THE NORTHERN HOSPITAL

ESMOLOL

"Campbell's Tomato Soup I ", acrylic and liquitex silkscreen on canvas, 1968, Andy Warhol. (Neue Galerie Ludwig Collection, Aachen).

"In the future, everyone will be famous for 15 minutes".

Andy Warhol, 1968

What makes great Art? Certainly unsurpassed technical brilliance does - Bernini and Caravaggio spring to mind. But there are many different kinds of "greatness". Technical brilliance, yes but there is also the Art that is brilliant in its revolutionary innovation. The Artist who does something that none else has previously done; either in technique - Picasso - or even in conception of what Art is or what it should be - Jeff Koons. Art may be great for its historical record, a timeless document of important or momentous times in history - Jacques Louis David. Art may be great for its emotional impact in timeless and universal human themes or symbolism. A work of Art may be great for the shear drama of the history behind its production and its provenance - Klimt's, "Portrait of Adele Bloch Bauer I". Like an important and priceless fossil, or archeological artifact a work of Art may represent an historical "missing link" in an evolution of genres. Or great Art may simply be a powerful symbol or icon of a time, and an age, an attitude or new way of seeing the world.

In 1962 a Czechoslovakian, immigrant living in New York, by the name of Andrew Warhola, better known to history as Andy Warhol, created a sensation with his first "Pop Art" solo show. Confused but amused patrons were confronted with works of supermarket tins of food, and brillo soap boxes! "is this Art - are we being taken for a ride here!?", people were asking themselves - but they still came in droves - unable not to come - the least of which reason being that everybody else was coming! The genius of Warhol, apart from an astonishing innovation which changed how Art was viewed, lay in his depiction of a changed world - from that which existed before the Second World War - to that which existed after it. The war changed the way the world interacted - how it did business, the aspirations of the general person. Industry as it had been applied to the war effort was now turned towards the general way of life in peace time. Production on the titanic scale, brought profits to a new generation of captains of industry on a scale previously unimagined. They key to success was coined in a new terminology - "consumerism".

Mass production on the industrial scale fed consumerism. Every single man woman and child, after the severe austerity of the Depression, the War years and the decade immediately after it, could suddenly aspire to possess material goods that their parents could have only have dreamed of. A house, a car, every conceivable food item from any part of the globe. The average person, could now eat and drink exactly as royalty or the President of the United Sates did. Items produced on the industrial scale were affordable, indeed, cheap. It was the new "throw away" society, with built in obsolescence, the precursor to the eternal captivity of the Microsoft slavery of the perpetual "upgrade". It was an astonishing contrast to society as it had existed before the war - frugality, savings, hoarding, never living beyond one's immediate needs.

What better symbol to represent the new global age of consumerism than Warhol's "200 Campbell's Soup Cans" 1962 - the very image of the endless supermarket shelf. And what more logical icon to represent the new post war age - which today would be termed,

"logo" or "brand" - a solitary can of Campbell's Tomato Soup of course - "Campbell's Tomato Soup I ", acrylic and liquitex silkscreen on canvas, 1968, Andy Warhol - genius!

After the initial shock of Warhol's work….well, people couldn't get enough of the new "Pop Art". Other Artists cashed in - literally. Like Warhol many of the new pop Artists had previously been commercial Artists working for companies and industry. They took the everyday commodities they helped to advertised and turned them into statements about society in the form of Art. In the throwaway society of popular culture, the new motifs of Art became the mass consumer items, comic strips, magazines, advertising, fast food, bulk packaging, pop music, images of the stars of the of the big screens, Elvis, Marilyn Monroe, JFK, chairman Mao, all icons of mass culture.

Warhol was one of the first Artists to become a "celebrity" - famous for being…famous! So famous indeed was Warhol that anyone who was anyone wanted him at their "it" or "happening" party. Warhol although a somewhat surprisingly retiring individual was more than happy to oblige - even if it meant being at two places at once! With his trademark large dark sunglasses and oversized blond wigs - it was easy for him to hire out "doubles" to attend ALL the "it" parties that mattered! All the double had to do was not speak - but simply be seen! Celebrity on the mass produced scale! Warhol was not only a celebrity, he was an astute businessman. He was one of the first to turn commercial Art into an industry for fine Art. Indeed he named his studio, "The Factory"! There were few "original" Warhols - he mass produced his works, and so like a can of Campbell's Tomato Soup - everyone could own an original Warhol!

The Pop Art movement, for better or worse, has become part of the established history of Western Art, irreversibly changing attitudes towards what "fine Art" may be or mean. Andy Warhol was amoung the avant-garde of the movement, and he knew it! He foresaw a future interconnected world, catalyzed into being by the new consumerism and the throw way society. He once famously predicted that "in the future everyone will be famous….for 15 minutes!". In the age of the internet and the mass, throw away communications of "twitter" "face book" and "instagram" - anyone can now indeed become "famous for being famous" - if purely for being a complete twit! Fame once meant something - universal and ageless - the sentiments of Homer defined it:

"….If they ever tell my story let them say that I walked with giants.

Men rise and fall like the winter wheat, but these names will never die.

Let them say I lived in the time of Hector, tamer of horses.

Let them say I lived in the time of Achilles…."

Today "fame" is defined as a twitter comment. But it's a fame of a rather different order to Homer - rather than the millennia, it's strictly for mass consumption, then throw away and forget - Warhol's 15 minutes only - yes yes, very fine - but please hurry, a lot to get through now - next please!

Andy Warhol's fame has endured for half a century - but what will history's long term verdict be of Campbell's Tomato Soup Can I, 1968? Of course it's too early to tell, as Zhou Enlai once famously said of the French Revolution! Warhol did revolutionize and alter the very concept of Art - but concepts of Art are themselves fluid, and ever evolving. What Art is in one age may not constitute Art in another. Like the French Revolution - it remains to be seen if Andy Warhol's fame will be of Homer's ages - or merely an forgotten but amusing 15 minute footnote in the history of Art.

The agent esmolol is famous for its beta-blocking action. Its fame is of the Pop variety however, with an average duration of just 15 minutes!

Left: Andy Warhol, Helmut Newton, 1974. Right: Brillo Box 1964, Silkscreen on Wood, 1964.

ESMOLOL

Introduction

Esmolol (trade name in Australia, "**Brevibloc**") is an **ultra-short-acting** *beta-1 - cardioselective* - beta-blocker.

Its primary advantage over other beta-blocking agents lies in its short duration of action, (about 15 minutes) making it suitable as a titrating agent.

Esmolol is therefore primarily used where there is concern that beta blockade may not be well tolerated. As it is very short acting if an adverse reaction should occur the drug can be rapidly terminated by ceasing the infusion.

Its primary uses in the ED include:

1. Rate control in **supraventricular tachyarrhythmias**
   - SVT/ AF/ Atrial flutter/ MFAT
2. Reduction of shear forces in cases of **acute aortic dissection** associated with hypertension.
3. Thyroid storm.

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Esmolol (like all beta-blockers) has number of important contraindications.

See also separate document "Beta - Blocker Overdose" in Toxicology Folder for the effects of beta blockers in overdose in general.

History

The Scottish pharmacologist, **Sir James W. Black** discovered the first clinically used beta blocker, propranolol in 1964.

He was awarded the Nobel Prize for Physiology or Medicine in 1988 for his work that led to the development of propranolol and cimetidine.

Chemistry

Esmolol's short duration of action is based on its ester-methyl side chain which allows for quick hydrolysis.

Esmolol's structure is reflected in its name, **es-m**olol as in ester-methyl.

Physiology

Three types of beta adrenergic receptors are known, designated:

1. **Beta 1:**

   - These are located mainly in the heart and in the kidneys.

     In the heart they increase chronotropy and inotropy.

     They enhance lipolysis in adipose tissue.

2. **Beta 2:**

   - These are located mainly in the lungs, GIT, liver, uterus, vascular smooth muscle, and skeletal muscle. They result in smooth muscle relaxation.

     In blood vessels, they result in vasodilation.

     In the lungs they result in bronchodilation.

     In the GIT they reduce motility.

3. **Beta 3:**

   - These are located in fat cells

     These enhance lipolysis in adipose tissue.

Classification

Beta blockers may be loosely classified as:

1. Beta blockers with some intrinsic sympathomimetic activity (ISA).

   These agents are capable of exerting low-level agonist activity at the β-adrenergic receptor while simultaneously acting as a receptor site antagonist

   Examples include:

   - Pindolol

2. Non-selective blocking agents, (i.e block beta1 and beta2 receptors):

   Examples include:

   - Propranolol
   - Sotalol (this agent also has class III antiarrhythmic activity).
   - Timolol

3. Selective (B1) blocking agents:

Examples include:

- Atenolol
- Bisoprolol
- **Esmolol**
- Metoprolol
- Nebivolol

4. Alpha and non-selective beta Blocking agents:

Examples include:

- Carvedilol
- Labetalol

Preparation

Esmolol hydrochloride as:

Ampoules:

- **100 mg in a 10ml vial (i.e. 10 mg/ml)**

Mechanism of Action

Esmolol is an ultra-short-acting beta-blocker ($beta_1$ selective).

It has no significant intrinsic sympathomimetic activity, (some older beta-blockers were partial agonists).

It has no membrane stabilizing activity at therapeutic doses.

$Beta_1$-selective (cardioselective) beta-blockers have a higher affinity for **$beta_1$** receptors in the heart, with less effect on $beta_2$ receptors in bronchi and peripheral vasculature. $Beta_1$-selectivity however diminishes with higher doses.

Pharmacodynamics

Esmolol reduces the stimulant effect of catecholamines.

Cardiac effects include:

1. Decreased heart rate

2. Decreased cardiac contractility and cardiac output.

3. Reduction of blood pressure

Its duration of action is very short at around 15 minutes, (following cessation of the infusion).

Pharmacokinetics

Absorption:

- Esmolol is given as a **continuous IV infusion**
- There is a rapid onset of action.
- Using the recommended loading dose, steady state blood levels of esmolol are obtained in 5 minutes

Distribution:

- Esmolol is 55% bound to human plasma proteins
- Esmolol can cross the human placenta.
- It is unknown if esmolol is excreted into human breast milk.

Metabolism and excretion:

- Esmolol is rapidly metabolized by hydrolysis of the ester linkage, chiefly by the esterases in the cytosol of red blood cells (but not by plasma cholinesterases)
- Consistent with the high rate of *blood based metabolism* of esmolol less than 2% of the drug is excreted unchanged in the urine.
- The half-life of esmolol is approximately **9 minutes** and substantial recovery from beta-blockade occurs **10 - 20 minutes after stopping the infusion.** [2]

Indications

*Although uncommonly used, principle indications for use within in the **ED** include:*

1. Rate control in some **supraventricular tachyarrhythmias**
    - SVT

- AF/ Atrial flutter *not* due to bypass tracts.
- MFAT

2. Reduction of shear forces in cases of **acute aortic dissection** associated with hypertension.

3. Thyroid storm.

Principle indications for use outside the ED include:

4. Hypertension in the peri-operative period, including patients with phaeochromocytoma who are fully alpha-blocked.

Contraindications/ Precautions

These include:

1. Significant sinus bradycardia, (< 45-50)

2. Shock states/ Hypotension

3. Significant conduction disease:

   - Second/ third degree heart block
   - Sick sinus syndrome, (sinus nodal dysfunction).

   First degree block is generally considered a relative contraindication - use with caution.

4. Supraventricular tachyarrhythmias due to **by-pass tracts:**

   - Blockade of the A-V node in situations such as WPW AF, by these agents will allow an unrestricted pathway via the bundle of Kent into the ventricles and risk the precipitation of VF.

5. Situations of compromised cardiac output:

   - Cardiogenic shock
   - Overt cardiac failure
   - **Right ventricular compromise:**
     - ♥ Right ventricular failure secondary to pulmonary hypertension

- ♥ Significant right ventricular hypertrophy

6. Asthma/ COPD:

   - Note that the use of "cardio-selective" beta-blockers can still result in significant bronchospasm in the predisposed, (i.e. asthma and COPD patients).

7. Untreated alpha receptor stimulation:

   Phaeochromocytoma:

   - Patients with phaeochromocytoma should receive an alpha-blocking agent prior to beta-blocker administration to avoid severe hypertension.

   Sympathomimetic drug overdose:

   - **Note that beta blockers are contraindicated in amphetamine toxicity.**

     Beta-blockers are **not** recommended, as they will leave alpha effects unopposed. Treating with beta-blocker to control the heart rate will leave an unopposed alpha activity that aggravates vasoconstriction, (beta $_2$ effects are blocked).

8. Known hypersensitivity to esmolol

9. Untreated phaeochromocytoma:

   - Patients with phaeochromocytoma should receive an alpha-blocking agent prior to beta-blocker administration to avoid severe hypotension.

10. Calcium channel blocker interaction:

    - The combination of beta blocker and calcium channel blocker *frequently* causes conduction delay problems in the *elderly*, especially in the presence of *renal impairment.*

    - Calcium antagonists of the verapamil type should *not* be given by *intravenous* administration to patients treated with beta-blockers.

    - **Esmolol should not be used in patients who are taking verapamil or other calcium channel blocking agents.**

11. Patients with vasospastic disorders:

    - Raynaud's syndrome (and similar)

12. **Prinzmetal angina** may be worsened by beta-blockers in general.

13. Patients with a history of anaphylactic reactions:

- Beta-blockers in general may prevent the therapeutic response to usual doses of adrenaline for anaphylaxis.

14. Interaction with inotropic agents: [4]

- Esmolol should **not** be used to control supraventricular tachycardia in the presence of agents which are vasoconstrictive and inotropic such as dopamine, epinephrine, and norepinephrine because of the danger of blocking cardiac contractility when systemic vascular resistance is high.

Pregnancy

Esmolol is classified as a Class C drug with respect to pregnancy.

Class C Drugs 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.

Maternal use of beta blockers have not been associated with an increased risk of congenital malformations. Case reports following maternal use of esmolol have been described with positive pregnancy outcomes.

If esmolol is the treatment of choice, monitor for possible adverse effects such as neonatal bradycardia, hypotension and hypoglycaemia and intrauterine growth restriction.

Breast feeding

Reports describing the use of esmolol during breastfeeding have not been located.

The medicine is unlikely to cause adverse effects in the breastfed infant, as it has a short half-life and poor oral bioavailability.

Therefore, esmolol is considered safe to use during breastfeeding.

Adverse Effects

The important adverse effects of beta blockers as a class include:

1. Bradycardia

2. Depressed cardiac contractility/ Hypotension

3. Conduction delays

4. VF in cases of supraventricular tachyarrhythmias due to **bypass tracts.**

5. Bronchospasm in predisposed (asthma/ COPD)

6. Allergic including **anaphylaxis** reactions may be exacerbated by beta-blockade, and are more difficult to treat with adrenaline

7. Beta-blockers may impair peripheral circulation in patients with pre-existing peripheral vascular disease.

8. Impairment of normal sympathetic responses:

   Beta blockers may reduce the normal sympathetic response to many illnesses and by so doing may mask underlying and potentially serious pathologies.

   Important examples include the masking of **early tachycardic** responses to:

   - Hypoglycaemia
   - Hypovolemia in general, including blood loss.
   - Infection and sepsis
   - Hypoxia in general, e.g. pulmonary embolism.

Dosing

For supraventricular tachyarrhythmias or acute aortic dissection:

For titrated control of rapid heart rates in supraventricular tachyarrhythmias (AF /Atrial flutter /MFAT) or for the control of shear forces in cases of acute aortic dissection:

- Loading dose: [2]

  ♥ **Esmolol 500 micrograms (i.e. 0.5 mg) /kg IV, over 1 minute.**

  (e.g. 70 kg patient = 3.5 ml of 10mg/ml, using a 10 mg/ml solution)

  Then infuse 50 micrograms/kg/minute over the next 4 minutes.

  If the initial response is inadequate, repeat loading procedure, increasing the 4-minute infusion by 50 micrograms/kg/minute; repeat this sequence until a satisfactory response is obtained (or a maximum of 200 micrograms/kg/minute is reached).

  Using the recommended loading dose, steady-state blood levels of esmolol are obtained in 5 minutes.

- Then titrate to achieve desired ventricular rate:
    - ♥ **Typically 50 to a maximum of 200 micrograms/kg/minute**

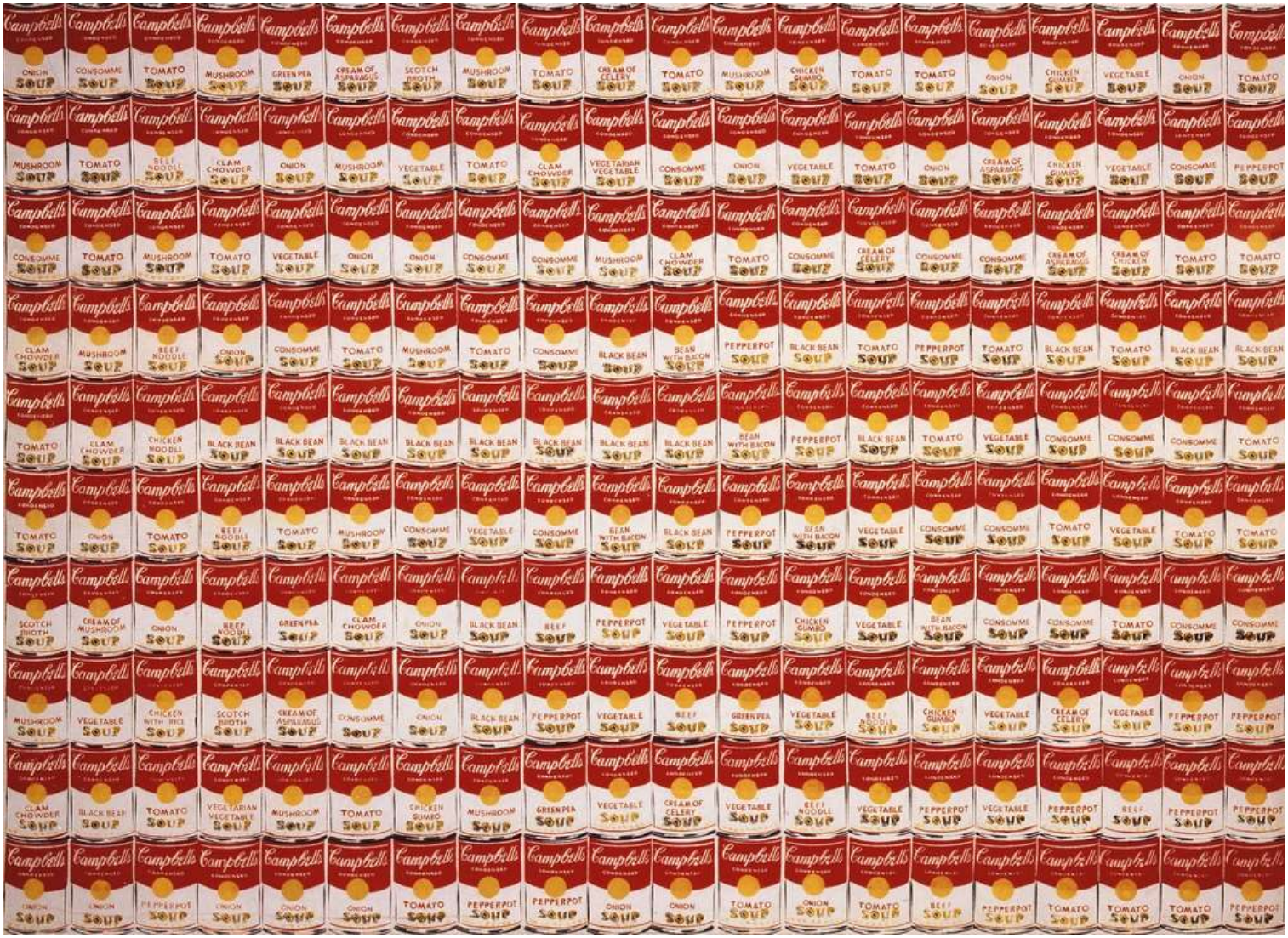
Once a satisfactory response is achieved, the infusion may be continued if necessary for up to 48 hours. [2]

For thyroid storm: [1]

- **Esmolol 250 to 500 micrograms/kg IV, over 1 minute as a loading dose.**

Followed by:

- **50 to 100 micrograms/kg/minute by continuous IV infusion**



“200 Campbell’s Tomato Soups”, silkscreen print, 1962, Andy Warhol.

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