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

- CV:
  - Negative chronotropic and dromotropic effects (above upper therapeutic level), reduced rise and amplitude on the AP in Purkinje fibers in atrial and ventricular myocardial cells
  - Sinus bradycardia, sinoatrial block, and AV block. Hypotension, vasoplegia (poisoning), pulm embolism, CAD and CHF, lymphedema and adenopathy. Very rarely: myocarditis
- Hematologic:
  - Rare: Leukopenia, thrombocytopenia, pancytopenia, hypogammaglobulinemia. Eosinophilia (aromatic structure associated with DRESS), more frequent in the presence of *HLA-A*3101* allele in European, Japanese, and Chinese pts.
  - Very rarely: Pancytopenia, agranulocytosis, variegate porphyria, acute intermittent porphyria
- Dermatologic:
  - More common: Maculopapular rash, urticarial, erythema multiforme, and lupus
  - Rare: Toxic epidermal necrolysis and Stevens-Johnson syndrome (10 times higher in Thai or Han Chinese pts with the *HLA-B*1502* allele). Known sensitivity to one anticonvulsant may increase the risk of serious rash with another anticonvulsant.
- Metabolic:
  - Weight gain, hyponatremia (SIADH, alterations of renal tubular electrolytes transport, V2R-dependent and V2R-independent ways with increased permeability by AQP2 expression, and resetting of osmoreceptors associated to renal impairment)
  - Increased T_4 and free T_4, increased TSH (particularly in children)
- GI:
  - Very common: N/V, dry mouth
  - Uncommon: Diarrhea, constipation
  - Rare: Abdominal pain
  - Very rare: Glossitis, stomatitis, and pancreatitis
- GU: Rare: Azotemia, renal failure, increased BUN, acute urinary retention, oliguria, erectile dysfunction
- Other:
  - Very rare: Allergy, conjunctivitis, leg cramps, hearing loss or hyperacusis, tinnitus
  - OXC: 25–35% crossed-hypersensitivity reaction with CMZ; hyponatremia possible but less; SJS and epidermal necrolysis very rare

Contraindications

- High degree of atrioventricular block
- Known hypersensitivity to CMZ or to any of the excipients or to tricyclic antidepressants
- Previous bone marrow suppression
- Acute intermittent porphyria, variegate porphyria, porphyria cutanea tarda
- Coadministration with telaprevir, voriconazole, nefazodone, *Hypericum perforatum*, MAO inhibitors

Acute Toxicity

- Lowest lethal doses: 3.2 g in adults and 1.6–4 g in children
- Peak levels delayed up to 96 h after massive ingestion of controlled-release forms. Clinical signs: Ataxia, nystagmus, mydriasis, movement disorders and anticholinergic syndrome, seizures and coma, hypotension, respiratory depression; decreased natremia, kalemia, and glycemia. Use diazepam or phenobarbital for seizures. Conventional cardiovascular and respiratory life support, charcoal-HP through gastric lavage, hemodialysis or hemoperfusion (rarely).

Drug Class/Mechanism of Action/Usual Dose

- Iminostilbene derivative (5H-dibenzazepine-5-carboxamide) blocks the IV-S6 transmembrane segment of the Na_V, prolongs the inactivated state (in a use- and frequency-dependent manner), blocks Na currents faster and in a concentration-dependent manner during high-frequency depolarization. Domains IV-S6 mutations are described, which lowers the affinity and activity of various Na_V blockers such as CMZ.
- Antihyperalgesic: Decreases presynaptic voltage-gated Ca channels, decreased presynaptic and post-synaptic NMDA, AMPA- and kainite-mediated inward currents. Modulation of central and peripheral adenosine receptors, α2a and α2c adrenoreceptors and P2X4 receptors of astrocytes. CMZ enhances synaptic protein activity and dendritic outgrowth, decreased pro-apoptotic Bcl-2 in neural cells, downregulates the arachidonic acid signaling and cascade in cerebral neurons via the NMDA and dopamine D2 signals.
- Available only orally as normal, chewable, and extended-release tablets and suspension
- Usual dose:
  - Epilepsy disorders: Adults and teenagers >15 y: maximal daily dose <1200 mg/24 h; children 6–12 y: <1000 mg/24 h; children <6 y: <35 mg/kg per 24 h
  - Trigeminal pain: 400–800 mg/d (<1200 mg/d); relapse prevention (bipolar disorders): 400–800 mg/d; treatment of manic or hypomanic excitation states: 600–1200 mg/d
  - Blood level for seizures disorders: 4–12 μg/mL; for trigeminal neuralgia: 5–18 μg/mL
- OXC:
  - Prodrug, reduced into active metabolite 10-hydroxy CBZ (MHD), 80% of S and 20% of R enantiomers of licarbazepine (ratio 4:1), S-licarbazepine in the main active metabolite in the CNS
  - Reduced impact on CYP450 system ($CYP2C19^{2+}$, $CYP3A4/5^{+}$), lower incidence of agranulocytosis and bone marrow depression while having similar seizure control. Same recommendation as CMZ for *HLA B*1502* testing. HypoNa 2.8% (risk factors: old age, polytherapy, diuretic use).

Drug Effects

System	Effect	Assessment by Hx	PE	Test
CV	Heart failure AV/sinoatrial block	Dyspnea, pulm edema Palpitations, bradycardia	Auscultation	X-ray, ECHO, BNP ECG
CNS	Sedation, confusion	Concomitant AED	Clinical assessment	
METAB	Hyponatremia SIADH-like hypothyroidism	Edema, drowsiness Wt gain Weakness, constipation, hair loss	Oliguria	Decreased Na, decreased serum osmolality, increased U_{na}/U_{crea}, increased U_k/U_{crea}, increased U osmolarity Increased TSH, decreased T_3, decreased free T_4
HEME	Anemia/aplasia Thrombocytopenia	Pallor Petechiae, bleeding	Clinical assessment Clinical assessment	CBC CBC
RENAL	Renal insufficiency	Edema Dyspnea	Azotemia, Acute oliguria	Cr, GFR, BUN, ABG
RESP/ DERM	Pneumonitis SJS-TEN	Pulm hypersensitivity Bullous rash	Clinical assessment Clinical assessment	X-ray, ECHO, *HLA-A*3101* screening Skin biopsy, *HLA B*1502* screening

Key References: Richard A, Girard F, Girard DC, et al.: Cisatracurium-induced neuromuscular blockade is affected by chronic phenytoin or carbamazepine treatment in neurosurgical patients, *Anesth Analg* 100(2):538–544, 2005; Yang YC, Huang CS, Kuo CC: Lidocaine, carbamazepine, and imipramine have partially overlapping binding sites and additive inhibitory effect on neuronal Na^+ channels, *Anesthesiology* 113(1):160–174, 2010.

Perioperative Implications

Preoperative Concerns

- CMZ must be continued, taken early in the morning in preop period, withdrawal can be associated with seizure and periop hyperalgesia.
- Functional evaluation, safety, and effectiveness of CMZ; previous systemic syndrome; determination of all other treatment, particularly neurologic, psychiatric, and cardiovascular drugs.
- Genetic screening for *HLA-A*3101* in European, Japanese, and Chinese pts and for *HLA B*1502* in Thai or Han Chinese pts usually proposed prior initiation therapy.
- Check the last blood level of CMZ (4–18 μmol/mL), taking into account the equilibration period and auto-induction by CMZ at the beginning of treatment.
- ECG for arrhythmias, AV block including second- and third-degree block, ischemic changes.
- Check lab tests:
  - Leukocytes, plts
  - Liver enzymes
  - Natremia in case of major surgery when other hyponatremia-induced drugs are associated with CMZ, surgery needing osmotherapy
  - Glomerular filtration rate (CKD-epinephrine [EPI]), BUN
  - TSH

Induction/Maintenance

- Be vigilant for arrhythmias, arterial hypotension or hypotension, and cardiac ischemia when using cardiodepressive drugs concomitantly.
- Use of propofol or thiopental possible. Both inhibit GABA and Na channels. Low dose of ketamine (high $GABA_A$ receptors potentiation, anti-NMDA effects) not contraindicated. No data for continuous IV lidocaine and CMZ. Etomidate should be avoided in epileptic pts.

- All NDMBs must be monitored from induction of anesthesia to emergence. Loading doses are not affected but maintenance dosing needs monitoring. Decreased potency and duration of aminosteroid NDMBs (rocuronium, vecuronium, and pancuronium) by PK/PD interaction, an increase in hepatic metabolism/biliary excretion, upregulation of acetylcholine receptors, and clearance. No impact on onset of NDMBs. Mivacurium and atracurium not concerned. No association between epileptic status, CMZ, and laudanosine. Faster recovery of neuromuscular block and more rapid speed of infusion with cisatracurium.
- Decreased blood level of midazolam (CTP3A4 induction); reduction of propofol concentration (common metabolic pathway CYP3A4, CYP2C8, and CYP2B6)
- No impact on sufentanil (total clearance > hepatic clearance) and remifentanil (esterase-dependent metabolic pathway not affected by CYP450). Higher dose of fentanyl needed (strongly catalyzed by CYP3A4). Combine objective assessment of analgesia (pupillometry or ANI) to usual hemodynamic variations to improve effective dosage. Morphine can be used without specific modification. CMZ decreases morphine-3-glucuronide-induced enhancement of $Na_v1.7$, and the combination of CMZ-morphine reverses late tactile allodynia in a neuropathic model of pain. No increase of morphine-induced hypercapnia/hypoventilation.
- CMZ decreases bioavailability of paracetamol. Short-term prescription of paracetamol with daily dose <4 g/d; risk of hepatotoxicity among long-term user of paracetamol, <3 g/d in adult. Ibuprofen can displace CMZ protein binding in uremic pt.
- PNB with recommended dose and performed under US is safe in CMZ pts. Lidocaine blocks the residue in the S6 segment of domain IV of Na_v with a lesser interaction with the S4 segment of domains III and IV (voltage sensor). A common site of binding for local anesthetics and CMZ was defined in the S6 segment. Lidocaine and CMZ produces an additive interaction on Na^+ ion passage. CMZ can induce the metabolism of lidocaine (CYP3A4 and CYP1A2 pathway and a high hepatic clearance). Ropivacaine and levobupivacaine are hydrolyzed by CYP1A2 and less by CYP3A4. Beneficial effect of combined oral CMZ and repetitive peripheral nerve block in pts suffering from trigeminal neuralgia. Clinical signs associated with LAST can mimic some signs of a CMZ overdose. In cases of suspected LAST, check blood level of CMZ and LA, initiate basic and advanced life support and pharmacologic measures according guidelines. US required to reduce vascular puncture and to obtain analgesia with a reduced total dose of LA.
- Consider increased tendency to hyponatremia in urologic procedures or neurosurgery (preop use of hyperosmotic solutions)

Postoperative Period

- Keep in mind the possible hemodynamic effects (arrhythmias, arterial hypotension or hypotension, cardiac ischemia).
- Neuromuscular monitoring of NDMB in PACU to confirm complete recovery.
- Resume CMZ after surgery at preop dosage. Use caution when oral alimentation is not rapidly obtained or when hypovolemic status after major surgery. Plasma level of CMZ must be checked after resuming and side effects evaluated.
- Thromboprophylaxis for the postop period according guidelines (cumulative risk of surgery and treatment by CMZ).
- Oral hormonal contraceptives call for additional safety precautions.
- Watch for natremia in the postop period after major and/or urologic interventions, geriatric or noncommunicating pts, and when pts are taking diuretics.
- Arrhythmias and atrioventricular block associated with CMZ remain possible. ECG and blood tests (troponin, BNP) in case of cardiovascular instability or after major surgery in pts receiving beta-blockers, CCBs, antiarrhythmics, or antihypertensives.

Anticipated Problems/Concerns

- PK/PD of CMZ and impact on CYP450 system
- Blood level of CMZ, hyponatremia
- Use caution in geriatric pts (confusion)
- Monitoring of neuromuscular block required (particularly aminosteroid muscle relaxants)
- CV impact and thromboembolism risk
- Antihyperalgesic drug
- Additive interaction between CMZ and lidocaine

Chemotherapeutic Agents

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Risk

- Cancer is the second most common cause of death in USA. In 2016, about 1,685,210 pts will be diagnosed with cancer and 595,690 will die of it.
- More than two-thirds of all cancers are diagnosed in people 50 y of age or older. Prostate cancer is the most common among men, while breast cancer is the most frequent in women. In both genders, lung cancer is the leading cause of death due to cancer.

Uses

- Drugs or biological agents (interleukins and interferon) are commonly used to (1) stop cancer cells from proliferating, migrating, and invading and/or (2) facilitate their recognition by the immune system.
- Traditional chemotherapy agents, targeted chemotherapies, and immunotherapies are still front-line drugs for the treatment of solid and hematologic malignancies.
- Neoadjuvant (before surgery) chemotherapy (and possibly radiation) remains the treatment of choice for many solid cancers.

Perioperative Risks

- Intraop bleeding due to thrombocytopenia, postop infection, complications (leukopenias), blood transfusions (anemia).
- Cardiac insufficiency and fluid overload (due to cardiotoxic agents such as the anthracyclines). Pulm toxicities can lead to periop pulm edema.
- Acute kidney injury (nephrotoxic agents).
- Mononeuropathy (neurotoxic drugs). Bone demineralization (osteopenia) is a risk for fracture after inadequate pt positioning.