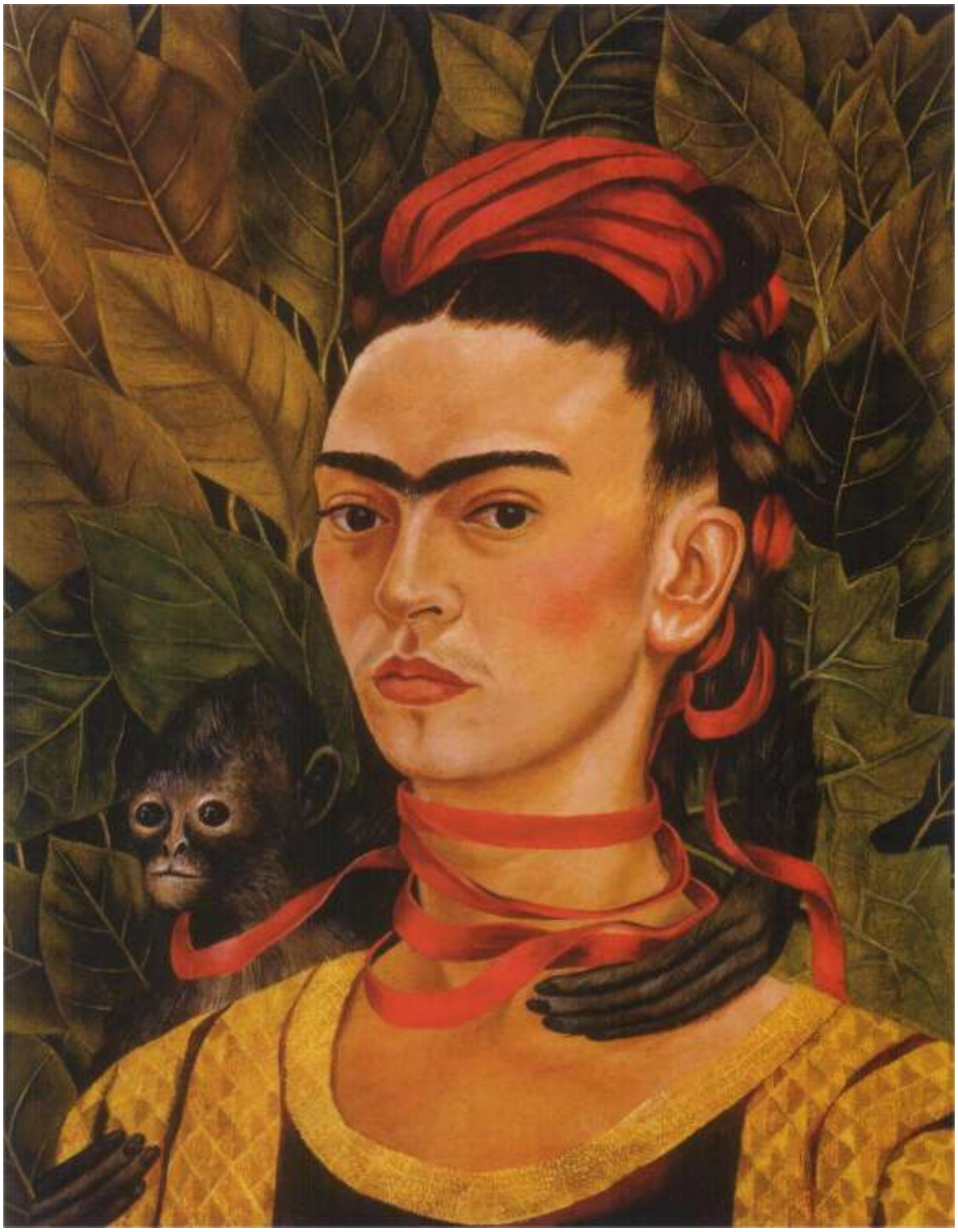
THE NORTHERN HOSPITAL

SOTALOL



"Self Portrait with Monkey", oil on canvas, 1940, Frida Kahlo

"There is no art more exclusively feminine, in the sense that, in order to be as seductive as possible, it is only too willing to play alternately at being pure and absolutely pernicious. The art of Frida Kahlo is a ribbon about a bomb".

Andre Breton, 1938

"Until I came the paintings were still in the custom house, because the son of a bitch, Breton didn't take the trouble to get them out. The photographs which you sent ages ago, he never received - so he says - the gallery was not arranged for the exhibit <u>at all</u> and Breton has no gallery of his own, long ago. So I had to wait days and days just like an idiot till I met Marcel Duchamp (marvellous painter) who is the only one who has his feet on the earth, amoung all this bunch of coocoo lunatic sons of bitches of the Surrealists.

He immediately got my paintings out and tried to find a gallery. Finally there was a gallery called "Pierre Colle" which accepted the damn exhibition. Now Breton wants to exhibit together with my paintings, 14 portraits of the XIX century (Mexican) about 32 photographs of Alvarez Bravo, and lots of popular objects which he bought on the markets of Mexico - all this junk - can you beat that? For the 15th of March the gallery suppose to be ready. But....the 14 oils of the XIX century must be restored and the dam restoration takes a whole month. I had to lend to Breton 200 bucks (Dlls) for the restoration because he doesn't have a penny. (I sent a cable to Diego telling him the situation and telling that I lended to Breton that money - he was furious, but now is done and I have nothing to do about it). I still have money to stay here till the beginning of March so I don't have to worry so much.

Well after things were more or less settled as I told you, a few days ago Breton told me that the associated of Pierre Colle, an old bastard son of a bitch, saw my paintings and found that <u>only two</u> were possible to be shown, because the rest are too "shocking" for the public!! I could kill that guy and eat it afterwards, but I am so sick and tired of the whole affair that I have decided to send everything to hell and scram from this rotten Paris before i get nuts myself....

Frida Kahlo, letter to Nicolas Muray, 16 February, 1939

Ella linda and Botito, my real cuates,

After two months I write to you. I already know that you are going to say the same things as always - that "chicua" is a mule! But this time believe me that it was not so much mulishness but rather that bandit luck. Here go the powerful explanations, a) since I arrived I have been in a frightful mess. I have been cross as hell since my exhibition had not been arranged. My paintings were waiting for me very calmly at the customs house because Breton hadn't even collected them. You do not have even the slightest idea of the kind of old cockroach Breton and almost all the Surrealist group are. In a word they are prefect sons of ....mother. I will tell you the whole story of said exhibition in detail when we see each other's faces again since it is long and sad. But in a summarized synthesis the thing was delayed by a month and a half before the date etc etc of the famous exhibition was completely sure.

All of this happened with the accompaniment of quarrels, insults, arguing, gossip much anger and annoyance of the worst kind. Finally Marcel Duchamp (the only one amongst the

painters and artists from here that had his feet on the ground and his brains in their place) was able to succeed in arranging the exhibition with Breton. It opened on the 10th of this month in the Pierre Colle Gallery, which according to what they tell me is one of the best here.

There were a lot of people on the day of the opening, great congratulations to the "chicua", amongst them a big hug from Juan Miro, and great praises for my painting from Kandinsky, congratulations from Picasso and Tanguy, from Paalen and from other big "cacas" of Surrealism. In sum I can say that it was a success, and taking into account the quality of the taffy (that is to say the crowd of congratulators) I believe that the thing went well enough.....

Frida Kahlo, letter to Ella and Bertram Wolfe, 17 March, 1939

In April of 1938 the French self proclaimed "Pope of Surrealism" André Breton and his wife, the painter Jacqueline Lamba, visited Mexico in order to meet the great Leon Trotsky, at that time an asylum seeker living with Frida Kahlo and Diego Rivera. It was then that Breton saw Frida's work and was astonished. He instantly fell in love with her paintings and declared to the world that Frida was a completely self-made Surrealist. He told Frida he would arrange for an exhibition of her work in Paris. The only problem was, Frida herself had no idea what a "Surrealist" was! And the more she heard about it from the pompous Breton the more she considered the genre a great load of "caca".

Nonetheless, she could not refuse Breton's offer, which could bring her international recognition at the very epicenter of the Art world, and so she agreed to the exhibition. When she got to Paris she realized what a bumbler Breton was, and the exhibition would not have gone ahead at all if it were not for Marcel Duchamp who got it all organized for her. Although she was not enamored with the Surrealists and their silly philosophies, she did very much like, of all people, the ex-Dadaist Marcel Duchamp, if for nothing else, for the common sense and hands on practicality that Breton totally lacked. There were some problems however. Some of Frida's work was so graphically shocking that the Gallery owner refused to exhibit it. Her works that were actually displayed however produced a sensation, not only among the Surrealists, but all the elite of the Art world of Paris, including Miro, Kandinsky and the great Picasso himself. Kandinsky was so moved by Frida's paintings he spontaneously lifted her off the ground kissing her cheeks while steaming tears down his face! In 1938 Frida had been a hit in New York, but now she had conquered Paris itself! Perhaps sensing some of Frida's ambivalence towards the supposed "epicenter" of Western culture, and given the shocking nature of some of her work, which could not be exhibited, Breton, even though he was totally enchanted by her and enthralled with her paintings famously cautioned Parisians, that the work of the volatile Mexican Artist was "a ribbon about a bomb".

When the drug sotalol first burst onto the scene it was loudly proclaimed as the greatest antiarrhythmic of all! - good for supraventricular and ventricular tachyarrhythmias alike. However soon it was seen to perhaps not be quite the miracle agent is had been expounded to be. In the case of supraventricular tachyarrhythmias due to pre-excitation pathways it had the potential to induce VF by virtue of its beta-blocking effects. In the case of ventricular tachycardia, secondary to prolonged QT interval, it had the potential to induce VF by virtue of its class III activity - we should exercise caution and good judgment therefore, we should not be seduced by the ribbon, lest a bomb lies hidden underneath!

SOTALOL

Introduction

Sotalol is a Vaughn Williams **class III antiarrhythmic** agent that also has significant **beta blocking** effects.

It is used in the treatment of both atrial and ventricular tachyarrhythmias.

It is used for both rate control and reversion to sinus rhythm

Indications in the ED include:

1. Atrial tachyarrhythmias, for either rate control or reversion to sinus rhythm:
    - SVT
    - Atrial fibrillation with fast ventricular rate
    - Atrial flutter with fast ventricular rate
2. Ventricular tachyarrhythmias for reversion to sinus rhythm:
    - VT due to **ischemic heart disease**

      But contraindicated in cases of VT induced by prolonged QT syndrome.

As for other beta blockers, sotalol has a number of important contraindications.

See also separate document on:

- **Beta Blocker Overdose (in Toxicology Folder).**

History

Sotalol was developed during the 1960s but did not become widely clinically used as a β-blocker until the 1980s.

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

Preparations

Sotalol hydrochloride as:

Tablets:

- 80 mg, 160 mg

Ampoules:

- 10 mg/mL, 4 mL

Mechanism of Action

Sotalol has two principle actions:

1. Class III antiarrhythmic activity:

   Blocks potassium channels and so:

   - Prolongs repolarization (ie acts on phase 3 repolarization)
   - Prolongs the refractory period of atria, ventricles and **bypass tracts.**
   - Prolongs action potential duration

2. Beta blocking activity:

   β-adrenergic receptor blocker activity is:

   - Non-selective, (i.e blocks both beta 1 and beta 2 receptors)
   - Competitive

Sotalol has no significant intrinsic sympathomimetic activity.

It has membrane stabilizing activity at therapeutic doses.

Pharmacodynamics

Principle clinical effects include:

1. Slowing of heart rate
2. Reduction in the force of contraction of the heart
3. Lowering of blood pressure
4. Like most other beta-blockers, sotalol also inhibits renin release.

Effects of ECG

Effects on the ECG include:

- Bradycardia
- Prolongation of the PR interval
- Prolongation of the QT interval

Pharmacokinetics

Absorption:

- Sotalol can be given orally or IV

  Sotalol is well absorbed from the gastrointestinal tract.

  Peak plasma concentrations are reached at two to three hours after a 160 mg oral dose.

  The absolute bioavailability of oral administration is close to 100%.

Distribution:

- The total apparent volume of distribution of sotalol ranges from 1.6 to 2.4 L/kg.

  The volume of distribution at steady state is approximately halved in the elderly.

- Sotalol does not bind to plasma proteins
- It does **not** significantly cross the blood-brain barrier.
- Sotalol can cross the human placenta.

- Sotalol is distributed into human breast milk

Metabolism and excretion:

- Sotalol is excreted by glomerular filtration and to a minor degree by tubular secretion.
- Sotalol is not metabolized by the liver. There is no first-pass effect.
- There is a direct correlation between sotalol dose and plasma concentration.
- Elimination half-life is around 11.1 - 14.3 hours.

Indications

Indication in the ED include:

1. Atrial tachyarrhythmias, for either rate control or reversion to sinus rhythm:
    - SVT
    - Atrial fibrillation with fast ventricular rate
        - ♥ Caution in cases of AF due to bypass tracts - theoretically its class III action should be effective, however the significant beta blocking effects may be problematic.
    - Atrial flutter with fast ventricular rate

    Although sotalol is also commonly used for acute reversion of atrial fibrillation, it has not been convincingly shown to be any more effective than standard intravenous beta blockers or even placebo in this regard.

    Sotalol (and other beta blockers) however do have the advantage of slowing the ventricular response even if reversion does not occur.
2. Ventricular tachyarrhythmias for reversion to sinus rhythm:
    - VT due to **ischemic heart disease**

        But contraindicated in cases of VT induced by prolonged QT syndrome.

Contra-indications/precautions

These include:

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

2. Shock states/ Hypotension

   - Systolic BP < 90 mm Hg

3. Significant conduction disease:

   - Second/ third degree heart block
     - ♥ Contraindicated in second or third degree heart block without pacemaker.
   - Sick sinus syndrome, (sinus nodal dysfunction).
     - ♥ Contraindicated without a pacemaker.

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

4. **VT/ torsades de pointes secondary to prolonged QT**

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:

7. Known hypersensitivity to sotalol

8. Untreated phaeochromocytoma:

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

9. Drug interactions:

   The most important include:

   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.

Antiarrhythmic agents interaction:

- Caution especially with other class I antiarrhythmic agents.

Drugs that prolong the QT interval

- Risk of the development of torsades des points.

10. Renal impairment:

    - Sotalol accumulates in renal impairment; increase dosing interval and/ or reduce doses.

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. Diabetes:

    - Sotalol may affect glucose metabolism and delay recovery from hypoglycaemia; may also mask signs of hypoglycaemia (e.g. tachycardia).

Pregnancy

Sotalol 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.

Sotalol has been used for the treatment of fetal tachycardia.

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

Breast feeding:

Serious harmful effects have not been reported in breastfed infants, despite the high relative infant dose following maternal use during breastfeeding.

If sotalol is the medicine of choice, observe the breastfed infant for signs of hypotension or bradycardia.

Adverse Effects

These include:

1. Bradycardia

2. Hypotension

3. Conduction delays

4. Proarrhythmic effect:

    - This is predominately due to **QT prolongation**, with subsequent risk of torsades des pointes

    - **The risk is dose dependent.**

5. CNS:

    - Delirium/ confusion:

      Sotalol and propranolol are the beta blocking agents that are most likely to cause CNS effects.

    Less commonly:

    - Seizures

    - Coma

6. 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

Oral

In general terms:

- **Sotalol 40 to 160 mg orally, twice daily.**

IV

In general terms:

- **Sotalol 0.5 to 1.5 mg/kg (range 20 - 120 mg) IV infusion, over 10 to 30 minutes.**

  Repeated once if necessary and followed, if indicated, by 80 to 160 mg IV infusion over 12 hours.

All patients receiving IV sotalol should be on ECG monitoring.

References

1. eTG - March 2020

2. Sotalol in Australian Medicines Handbook Website, January 2020.

3. Sotalol in MIMs Website, 1 February 2020.

4. Sotalol in RWH Pregnancy & Breastfeeding Guidelines, 19 August 2019.

Dr J. Hayes

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