Current drug topics in the Neurosciences ICU

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JUNE 5, 2010
Objectives

- Discuss utility of dexmedetomidine in the Neurosciences ICU (NSICU)
- Compare and contrast clevidipine to other agents used for hypertensive crisis
- Describe the new anti-epileptic drug lacosamide
- Discuss new data on clopidogrel regarding drug interactions and genetic polymorphisms
Dexmedetomidine (Precedex)

- Approved in 1999
- Selective agonist of $\alpha_2$-adrenergic receptor
  - $\alpha_2: \alpha_1$ effect ratio 1620: 1
- Uses:
  - Neurosurgery
  - ICU sedation
  - Extubation
  - Shivering
  - Analgesia
  - Alcohol/ substance withdrawal

Curr Opin Anaesthesiol 21:537-543
**Dexmedetomidine (DEX)**

- Stimulation of pre-synaptic $\alpha_2$ receptor = ↓ release of norepinephrine
- Stimulation of post-synaptic $\alpha_2$ receptor = ↓ nociception
- Effects:
  - Locus ceruleus: ↓ arousal, sedation, ↓ anxiety, ↓ consciousness
  - Spinal cord: ↓ nociception
  - NO GABA effects
Effects in central nervous system

- **Cerebral blood flow (CBF)**
  - Can cause vascular reactivity
    - $\alpha$-agonist activity in CNS = vasoconstriction
  - Prielipp et al. $\Rightarrow$ 30% ↓ in CBF in healthy human volunteers using PET scans
  - Drummond et al. $\Rightarrow$ ↓ in CBF in healthy human using TCDs

- **Seizures**
  - Animal studies show both pro and anticonvulsant activity
  - $\alpha_2$ agonist activity may produce epileptiform activity in some patients with epilepsy

- **Neuroprotection**
  - Decreases glutamate release
    - ↓ excitotoxicity and cellular oxygen demands

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Curr Opin Anaesthesiol 21:537-543
Neurosurg 2005;57:ONS 1-10
Indications:
- Sedation of intubated and mechanically intubated patients during treatment in an ICU setting
- Sedation of non-intubated patients prior to and/or during surgical and other procedures.

Dosing:
- ICU sedation:
  - Start infusion at 0.2 mcg/kg/hr (range 0.2-0.7 mcg/kg/hr), titrate every 10 min as needed to achieve goal level of sedation
- Procedures:
  - Loading dose 1 mcg/kg over 10 min, start infusion 0.6 mcg/kg/hr (range 0.2-1 mcg/kg/hr)

Loading dose?
- Can cause hypertension or hypotension
- Generally avoided in ICU for sedation

Drug info
Drug information

- **Adverse effects:**
  - Hypotension, bradycardia
  - Nausea, dry mouth
  - Heart block, AV block
- **Administration:**
  - Continuous infusion; concentration 4 mcg/ml (NS)
  - Good compatibility
- **Kinetics:**
  - Half-life: 6 minutes
  - Metabolism: hepatic, no active metabolites
  - Elimination: 2 hours, urine and feces
- **No significant drug interactions**
Drug information

- No specific recommendations for renal or hepatic impairment

- Monitoring:
  - Blood pressure, heart rate, mental status

- Warnings:
  - Bradycardia and sinus arrest
  - Hypotension
  - Co-administration with other vasodilators or negative chronotropic agents

- Precaution or contraindication (?)
  - Advanced heart block or severe ventricular dysfunction
Safety and efficacy in neurosurgery patients

Results:
- 38% were exubated successfully with no adverse reactions
  - Agitation was most common adverse reaction (26%)
- 25.6% hypotension (SBP < 120 mmHg)
- 5% hypertension (SBP > 160 mmHg)
- 1 patient had HR < 60 bpm
- CPP $\rightarrow$ overall increase
- ICP $\rightarrow$ overall decrease

Conclusions:
- Avoid loading doses and use higher infusion rates (?)
- Appears to be safe and effective
- Need more studies with longer follow up
- WIDE standard deviations looking at MAP, SBP, HR in this study

Brain injury 2006;20:791-798
Safety and efficacy in neurosurgery patients

- Retrospective chart review of DEX in 39 neurosurgical patients
- Loading dose of 1 mcg/kg, 0.2-0.7 mcg/kg/hr
- MAP, SBP, DBP, HR, ICP, CPP for 24 hours

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age</td>
<td>34</td>
</tr>
<tr>
<td>Male</td>
<td>67%</td>
</tr>
<tr>
<td>Aneurysm/ SAH</td>
<td>38%</td>
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<tr>
<td>Head trauma</td>
<td>31%</td>
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<tr>
<td>AVM</td>
<td>18%</td>
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</table>

Brain injury 2006;20:791-798
Points for discussion

- **Duration**
  - Approved for only 24 hours
  - Has been shown to be safe up to 5 days in clinical trials

- **Dose range**
  - For ICU sedation → 0.2-0.7 mcg/kg/hr
  - Has been shown to be safe in doses up to 1.5 mcg/kg/hr
    - Bradycardia/ hypotension seen in higher doses

- **Prevention of ICU delirium (?)**
  - SEDCOM found 20 % ↓ incidence vs. midazolam
  - MENDS found significant ↓ in delirium vs. lorazepam

- **Withdrawal (?)**
<table>
<thead>
<tr>
<th>Comparator</th>
<th>Population</th>
<th>End points</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lorazepam vs. dexmedetomidine</td>
<td>N= 106, mixed medical/surgical ICU</td>
<td>• Delirium-free and coma-free days</td>
<td>• Delirium and coma free days, 7 vs. 3 days p= 0.01</td>
</tr>
<tr>
<td></td>
<td>• Mean age ~60 years</td>
<td></td>
<td>• Delirium-free days, 9 vs. 7 days p = 0.09</td>
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<tr>
<td></td>
<td>• 70% were medical ICU</td>
<td></td>
<td>• Coma-free days, 10 vs. 8 p &lt; 0.001</td>
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<tr>
<td></td>
<td>• Requiring mechanical ventilation</td>
<td></td>
<td>• No difference in ICU length of stay</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Time to extubation ↓ with dex</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• HR &lt; 60 bpm 17% vs. 4%, p= 0.03</td>
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</tbody>
</table>

JAMA 2007; 298 (22):2644
## Clinical trials-SEDCOM

<table>
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<th>Comparator</th>
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<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Midazolam vs. dexmedetomidine</td>
<td>N= 375, mixed medical/ surgical ICU</td>
<td>• Time within target sedation range</td>
<td>• No difference between time in target sedation, 77% vs. 75%</td>
</tr>
<tr>
<td>• Fentanyl for pain</td>
<td>• Mean age ~61 years</td>
<td>• Prevalence and incidence of delirium</td>
<td>• Time to extubation, 3.7 vs. 5.6 days, p= 0.01</td>
</tr>
<tr>
<td></td>
<td>• ~85% were medical ICU</td>
<td></td>
<td>• Delirium 54% vs. 76.6%, p&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>• Requiring mechanical ventilation for ≥ 3 days</td>
<td></td>
<td>• ICU length of stay 5.9 vs. 7.6 days, p= 0.24</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• HR &lt; 40 bpm 42.2% vs. 18.9%, p&lt; 0.001</td>
</tr>
</tbody>
</table>

JAMA 2009; 301 (15): 489
• Hospira recalled several lots in mid-October due to particulate matter found in some of the vials
• Teva recalled several lots at the end of October due to bacterial contamination and then suspended further manufacturing
• Anticipated to resolve in fall 2010
• FDA temporarily allowing importation of Fresenium Propoven 1% into U.S.
Fresenius Propoven 1%

- Does NOT contain preservatives (e.g. EDTA, benzyl alcohol, etc)
- Each vial is intended for single administration
  - Discard within 6 hours
- Contra-indicated in patients allergic to soy or peanut
- Contains both long-chain and medium-chain fatty acids
  - Dipirivan only contains long-chain fatty acids

<table>
<thead>
<tr>
<th>Drug</th>
<th>Drug cost per vial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Midazolam</td>
<td>$0.62</td>
</tr>
<tr>
<td>Lorazepam</td>
<td>$0.55</td>
</tr>
<tr>
<td>Propofol</td>
<td>$6.77</td>
</tr>
<tr>
<td>Dexmedetomididine</td>
<td>$63.45</td>
</tr>
</tbody>
</table>
Hypertension incidence = > 50 million people in U.S.
  - Incidence ↑ due to aging population and obesity
~ 1% of people will develop “hypertensive crisis” at some point (i.e. SBP > 179 or DBP > 109 mmHg)
Post operative hypertension occurs ~ 4-35%
  - Within 2 hours of surgery
  - Increased incidence in coronary artery bypass surgeries (CABG) or procedures involving clamping of aorta and carotid artery
  - Can lead to serious complications
    - stroke, cerebral ischemia, encephalopathy, arrhythmias, surgical site bleeding, and myocardial ischemia
# Management of hypertension in ICU

<table>
<thead>
<tr>
<th>Drug</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nicardipine (Ca(^{2+}) channel blocker)</td>
<td>Well tolerated; no effects on HR</td>
<td>Long duration (4-6 hrs); not readily titratable</td>
</tr>
<tr>
<td>Esmolol (selective β blocker)</td>
<td>T ½ ~ 2 min; easy to titrate; quick onset</td>
<td>PG solvent; renal excretion; ↓ HR</td>
</tr>
<tr>
<td>Nitroprusside (PGE inhibitor)</td>
<td>Short t ½; ↓ preload &amp; afterload; easy to titrate; very potent</td>
<td>Cyanide (hepatic failure) and thiocyanate (renal failure) toxicity; ↓ CBF</td>
</tr>
<tr>
<td>Nitroglycerine (PGE inhibitor)</td>
<td>Rapid titration, short t ½; ↓ preload &amp; afterload</td>
<td>Reflex tachycardia; arterial vasodilatation only with high doses</td>
</tr>
<tr>
<td>Labetalol (non-selective β blocker; α blocker)</td>
<td>Onset 2-5 min; duration 2-4 hr; maintains cardiac output and CBF</td>
<td>Not as easily titratable; bronchospasms</td>
</tr>
</tbody>
</table>
Anti-hypertensive: Clevidipine

- Binds to L-type calcium channel and blocks influx of calcium
  - Dihydropyridine
  - “L-type” → long lasting voltage gated
  - Found in myocardial and smooth muscle vasculature
  - Made up of several subunits (i.e. alpha 1 and 2, beta, gamma, delta)
    - Calcium channel blocker medications bind to the alpha-1 subunit

Pharmacotherapy 2010;30:515-28
Clevidipine (Cleviprex™)

- **Indications:**
  - Reduction of blood pressure when oral therapy is not feasible

- **Dosing:**
  - Start at 1-2 mg/hr
  - Titration: ↑ infusion at 90 second intervals; each 1-2 mg/hr increase will ↓ SBP by ~2-4 mmHg
  - 4-6 mg/hr is common maintenance dose
  - Max: no more than 1000 ml in 24 hrs; limited data with 32 mg/hr
    - Little experience with > 72 hrs of use
  - Rebound hypertension: within 8 hours of transition from clevidipine

Pharmacotherapy 2010;30:515-28
<table>
<thead>
<tr>
<th><strong>Advantages</strong></th>
<th><strong>Disadvantages</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Favorable kinetics</td>
<td>• Contains 20% lipid emulsion</td>
</tr>
<tr>
<td>○ Half life ~ 1 min</td>
<td>• Vial has to be discarded within 4 hours</td>
</tr>
<tr>
<td>○ Onset ~ 5 min</td>
<td>• Approved use up to 24 hours</td>
</tr>
<tr>
<td>• Allows for rapid titration and tight control</td>
<td>• Cost ($85 per vial)</td>
</tr>
<tr>
<td>• Vials are ready to use</td>
<td></td>
</tr>
<tr>
<td>• No adjustments for renal/hepatic impairment</td>
<td></td>
</tr>
<tr>
<td>• No significant drug interactions</td>
<td></td>
</tr>
<tr>
<td>• Well tolerated</td>
<td></td>
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</tbody>
</table>

Pharmacotherapy 2010;30:515-28
Clevidipine (Cleviprex™)

- Arterial-selective vasodilator
- Inotropic activity > > chronotropic activity

**Kinetics**
- > 99.5% protein bound
- Small volume of distribution
- Metabolized by plasma esterases to inactive metabolite

- Duration significantly ↑ with ↓ in body temperature
- No significant CYP P450 interactions
- “Cardioprotective” → ↓ infarct size & preserved endothelial function in animal studies

Pharmacotherapy 2010;30:515-28
ECLIPSE trials

- Three phase III safety studies “Evaluation of Clevidipine in the Perioperative Treatment of Hypertension Assessing Safety Events”
  - Peri-operative use in cardiac surgery patients
  - End points: death, stroke, myocardial infarction (MI), or renal dysfunction
  - N = 1506 randomly assigned to clevidipine (n = 752), nitroglycerin (n = 278), sodium nitroprusside (n = 283), nicardipine (n = 193)
  - Infusions started immediately before, during, and after cardiac surgery

Anesth Analg 2008;107:1110-21
Results of ECLIPSE

- No difference in MI, stroke, or renal dysfunction
- No difference in mortality
- Clevidipine patients spent more time at target blood pressure goal compared to nitroglycerine ($p = 0.0006$) and nitroprusside ($p = 0.003$)
  - No difference between nicardipine group
- No differences in adverse effects between all groups
“Clevidipine rapidly and safely reduced blood pressure in patients with acute intracerebral hemorrhage: interim results of the Accelerate Trial—first clinical experience in ICH”

- Multi-centered, open-label
- Patients with ICH within 6 hours and SBP > 160 mmHg
- Clevidipine titrated for goal SBP 140-160 mmHg
ACCELERATE

- N = 30, mean age 63.7 years
- Time to target SBP $\rightarrow$ 6.5 min
- 100% achieved goal SBP within 30 min
- Infusion duration, mean 29.5 hrs
- NO patients had SBP < 90 mmHg within 30 min of initiation
- Adverse effects:
  - 20% pyrexia
  - 10% hypotension
  - 1 pt experienced elevated triglycerides (i.e. > 300 mg/dl) which resolved after treatment
Epilepsy

- Incidence: 2.3 million in U.S.
- Medications are mainstay of therapy
  - 2/3 will be seizure free on one AED
  - 1/3 are refractory to multiple medications
- Complications of AEDs:
  - Drug interactions
  - Tolerability
  - Toxicity
  - Frequency of dosing

Neurologist 2007;13:133-139
Anti-epileptic agents

- **1st generation**
  - Phenobarbital
  - Valproic acid
  - Phenytoin/ fosphenytoin
  - Carbamazepine
  - Primidone
  - Ethosuximide

- **2nd generation**
  - Felbamate
  - Gabapentin
  - Lamotrigine
  - Topiramate
  - Zonisamide
  - Levetiracetam
  - Oxcarbazepine
  - Pregabalin
  - Lacosamide
2\textsuperscript{nd} Generations

- Fewer drug interactions
- Better tolerated than 1\textsuperscript{st} generation
- IV forms:
  - Levetiracetam (Keppra)
  - Lacosamide (Vimpat)
- Black Box Warnings:
  - Felbamate $\rightarrow$ aplastic anemia, hepatotoxicity
  - Lamotrigine $\rightarrow$ Stevens-Johnson syndrome
Newest AED: Lacosamide

- **Indications:**
  - Partial onset seizures in patients > 17 years old
  - Use as adjunct for status epilepticus (?)
  - Neuropathic pain
    - Diabetic neuropathy: awaiting FDA approval
    - Same doses used in epilepsy
    - Found to improve pain scores, sleep, and activity levels in patients compared to placebo

- **Controlled substance (C-V)**
  - Euphoria-type responses (< 1%) compared to placebo
Lacosamide (Vimpat®)

- **Mechanism of action**
  - Enhancement of slow inactivation of voltage-gated sodium channels
    - Prolongs depolarization → ↓ spread of seizures
  - Differs from other AEDs (binds to CRMP-2)

- **Kinetics**
  - Oral tablets are 100% bioavailable
  - Peak plasma concentrations ~ 1-4 hrs
  - $T_{1/2} = 12$ hrs
  - CPY2C19 metabolism to inactive metabolite
  - Renal elimination
  - No significant drug interactions
Lacosamide (Vimpat®)

**Adverse effects:**
- ↑ LFTs
- ECG changes
  - ↑ QTc and PR intervals
- Dizziness, somnolence
- Injection site pain
- Blurred vision, diplopia
- Tremor, ataxia

**Precautions:**
- Hepatic impairment
- Concurrent medications that can ↑ QTc and PR interval
- Heart disease
- Can increase risk of suicidal thoughts and behaviors

Lacosamide package insert; UCB 2009
Lacosamide (Vimpat®)

- **Dosing**
  - 100-200 mg BID
  - IV = PO
  - IV infuse over 30-60 min
  - Tablets: 50 mg, 100 mg, 150 mg, 200 mg
  - CrCl < 30 ml/min dose adjust
    - Max dose ~ 300 mg/day
    - 50% removed during dialysis
  - Loading dose?

- **Cost:**
  - $43 for 200 mg IV vial
  - Monthly cost for patient = $260-475
Uses of lacosamide

- Case reports as an adjunctive agent with levetiracetam and phenytoin
- Rodent models of status epilepticus (SE)
- Current trials
  - Safety and kinetics in children with partial seizures
  - Pilot study in NSICU as seizure prophylaxis compared to phenytoin in traumatic brain injury patients
  - Single dose IV (bolus dose) followed by oral dosing
  - Use as monotherapy for partial onset seizures in adults
  - Migraine prophylaxis
  - Diabetic neuropathy
  - Fibromyalgia
  - Osteoarthritis of the knee

Clinicaltrials.gov; accessed 5/25/10
Anti-platelet therapy with clopidogrel (Plavix)
Anti-platelet therapy with clopidogrel
- ↓ rate of cardiovascular death, myocardial infarction (MI), stroke, or refractory ischemia in NSTEMI patients
- Indications:
  - Acute coronary syndrome
  - Recent MI, stroke, or established peripheral artery disease
  - Post-stent placement
- Irreversible platelet binder
  - Duration ~ 7 days
- ↑ risk of bleeding when combined with aspirin
  - CURE (GI and puncture sites)
  - COMMIT → significant ↑ in non-major/ non-cerebral bleeding
Updates with clopidogrel

- Concomitant therapy with proton-pump inhibitors (PPIs) = ↓ effectiveness
- Genetic variations in metabolism = ↓ effectiveness
**Clopidogrel metabolism**

- **Prodrug → active drug**
  - CYP2C19 is required to convert clopidogrel to active form (R-130964)
  - Irreversible binding to P2Y12 receptor → prevents platelet activation by adenosine diphosphate (ADP)

*Ann Pharmacother 2009;43:1266-74*
Proton pump inhibitors

- PPIs are recommended for therapy and prophylaxis of aspirin-associated gastrointestinal injury
  - Dual anti-platelet therapy
- > 100 million prescriptions/year in U.S. for both PPI and clopidogrel
- Omeprazole is OTC
- Metabolized by CYP P450 system
  - 2C19 and 3A4
- CYP 2C19 metabolism:
  - omeprazole = esomeprazole > pantoprazole > lansoprazole > rabeprazole

Ann Pharmacother 2009;43:1266-74
Clopidogrel and PPIs

Most of data comes from platelet-reactivity trials

- Measuring PRI (platelet reactivity index)
  - PRI > 50% = low response
  - < 50% = good response
- Aetna insurance company did retrospective review on their patients taking both PPI and clopidogrel:
  - 1-year acute MI rates:
    - 1.38% with NO PPI
    - 3.08% with daily PPI
    - 5% with twice daily PPI
  - Data sent as “letter to editor” suggesting that PPI use ↓ ability of clopidogrel to prevent cardiovascular events

Ann Pharmacother 2009;43:1266-74
Clopidogrel and PPIs

- Clopidogrel Medco Outcomes Study
  - ~17,000 patients taking clopidogrel s/p coronary stenting
  - 41% took PPI
  - Risk of major adverse CV events ↑ from 17.9 to 25.1% with PPI therapy (p< 0.0001)
    - Omeprazole > esomeprazole> pantoprazole> lansoprazole
  - Incidence of hospitalization for GI bleeding was 1.1% among patients taking PPI and 0.07% with no PPI

- CREDO found no difference in CV events in patients taking PPI vs. no PPI

- Ontario Public Drug Program found 40% ↑ risk of MI at 90 days post-stenting with PPI
  - No risk seen with pantoprazole

Ann Pharmacother 2009;43:1266-74
Clopidogrel and PPIs

- Retrospective trials
- Patients taking PPIs may have more comorbidities
- Prilosec OTC
- FDA recommended reevaluating the need to start or continue PPI in patients on clopidogrel
- Consider H2-blocker or PPI with less affinity for CYP2C19
  - pantoprazole
Poor metabolizers

- New black box warning for clopidogrel: “diminished effectiveness in poor metabolizers”
- Genetic polymorphisms of CYP2C19:
  - ~ 3% of studied population
  - Poor metabolizers have a loss of function of alleles *2 and *3
  - 2-14% of population are poor metabolizers
    - 2% whites, 4% blacks, 14% Chinese population
- Poor metabolizers will not receive the full benefits of this drug
Clopidogrel and poor metabolizers

- Cross-over study with 40 patients
  - 10 patients in each group: ultra-rapid, extensive, intermediate, and poor CYP2C19 metabolizers
  - Randomized to 2 groups: 300 mg load, 75 mg daily or 600 mg load, 150 mg daily x 5 days
    - Washout period and then crossed over to other dosing group
  - Poor metabolizers had ↓ active metabolite and ↑ platelet aggregation in lower dosing regimen
  - Poor metabolizers had greater active metabolite exposure and antiplatelet response with 600mg/150 mg than the 300mg/75 mg dose
- Appropriate dose is still unknown for poor metabolizers

Plavix updated package insert, May 2010
Clopidogrel and poor metabolizers

- FDA recommendations:
  - Be aware that some patients have low CYP2C19 activity
  - Blood tests are available to determine patients’ CYP2C19 status
  - Consider use of other anti-platelet medications or alternative dosing strategies in clopidogrel in poor metabolizers
  - Be aware that a higher dosing regimen 600 mg loading dose followed by 150 mg once daily in poor metabolizers increases anti-platelet response, an appropriate dose regimen to poor metabolizers has not been established in a clinical outcome trial

Plavix updated package insert, May 2010
Conclusions

- Dexmedetomidine is an option for sedation in the NSICU and may have neuroprotective properties.

- Clevidipine is a new rapid acting calcium channel blocker for short-term treatment of hypertension.

- Lacosamide has a unique mechanism of action and may be an option for refractory status epilepticus.

- Be aware of the updates with clopidogrel therapy in patients who are taking a PPI and in patients who are “slow metabolizers”.