Pseudocholinesterase

Definition

Plasma cholinesterase (also known as pseudocholinesterase, butyrylcholinesterase, or BuChE) is a serine hydrolase synthesized in the liver and present in the plasma, that catalyses the hydrolysis of esters of choline. It is structurally and functionally related to acetylcholinestrase, an enzyme that catalyzes the hydrolysis of acetylcholine.

It is most known for the metabolism of depolarizing neuromuscular blocking agent succinylcholine by hydrolysis of the two ester links of choline to succinylmonocholine and choline. When succinylcholine is injected intravenously, about 90% of its dose is hydrolyzed by BChE within 1 min and only 10% reaches the neuromuscular junction. Because little or no butyrylcholinesterase is present at the neuromuscular junction, the neuromuscular blockade of succinylcholine is terminated by its diffusion away from the neuromuscular junction into the circulation. The effect of butyrylcholinesterase on onset and duration of action of succinylcholine is therefore exerted by the rate of hydrolysis of succinylcholine before it reaches, and after it leaves the NMJ.

BuChE deficiency is usually recognized when an anesthetized patient has prolonged neuromuscular blockade from the administration of SCh. First report of BuChE deficiency by Nilsson in 1953 described a patient who failed to resume spontaneous ventilation after completion of a short operation in the setting of SCh administration; therefore the colloquial name “suxamethonium apnea” was introduced.

Butyrylcholinesterase catalyzes the hydrolysis of esters of choline, including acetylcholine, butyrylcholine, as well as the hydrolysis of esters such as acetylsalicylic acid and heroin. BuChE is also responsible for the metabolism of mivacurium, and the concomitant use of mivacurium and SCh in susceptible patients may exaggerate paralytic effect. Since, BuChE enzymes contribute to ester-type local anesthetics hydrolysis to an alkylamine and paraaminobenzoic acid (PABA), patients with abnormal

BuChE levels may be at increased risk for toxic side effects. BuChE also accelerates the metabolism of cocaine and has been proposed as a possible pharmacologic agent for the treatment of cocaine toxicity.

There are different molecular forms of BuChE, including monomers and oligomers that are built of identical subunits. The symmetric monomeric form is called the G1 form. The dimeric form, G2, consists of two molecules that are joined by a disulfide bridge between the cysteine residues of each monomer. Two G2 forms held together by hydrophobic interactions can form a tetramer, the G4. These are synthesised in the liver and can be additionally found in kidneys, pancreas, brain and plasma. Interestingly, BuChE enzymes are widely distributed in the nervous system. It has been postulated that BuChE may have important roles in cholinergic neurotransmission and neurodegenerative diseases.

More than 40 mutations of BCHE have been recognized, but not all of them have been fully characterized. In general, these mutations manifest as different levels of catalytic activity. Normally, SCh is rapidly hydrolyzed after administration (the elimination half-time is estimated to be 2–4 minutes); however, when BuChE mutations are present SCh action may be prolonged. The duration of “suxamethonium apnea” cited for most common mutations ranges from 10 minutes to 2 hours; however, SCh effect may persist up to 8 hours and longer in some cases. Supportive ventilation is all that is required for treatment; there is no pharmacologic agent commonly used to increase the rate of recovery from abnormally prolonged SCh neuromuscular blockade.

Most variants of plasma BuChE can be variably inhibited by dibucaine and different phenotypical manifestations of BuChE deficiency have been studied by using dibucaine inhibition to differentiate among them. In normal patients, dibucaine will inhibit 80% of enzyme activity which corresponds to dibucaine number of 80. Heterozygous atypical plasma BuChE occurs in about 4% of the population with the corresponding dibucaine number between 30 and 65. Homozygous atypical plasma

BuChE occurs in about 0.04% of the population and corresponds to a dibucaine number of 20.

The most prevalent, wild-type BuChE is also inhibited by fluoride. However, there are two known less-prevalent fluoride-resistant forms of BuChE which allows for additional testing in cases of suspected clinical deficiency.

Plasma BuChE levels are affected by certain physiologic and pharmacologic factors.

1.For example, alcoholism or obesity increase BuChE levels, so that higher doses of SCh may be necessary in obese patients, up to 1–2 mg/kg based on TBW and not IBW.

2. BuChE levels may decrease to 75% of normal during pregnancy and to 67% of normal during immediate postpartum period; this degree of decrease is usually not clinically significant, but occasional prolonged apnea from SCh administration may result.

3.Similarly, significant decrease of synthetic liver funciton may also result in prolonged apnea.

4. In addition, plasma BuChE may be inhibited by exogenous compounds such as organophosphates (e.g., insecticides, chemical warfare agents, and echothiophate, a topical glaucoma agent), anticholinesterase agents (e.g., neostigmine, pyridostigmine, edrophonium), and MOAs.

Esmolol

Mechanism of Action/Pharmacology

Reduced rate of Phase 4 (precedes the sharp upstroke in Phase 0) depolarization

Has a methylester group and is hydrolyzed by **red cell esterases** (**half-life 9 minutes**)

Hemodynamic Effects

Decreases heart rate, contractility, and sometimes blood pressure. **Note that beta blockers do not *always* decrease blood pressure**, especially during acute administration, although esmolol is more likely than propranolol. Decreases myocardial work and *usually* increasing coronary blood flow (improved by a relative increase in diastolic time, potentially worsened if diastolic pressure gradients are decreased) **improve the myocardial supply:demand ratio**

Systemic

Unlike non-selective beta-blockers, esmolol does not block B2 receptors and thus is more likely to cause hypotension

Pulmonic

Because it is highly B1-selective, esmolol **appears to be safe in patients with pulmonary disease**

Cardiac

Clinical Use

Hemodynamic Control

Loaded at 0.5 mg/kg followed by an infusion of 50-300 ucg/kg/min. Used for blood pressure and heart rate control (especially in atrial fibrillation).

Alternative to Opioids

It has been well documented that even **a single dose of fentanyl with induction can increase the incidence of PONV, increase post-**

operative opioid consumption, and delay PACU discharge [Sukhani R. Anesth Analg 83: 975, 1996]. In light of this, alternative agents may warrant consideration for control of hemodynamic changes, in particular the sympathetic response to noxious stimuli under general anesthesia – interestingly, **two randomized controlled trials have show comparable or even favorable outcomes when esmolol is used in lieu of opioids to control sympathetic nervous system responses to noxious stimuli under general anesthesia** [Coloma M et al. Anesth Analg 92: 352, 2001; Collard V et al. Anesth Analg 105: 1255, 2007]

Remifentanil pharmacokinetics

Remifentanil is a potent intravenous short-acting synthetic opioid. It acts as a μ-receptor agonist. Remifentanil is rapidly hydrolyzed by plasma and tissue esterases. It is unique in that it displays no context-sensitivity. In other words, it does not accumulate with prolonged infusion. The context-sensitive half-life is ~4 minutes. It is useful for procedures requiring profound analgesia and rapid emergence, such as neurosurgical and otolaryngology procedures. It is typically administered as an infusion but bolus doses are very effective for brief noxious stimuli. Caution must be taken when using remifentanil in non-intubated patients as it is a potent respiratory depressant and can cause muscle rigidity with inability to mask ventilate.

Metabolism – Meperidine

Definition

Meperidine is a synthetic opioid widely used for treating pain. It is also used for controlling post anesthetic shivering. Its main pharmacological action is produced through μ receptors on the central nervous system (CNS). Meperidine is metabolized extensively in the human liver by 1) N-demethylation to normeperidine (6-N-desmethylmeperidine), which may

be further hydrolyzed to normeperidinic acid and subsequently conjugated; and 2) by hydrolysis to meperidinic acid by human carboxylesterase-1 followed by conjugation. Meperidine metabolites account for over half the drug in the urine.

Normeperidine is devoid of analgesic activity, but it is a potent stimulant of the CNS. Its main adverse effect is neurotoxicity, producing symptoms that include nervousness, tremors, muscle twitches, and seizures. Multiple doses of meperidine result in accumulation of normeperidine due to its long elimination half-life (15-30 h) as compared with the meperidine (2.4-4 h). Meperidine is metabolized chiefly in the liver, with a half-life of ~3 hours. In patients with cirrhosis, the bioavailability of meperidine is increased to as much as 80%, and the t1/2 of both meperidine and normeperidine are prolonged. **Normeperidine is eliminated via the liver and kidney; patients with significant impairment of hepatic or renal function have prolonged normeperidine half-lives and are especially predisposed to its toxic effects.** Other individuals susceptible to the adverse effects of normeperidine include 1) individuals who receive prolonged administration of meperidine (such as cancer and chronic pain patients) or high meperidine doses (>400-600 mg/day), 2) patients receiving oral meperidine, 3) individuals treated with monoamine oxidase inhibitors, and 4) patients receiving medications that induce hepatic enzyme systems. As a result of these, meperidine is not recommended for the treatment of chronic pain because of concerns over metabolite toxicity. It should not be used for longer than 48 hours or in doses >600 mg/day (see www.ahrq.gov).

Interactions with Other Drugs

Severe reactions may follow the administration of meperidine in patients being treated with MAO inhibitors. Two basic types of interactions can be observed. The most prominent is an excitatory reaction (“serotonin syndrome”) with delirium, hyperthermia, headache, hyper- or hypotension, rigidity, convulsions, coma, and death. This reaction may be

due to the ability of meperidine to block neuronal reuptake of 5-HT, resulting in serotonergic overactivity . Conversely, the MAO inhibitor interaction with merperidine may resemble acute narcotic overdose owing to the inhibition of hepatic CYPs. **Therefore, meperidine and its congeners are contraindicated in patients taking MAO inhibitors or within 14 days after discontinuation of an MAO inhibitor.** Similarly, dextromethorphan (an analog of levorphanol used as a non-narcotic cough suppressant) also inhibits neuronal 5-HT uptake and must be avoided in these patients.

MAO inhibitor: meperidine toxicity

Definition

The original antidepressants, phenelzine (Nardil), isocarboxazid (Marplan), and tranylcypromine (Parnate) are all irreversible inhibitors of MAO-A and MAO-B, leading to pronounced effects on metabolism of endogenous (5-HT, NE, and DA) and exogenous (tyramine) monoamines. Selegeline is a selective MAO-B inhibitor – serotonin is deaminated by MAO-A (MAO-B primarily breaks down dopamine and phenethylamine), so the risk of serotonin syndrome is lower (unless high doses of selegiline are used, in which case MAO-A inhibition may occur).

All phenylpiperidine opioids (meperidine, methadone, tramadol) are weak serotonin reuptake inhibitors and can lead to serotonin syndrome (confusion, fever, diaphoresis, shivering, ataxia, myoclonus, hyperreflexia, and death) caused by excessive serotonergic stimulation of the 5-HT1A receptor.

MAOIs and Meperidine (and other phenylpiperidine opioids)

- MAOIs: phenelzine (Nardil), isocarboxazid (Marplan), and tranylcypromine (Parnate)

- Opioids: All phenylpiperidine opioids (meperidine, methadone, tramadol) can react with MAOIs
- Selegiline: selective MAO-B inhibitor (serotonin is deaminated by MAO-A), relatively safe
- Symptoms: confusion, fever, diaphoresis, shivering, ataxia, myoclonus, hyperreflexia

Tramadol: Pharm

Tramadol and its active metabolite (O-desmethyltramadol) binds to μ-opioid receptors in the CNS causing inhibition of ascending pain pathways and altering the perception of and response to pain. Tramadol also inhibits the reuptake of norepinephrine and serotonin, which are neurotransmitters involved in the descending inhibitory pain pathway responsible for pain relief.

Tramadol is indicated for treatment of moderate-to-severe pain in adults. Among specific adverse effects is an increased risk of serotonin syndrome and seizures in patients taking SSRIs, SNRIs, TCAs and MAOI. Compared to other opioid analgesics, tramadol has similar analgesic profile with less respiratory depression and sedative effects.

Metabolism: Extensively hepatic via demethylation (mediated by CYP3A4 and CYP2B6), glucuronidation, and sulfation; has pharmacologically active metabolite formed by CYP2D6 (O-desmethyltramadol). Of note, O-desmethyltramadol is a more potent opioid agonist.

Time to peak: Immediate release: ~2 hours; Extended release: ConZip™: ~10-12 hours, Tridural™: ~4 hours; Durela™, Ultram® ER: ~12 hours

Excretion: Urine (30% as unchanged drug; 60% as metabolites)