Capsaicin

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Uses

- Topical analgesic treatment for diabetic polyneuropathy, postherpetic neuralgia, and other peripheral neuropathic pain; also for osteoarthritis, rheumatoid arthritis, and other painful disorders
- Spray used as nonlethal force by law enforcement

Perioperative Risks

- None reported.
- After exposure to aerosolized capsaicin (e.g., in a trauma pt restrained by police), airway irritability, coughing, and bronchospasm may occur.

Overview/Pharmacology

- Topical effects only since very poorly absorbed from the skin

Drug Class/Mechanism of Action/Usual Dose

- Analgesic; 8-methyl-N-vanillyl-noneamide, an agonist of temperature-sensitive TRPV1.
- Selective binding to afferent nociceptive C fibers in the skin causes neuronal excitation and the release of substance P.
- Repeated application to the skin depletes C fibers of substance P and calcitonin gene–related peptide, which subsequently reduces sensitivity to pain.
- Reversible degeneration of small nerve fibers in the epidermis occurs with long-term use.
- Various creams and patches are available over the counter in a wide range of strengths as low as 0.025%.
- 8% capsaicin patch is approved in Europe for treatment of peripheral neuropathic pain. In USA, it is approved only for postherpetic neuralgia. Treatment is given in a series of 30–60-min applications.

Drug Effects

System	Effect	Assessment by Hx	PE	Test
DERM (topical)	Burning sensation at site, possibly also redness	Hx of chronic pain	Thermal allodynia at site, or hypesthesia at site of application	
HEENT (topical or inhaled)	Lacrimation, blepharospasm	Accidental exposure of topical agent to the eye; exposure to aerosol in confrontation with law enforcement	Eye exam	
RESP (inhaled)	Extreme airway irritability, coughing and bronchospasm, possibly death with heavy exposure	Exposure to aerosol in confrontation with law enforcement or in industrial accident	Auscultation, pulse oximetry	

Key References: Burness CB, McCormack PL: Capsaicin 8% patch: a review in peripheral neuropathic pain, *Drugs* 76(1):123–134, 2016; Knotkova H, Pappagallo M, Szallasi A: Capsaicin (TRPVI agonist) therapy for pain relief, *Clin J Pain* 24(2):142–154, 2008.

Perioperative Implications

- None known

Drug Interactions

- None known

Anticipated Problems/Concerns

- Moderate efficacy in chronic pain syndromes that have an anatomically superficial and localized pain generator.
- Compliance is poor because of burning pain with application.
- Topical or regional anesthesia is necessary for application of high-dose 8% concentration.

Carbamazepine–Oxcarbazepine

Christophe Aveline

Uses

- Synthesized in 1953, introduced for trigeminal pain in 1962 and for epilepsy in 1965; approved by the USA FDA since 1976 for the following:
  - Epilepsy: Generalized tonic-clonic seizures, partial seizures with complex pathology (psychomotor, temporal), partial seizures with or without generalization, mixed generalized and partial seizures
  - Chronic pain: Pain associated to trigeminal and/or glossopharyngeal neuralgia
  - CNS disorders: Acute or mixed episodes associated with bipolar I disorder
  - Off-label uses: Central and diabetic neuropathic pain; postherpetic neuralgia, phantom limb pain, alcohol withdrawal, preventing relapse in pts with bipolar disorders having a resistance or intolerance to lithium, treatment of manic or hypomanic excitation states, schizophrenia
  - Oxcarbazepine (OXC): 10-keto derivative of carbamazepine (CMZ), FDA-approved since 2000 as adjunctive therapy for partial seizures in adults and children >4 y and as monotherapy in adults for partial seizures

Perioperative Risks/Worry About

- Pharmacologic: Clinically significant drug interactions
- CNS: Increased sedation, dizziness, and ataxia
- CV: Aggravation of Htn, hypotension, CAD, arrhythmias, and rarely AV block
- Laboratory: Higher incidence of hyponatremia, aplastic anemia, agranulocytosis, thrombopenia and leukopenia, as well as elevated LFTs and hypothyroidism

Overview/Pharmacology

- The main activated form is the carbamazepine-10, 11 epoxide after transformation by hepatic CYP3A4 and CYP2C8.
- Peak plasma concentrations: tablet 2–6 h after ingestion, suspension 1.5 h, extended release 26–96 h. Bioavailability 85–100%, no gender differences, highly lipophilic, protein binding 70–80%, apparent volume of distribution: 0.8–1.5 L/kg. CMZ crosses the placental barrier and passes into breast milk, where it is half as concentrated.
- Hepatic biotransformation 98%. $T_{½}$: 10–20 h after 1 dose, 4–12 h after repeated administration (transcriptional upregulation of its own metabolism occurring from day 5 and stabilized between 3–5 wk). SNP in CYP450, in microsomal epoxide hydrolase, in ABCB1 and ABCB2 and Na_V are involved in the variation of metabolism of CMZ.
- Mainly metabolized by the CYP3A4 and CYP2C8, others CYP-involved are CYP2B6, CYP3A5, EPHX, and UGT2B7.
  - Inhibitors of CMZ: Aprepitant, erythromycin, clarithromycin troleandomycin, verapamil, diltiazem, ketoconazole, fluconazole, itraconazole, voriconazole, acetazolamide, ticlid, nefazodone, valproate, fluvoxamine, fluoxetine, trazodone, olanzapine, loratadine, terfenadine, omeprazole, oxybutynin, dantrolene, and grapefruit juice
  - Inducers of CMZ: Glucocorticoids, rifampicin, cotrimoxazole, ritonavir, sertraline, felbamate, cisplatin, doxorubicin, phenytoin, phenobarbital, theophylline, and CMZ autoinduction
  - CMZ decreases the plasma concentration of valproic acid, lamotrigine, phenytoin, felbamate, tiagabine, ethosuximide, aripiprazole, lapatinib, itraconazole, tramadol, protease inhibitors, dicumarol, doxycycline, levothyroxine, tricyclic antidepressant, cyclosporine, felodipine, aminosteroid NDMB (pancuronium, vecuronium, rocuronium), and benzodiazepines (interactions compensated by the antiepileptic effect of the added molecule and inductor/inhibitor effects of added molecule). Gabapentin, pregabalin, and levetiracetam are not affected by CMZ. CMZ reduces ethinyl estradiol and progestagen concentrations on the order of 50%.
  - OXC: Prodrug converted into active metabolite (S-licarbazepine) in liver by reductase; apparent volume of distribution 49 L, low protein binding fixation (40%), T_{max} 3–13 h, $T_{1/2}$ 7–20 h (for the active compound); steady-state 2–3 d; fewer drug-drug interaction (reduced impact on CYP450 system, $CYP2C19^{2+}$, $CYP3A4/5^{+}$), decreased dihydropyridine calcium antagonist and oral contraceptive

Side Effects

- Neurologic:
  - Very common: Dizziness, ataxia, drowsiness, fatigue (particularly in elderly)
  - Common: Headache, diplopia, accommodation disorders
  - Uncommon: Tremor, dystonia, orofacial dyskinesias, nystagmus
  - Rare: Oculomotor disturbances, ataxia, speech disorders, agitation, convulsion, suicidal behavior
  - Very rare: Neuroleptic malignant syndrome, dysgeusia, aseptic meningitis
- Respiratory:
  - Rare, pulm hypersensitivity usually associated with eosinophilia and systemic syndrome