti-arrhythmics: Mexiletine (Mexitil®)-
ECG