Pharmacology of Octreotide

Clinical Implications for Anesthesiologists and Associated Risks

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KEYWORDS

• Carcinoid syndrome • Carcinoid crisis • Octreotide • Sandostatin • Somatostatin

KEY POINTS

- Octreotide (Sandostatin, as octreotide acetate, Novartis Pharmaceuticals) is a longer acting synthetic octapeptide and analog of somatostatin, a naturally occurring hormone.
- Many patients presenting with a history of foregut, midgut neuroendocrine tumors or carcinoid syndrome can experience life-threatening carcinoid crises during anesthesia or surgery.
- Clinicians should understand the pharmacology of octreotide and appreciate the use of continuous infusions of high-dose octreotide, which can minimize the incidence of intraoperative carcinoid crises.

BACKGROUND

Octreotide (Sandostatin as octreotide acetate, Novartis Pharmaceuticals) is a longer acting synthetic octapeptide and analog of somatostatin, a naturally occurring hormone. The chemist Wilfried Bauer first synthesized octreotide in 1979.

CLINICAL PHARMACOLOGY

Octreotide acetate acts similar to somatostatin. It is an even more potent inhibitor of growth hormone, glucagon, and insulin. Somatostatin's inhibitory effects can be found throughout the human body, but particularly the endocrine and gastrointestinal

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systems via neurotransmission and cell proliferation. In the hypothalamus, somatostatin inhibits the secretion of thyroid-stimulating hormone, growth hormone, adrenocorticotrophic hormone, and prolactin. It also inhibits the release of insulin, glucagon, gastrin, and other gastrointestinal peptides, thus reducing splanchnic blood flow, hepatic blood flow, and gastrointestinal motility, and increasing water and electrolyte absorption. Somatostatin is also an inhibitory neurotransmitter that inhibits cell proliferation.[1,2]

There are 5 subtypes of somatostatin receptors that have been identified. These 5 somatostatin receptors, referred to as sst1 through sst5, have been described as G-protein–coupled receptors. Of these receptors, most carcinoid tumors have a high concentration of type 2 receptors (sst2). Octreotide does not bind receptor types sst1 and sst4. However, receptor types sst2, sst3, and sst5 display a high, low, and moderate affinity, respectively, for the somatostatin analogs.[2,3]

PHARMACOKINETICS

Octreotide is absorbed poorly from the gut and thus it is administered parenterally. It is generally given as a subcutaneous bolus, although it can be given intravenously (IV) if a rapid effect is required.[1]

After subcutaneous injection, octreotide is absorbed rapidly and completely from the injection site. Peak concentrations of 5.2 ng/mL (100 μg dose) have been demonstrated 0.4 hours after dosing. Using a specific radioimmunoassay, IV and subcutaneous doses have been found to be bioequivalent. Peak concentrations and area under the curve values are dose proportional after IV single doses up to 200 μg and subcutaneous single doses up to 500 μg and after subcutaneous multiple doses up to 500 μg 3 times a day(1500 μg/d).[4]

The characteristics of octreotide include[4]:

- The distribution from plasma: rapid ($t\alpha 1/2 = 0.2$ h).
- Onset of action: 30 minutes.
- The volume of distribution (V_d): estimated to be 13.6 L, and the total body clearance ranged from 7 to 10 L/h.
- Time to peak plasma concentration: 30 minutes.
- Binding: mainly to lipoprotein and, to a lesser extent, to albumin.
- Metabolism: hepatic.
- The duration of action: variable, but extends up to 8 to 12 hours depending on the type of tumor.
- The elimination: has a half-life of 1.7 to 1.9 hours compared with 1 to 3 minutes with the natural hormone.
- Excretion: about 32% of the dose is excreted unchanged into the urine.
- Renal impairment: the elimination of octreotide from plasma is prolonged and total body clearance reduced.
  - In mild renal impairment (creatinine clearance 40–60 mL/min), the octreotide half-life is 2.4 hours and total body clearance is 8.8 L/h.
  - In moderate impairment (creatinine clearance 10–39 mL/min), the half-life is 3.0 hours and total body clearance 7.3 L/h.
  - In severely renally impaired patients not requiring dialysis (creatinine clearance <10 mL/min), the half-life is 3.1 hours and total body clearance is 7.6 L/h.
  - In patients with severe renal failure requiring dialysis, total body clearance is reduced to about one-half that found in healthy subjects (from approximately 10 to 4.5 L/h).