THE NORTHERN HOSPITAL

OCTREOTIDE

Maud Abrantes; study in watercolour, c. 1907, Amedeo Modigliani.

"He usually began by sketching, with a very fine brush, a drawing similar to his well-known pencil drawings, sometimes soft and tender, sometimes hard and violent, according to the character of his sitter and his own mood. The more studied and deliberate elements were combined with a fair measure of improvisation. Starting from an initial conception of main lines and angulations, which represented the sitter and extended outwards to take in surrounding objects such as chairs, tables, wall corners and door and window frames, he scattered, rhythmically and in a strictly geometrical style, a flood of detail that was painted with great delicacy and force. So fond was he of fathoming the unfathomable that it did not weary him to do seventeen of even nineteen portraits of the same person at near intervals"

Leopold Survage

Amedeo Modigliani's works look deceptively simple, yet they are full of emotion and expression. His genius lay partly in his ability to capture the true essence of his subjects in just a few simple lines. He worked over his preliminary sketches and studies time after time until he was satisfied he had captured this essence. His biographer, Meryl Secrest wrote, that in "painting after painting Modigliani sought the chimera of the ideal, a form that summed up and personified the secret essence of life itself...." Agnes Morgan wrote of his simple elegant lines, that they had developed from "the stylized yet energetic lines of (his) early caryatids to...exquisitely sensitive and marvellously succinct lines...". Secrest continued, saying that he made it "look so simple, effortless even, which has deceived many a would be forger. Such artlessness testifies to an acute and rarefied mastery of form".

Once such example of Amedeo's "mastery of form", achieved in just a few quick lines, is his study of the mysterious Maud Abrantes produced around 1907. Great blotches cover her eyes, giving her an enigmatic sense of pain and mystery. We know virtually nothing of this woman, but apparently she was a married American, who seems to have "kept" Amedeo for a short while at a hotel on the Rue Caulaincourt. Amedeo sketched her many times, and eventually produced an oil of her. She left Paris suddenly in November of 1908, and returned to New York, amidst whispered rumours that she was pregnant by Amedeo. Nothing more is known of her.

Our indications for the use of octreotide in toxicology are not completely defined, and so this agent excites learned discussion. Its role in situations of therapeutically induced hypoglycaemia, is less clear than the situation of acute intentional overdose. Similarly its optimal route of administration, IV verses SC remains uncertain, and with regard to pregnancy it is classified as a category C drug. And yet it really has no serious adverse effects, and so we may revert to the principle of "KISS"- or, "keep it simple, see"! It does no great harm and so the benefit of treating potentially lethal hypoglycaemia, in the end seems a simple choice! So we need not unnecessarily agonize, but rather keep things quite simple - a principle by which Amedeo Modigliani achieved great things!

OCTREOTIDE

Introduction

Octreotide (trade name in Australia, "**Sandostatin**" amoung others) is a synthetic octapeptide analogue of the naturally **somatostatin** with similar properties but a longer duration of action.

It is used in a variety of medical scenarios, but in Emergency Medicine it has two major roles:

1. As an adjunctive measure to reduce bleeding in **esophageal varices.**

2. As an antidote to drugs which induce hypoglycemia due to stimulation of pancreatic release of insulin, principally in:

    - **Sulphonylurea toxicity**

    - **Quinine toxicity.**

See also separate documents on

- **Sulfonylurea Toxicity (in Toxicology folder)**

- **Hematemesis and melaena (in GIT folder)**

History

Octreotide was first synthesized by the chemist Wilfried Bauer in 1979.

Preparation

Octreotide acetate as:

Ampoules:

- 50 mcg/ml in 1 ml

- 100 mcg/ml in 1 ml

- 500 mcg/ml in 1 ml

Mechanism of Action

Somatostatin analogues, in general, inhibit the release of growth hormone and of various other peptides of the gastro-entero-pancreatic endocrine system (including insulin). They have a more prolonged duration of action than somatostatin (the natural growth hormone inhibiting peptide). They also reduce splanchnic blood flow.

Octreotide strongly suppresses endogenous insulin secretion from the pancreas, and so acts as a useful antidote to drugs which induce hypoglycemia by stimulating the release of insulin from the pancreas.

In the setting of variceal bleeding octreotide can help by reducing splanchnic blood flow.

Pharmacodynamics

Octreotide effects include: [3]

1. Reduction of *splanchnic* blood flow.

2. Inhibition of the secretion of various hormones, including:

    - Serotonin
    - Growth hormone
    - A range of gastroenteropancreatic peptides including :
        - **Insulin**, glucagon, gastrin, motilin, pancreatic polypeptide, secretin and vasoactive intestinal peptide (VIP).

3 Octreotide also has a **direct vasoconstrictive action.**

Pharmacokinetics

Absorption:

Octreotide is given by:

- SC injection:
    - It has a bioavailability of 100 % via this route.
    - Peak levels occur within 30 minutes (but are half those of the IV route)
- IV bolus and infusion

Distribution:

- The volume of distribution after intravenous dosing is 0.27 L/kg bodyweight.
- Binding is mainly to lipoprotein and, to a lesser extent, albumin.
- Octreotide can cross the human placenta.

- It is thought likely octreotide is excreted in human breast milk

Metabolism:

- Hepatic metabolism: 30- 40%, and urinary excretion of unchanged drug.
- The elimination of octreotide from plasma has an apparent half-life of 1.5 hours compared with one to three minutes with the natural hormone.

Indications

Indications for use in the ED include:

1. Patients with bleeding from **esophageal** varices:
    - In patients with portal hypertension and gastrointestinal bleeding, splanchnic blood flow and portal pressure can be reduced by an octreotide infusion, which should be commenced as soon as possible. [4]
2. Toxicological indications are drug induced hyperinsulinemic states resulting in persistent hypoglycemia **(< 4 mmol/L**), including:
    - Sulphonylurea drugs:
        - ♥ Intentional acute overdose
        - ♥ Therapeutic sulphonylurea induced hypoglycemia.
    - Quinine induced hypoglycemia.

Other non-ED indications include:

3. Acromegaly (symptomatic control and reduction of growth hormone).
    - This is primarily for cases of acromegaly where surgery or radiotherapy are contraindicated or have failed to control disease, or until radiotherapy becomes fully effective.
4. Relief of symptoms associated with carcinoid tumours and VIPomas and other secretory neoplasms
5. Reduction of the incidence of complications following pancreatic surgery

Contra-indications/precautions

In serious toxicological scenarios there are no specific contra-indications, other than known allergy. [1,2]

Pregnancy

Octreotide is classified as a category C drug with respect to pregnancy.

Category C drug are those drugs which, owing to their pharmacological effects, have caused or may be suspected of causing harmful effects on the human fetus or neonate without causing malformations. These effects may be reversible. Specialised texts should be consulted for further details.

Several successful pregnancies have been reported following the use of octreotide during early pregnancy or throughout the pregnancy. However, most case reports described cessation of somatostatin analogues as soon as pregnancy is confirmed.

Therefore, due to the possibility of fetal growth retardation, possibly via suppression of growth hormone, follow-up and monitoring of both maternal and fetal wellbeing throughout the pregnancy is recommended.

Safety is not established in pregnancy **however administration in toxicological cases should not be withheld where clinically it is indicated**. [1,2]

Breast feeding

Animal studies have shown excretion of octreotide into breast milk.

Infants exposed to octreotide via breast milk are unlikely to receive significant amounts, as the transfer of octreotide is limited by the high molecular weight of the medicine.

In a single study, adverse events were not observed in a breastfed infant following maternal treatment with octreotide for acromegaly.

However, due to potential adverse effects in the breastfed infant, consider an alternative treatment or avoid breastfeeding while undergoing octreotide therapy.

Adverse Effects

Adverse effects include:

1 GIT upset:

- Usually mild nausea only.

2. Hyperglycemia:

- Intravenous infusions are well tolerated, but blood glucose concentrations can rise and should be monitored.

3. Biliary tract disease:

- Octreotide inhibits gallbladder contractility and may predispose to biliary tract disease such as cholecystitis and ascending cholangitis or gallstones or biliary sludge, (with long-term therapy).

4 Minor local skin inflammation; usually resolves within a few minutes.

Dosing

For oesophageal varices:

If **esophageal varices** are the suspected cause of GIT bleeding give:

- **Octreotide 50 micrograms IV, immediately,**

  Then

  25 - 50 micrograms per hour by IV infusion for up to 5 days. [3]

For sulphonylurea induced hypoglycaemia:

The optimal dose and route for octreotide has not been established, but the following is recommended: [7]

For SC administration:

- 50 -100 micrograms SC, every 6 -8 hours, as needed.
- Children 1-2 microgram/kg (to a maximum 50 micrograms) every 8 hours.

For IV administration:

- 50 micrograms IV stat dose,

  Followed by:

  An infusion of 25 micrograms per hour, by diluting 500 micrograms in 500 mls of normal saline and infusing at 25 mls per hour.

  Children:

  Give 1 microgram/kg IV stat dose

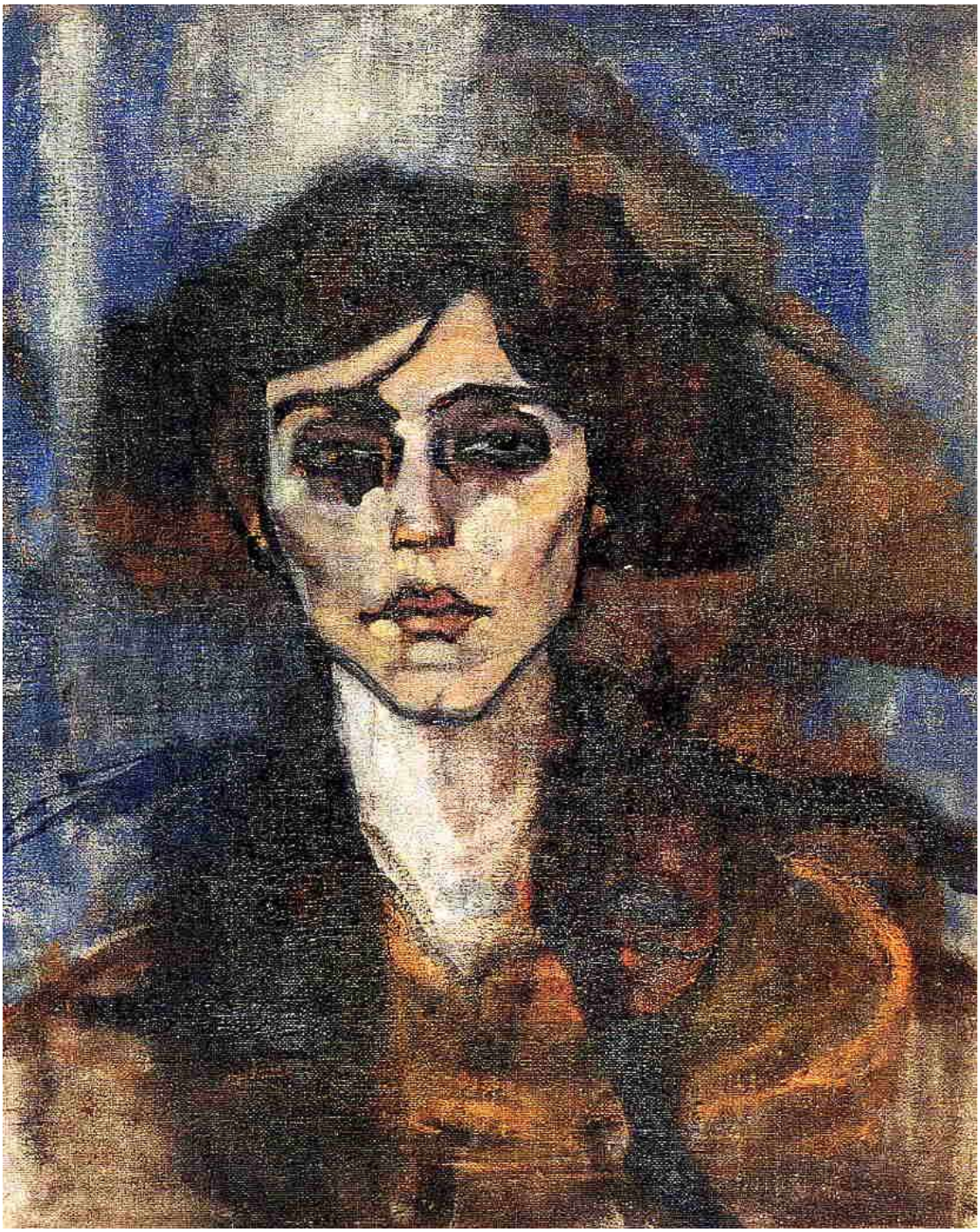
  Followed by:

  An infusion of 1 microgram/kg/hour, (to a maximum of 25 micrograms / hour).

If hypoglycaemia recurs, treat with dextrose bolus, and double the infusion rate of octreotide.

Therapeutic end point:

Normoglycemia must be maintained for **8 hours** off octreotide and on a normal diet before the patient can be medically cleared. [7]



Portrait of Maude Abrantes, oil on canvas, 1907, Amedeo Modigliani

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