THE NORTHERN HOSPITAL

GLUCAGON

"The Dodo" oil on canvas, 1627, attributed to Roelandt Savery. Title on painting "The Dodo & Given by G. Edwards FRS, A.D 1759". British Museum, London.

"It was painted in Holland from the living bird, brought from St. Maurice's Island in the East Indies, in the early times of the discovery of the Indies by the way of the Cape of Good Hope. It was the property of the late Sir Hans Sloane to the time of his death; and afterwards becoming my property, I deposited it in the British Museum, as a great

curiosity. The above history of the picture I had from Sir Hans Sloane, and the late Dr. Mortimer, Secretary to the Royal Society.

George Edwards, c. 1758-1764.

The British Museum holds what is probably the most famous image of an extinct bird, the legendary Dodo. The work is attributed to the Seventeenth century Dutch Artist Roelandt Savery. Sir Hans Sloane owned it in the early Eighteenth century, but it is not known how it came into his possession. He may have procured it from a friend of his, François Leguat, who had lived in Holland. George Edwards procured it on Sloane's death. In 1759 Edwards gave it to the British Museum and in 1881 it was transferred to the Natural history Museum. Savery painted the image of the Dodo a number of times in his works of Edenic nature scenes.

This large harmless and flightless bird lived in peace on the island of Mauritius for untold eons, until the late Sixteenth century when Portuguese and Dutch seafarers landed on the their Island. Like the creatures of the Galapagos, never having encountered humans before, they were utterly tame, and would happily approach the sailors out of friendly curiosity. Within a century the species was extinct. The story of the Dodo of Mauritius is simply another tale of the extinction of species at the hands of Homo Sapiens. It is a shocking story of the senseless of destruction of life on planet Earth; just another victim of the Sixth great extinction, and probably one of the most famous. So quickly did the poor bird go extinct that we do not even have sufficient evidence of its appearance in life, nor a full understanding of its biology or ecology. By the Eighteenth century all that was left of the Dodo was a misty legend amoung seafarers and Savery's canvases. Then in the Nineteenth century Lewis Carroll's use of the Dodo in his "Alice's Adventures in Wonderland", suddenly brought the creature back into the lime-light elevating it to fantastical status and sparking a permanent leitmotif of Dodo as emblem and icon of tragic and pointless extinction.

Today there no compete stuffed specimen in existence - only scattered poorly preserved parts. The only hard evidence we have of a living Dodo having been brought to Europe is an account given by Sir Hamon L'Estrange written in 1638...

"About 1638 as I walked London streets, I saw the picture of a strange looking fowle hung out upon a clothe and myselfe with one or two more in company went in to see it. It was kept in a chamber, and was a great fowle somewhat bigger that the largest Turkey cock and so legged and footed, but stouter and thicker and of a more erect shape, colored before like the breast of a young cock fesan, and on the back of a chimney there lay a heape of large pebble stones, whereof hee gave it many in our sight, some as big as nutmegs, and the keeper told us she eats them (conducing to suggestion), and though I remember not how far the keeper was questioned therein, yet I am confident that afterwards she cast them all again".

Accounts of the Dodo continued into to the 1680s, but by the early 1690s it had become clear that it had been driven to extinction, by hunting, "sport", the destruction of its habitats and predation by introduced species. In 1693 the French explorer, Francois Leguat, spent several months on the Mascarene Islands searching for it but without

success. Savery's image of the Dodo remains a critically important record of this extinct species, in light of the pitful few actual remains of the creature itself and the fact that there are less than a handful of paintings and drawings of it that date from the period of its catastrophic coexistence with humans in the Seventeenth century. The painting itself is thought to be a life-sized representation of the bird, possibly confirming that it was indeed painted from life. The famous Nineteenth British Anatomist, Sir Richard Owen, certainly thought so. In 1867 he wrote, "With a view to testing the tradition recorded by Edwards as to the date and origin of the painting of the Dodo in the British Museum, I took a copy of the outline of the bird and laid upon it outlines of the bones of the Dodo...and thus obtained proof that the painting truly represented the natural size and shape of the Didus ineptus, and had no doubt been drawn from the living bird".

The agent glucagon was once widely recommended as an antidote to beta-blocker poisoning. But this was never supported by any scientific evidence base. So whilst it remains an invaluable agent for the treatment of hypoglycaemia where IV access is problematic, its traditional indication as an antidote for beta-blocker poisoning is now dead as the proverbial dodo!

"Dodo", oil on canvas, 1626, Roelandt Savery

GLUCAGON

Introduction

Glucagon hydrochloride (rDNA origin) is synthesised by genetic engineering techniques from yeast *(Saccharomyces cerevisiae)* and has the same amino acid sequence as the natural human pancreatic peptide hormone, glucagon.

It is no longer considered a useful agent for beta blocker overdose.

It is now primarily used in the ED to treat hypoglycemia in cases where IV access cannot be obtained in a patient with significant hypoglycemia requiring immediate glucose therapy.

Preparation

Ampoules:

- 1 mg

Mechanism of Action

Glucagon is a pancreatic hormone that mobilizes hepatic glycogen, which is released into the blood as glucose.

It is an insulin antagonist, (along with adrenaline, GH, and cortisol)

It also increases intracellular cyclic AMP independent of beta-receptors or calcium flux, positive chronotropic and inotropic effect.

Pharmacokinetics

Absorption:

- Glucagon can be given IM or IV

  The onset of effect occurs within 5 to 15 minutes after an intramuscular injection, with a duration of action of around 10 to 40 minutes. When used in the treatment of severe hypoglycaemia, an effect on blood glucose is usually seen within 10 minutes.

  Onset of effect occurs within 1 minute after intravenous injection. Duration of action is in the range 5 to 20 minutes depending on dose and organ.

- As glucagon is degraded in the digestive tract and so cannot be absorbed in its intact form from the gut.

Metabolism and excretion:

- The metabolism of exogenous glucagon is identical to that of endogenous glucagon

  Glucagon is degraded enzymatically in blood plasma and in the organs to which it is distributed.

  The liver and kidney are major sites of glucagon clearance, each contributing about 30% to the overall metabolic clearance rate.

  Glucagon has a short half-life in the blood of about 5 minutes.

Pharmacodynamics

Clinical effects include:

1. Increases blood glucose:

   - Glucagon is a hyperglycaemic agent that **mobilises hepatic glycogen**, which is released into the blood as glucose.

   - Glucagon is therefore only of benefit when liver glycogen is present.

     For this reason, glucagon has little or no effect when the patient has been fasting for a prolonged period, or is suffering from adrenal insufficiency, chronic hypoglycaemia or alcohol induced hypoglycaemia.

2. GIT smooth muscle relaxant:

   - Glucagon inhibits both the tone and motility of the smooth muscle within the gastrointestinal tract.

3. Positive inotropic and chronotropic effects:

   - Glucagon has some positive inotropic and chronotropic effects similar to those of beta adrenergic agonists.

     These occur due to binding to specific intracellular glucagon receptors leading to activation of cardiac adenylate cyclase and increases cAMP concentrations

Indications

Indications within the ED include:

1. **Hypoglycemia**:

- Where timely IV access cannot be obtained in a hypoglycemia patient, who requires urgent glucose therapy.

Less certain indications include:

2. Impacted esophageal food bolus.

3 Adjunctive treatment to adrenaline:

- For cases of anaphylaxis refractory to adrenaline in patients who are taking beta blockers

Indications outside the ED include:

4. Some diagnostic studies:

- Glucagon can be used as a motility inhibitor in examinations of the gastrointestinal tract, e.g. double contrast radiography and endoscopy.

Glucagon was also previously recommended for overdoses of beta blockers and calcium channel blockers, refractory to other measures.

Current expert Toxicological opinion however says that glucagon does not confer any clear benefit over conventional inotropes, and thus it is no longer recommended for these indications. Indeed its propensity to cause nausea and vomiting in *high doses* makes its hazardous in patients with severe poisoning and a reduced conscious state or at risk of a reduced conscious state.

Contraindications/ Precautions

1. Patients with insulinoma:

- It should be borne in mind that glucagon is an insulin antagonist. Caution should be observed with regard to rebound hypoglycaemia if glucagon is used in patients with **insulinoma** (after an initial rise in blood glucose, hypoglycaemia may be exacerbated by glucagon induced insulin hyper-secretion).

2. Phaeochromocytoma:

- Glucagon can provoke a release of catecholamine resulting in sudden and severe hypertension

Pregnancy

Glucagon is a category B3 drug with respect to pregnancy.

B3 drugs are drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans.

Breast feeding

Considered safe in breast feeding

Adverse Effects

1. **High doses** *commonly* cause **nausea and vomiting**

2. Hyperglycemia

3. Allergic reactions, (rare)

Dosing

Hypoglycemia

- Glucagon 1 mg SC or IM or IV [1,2]

Anaphylaxis

- A suggested regime in is setting is: [3]

  Adult: IV 1 - 5 mg

  Child: IV 20 - 30 micrograms/kg (maximum 1 mg)

  Give initial dose over 5 minutes, then infuse 5-15 micrograms/minute titrated to response.

Oesophageal food impaction:

- Glucagon 1 mg SC or IV, as a single dose. [1]

References

1. eTG - November 2015.

2. Glucagon in MIMs, December 2013

3. Critical Care Drug Manual, Dr Paul Young Wellington Hospital Intensive Care Unit, NZ 2010.

4. Australian Medicines Handbook, July 2013.

Dr J. Hayes.
Reviewed March 2016.