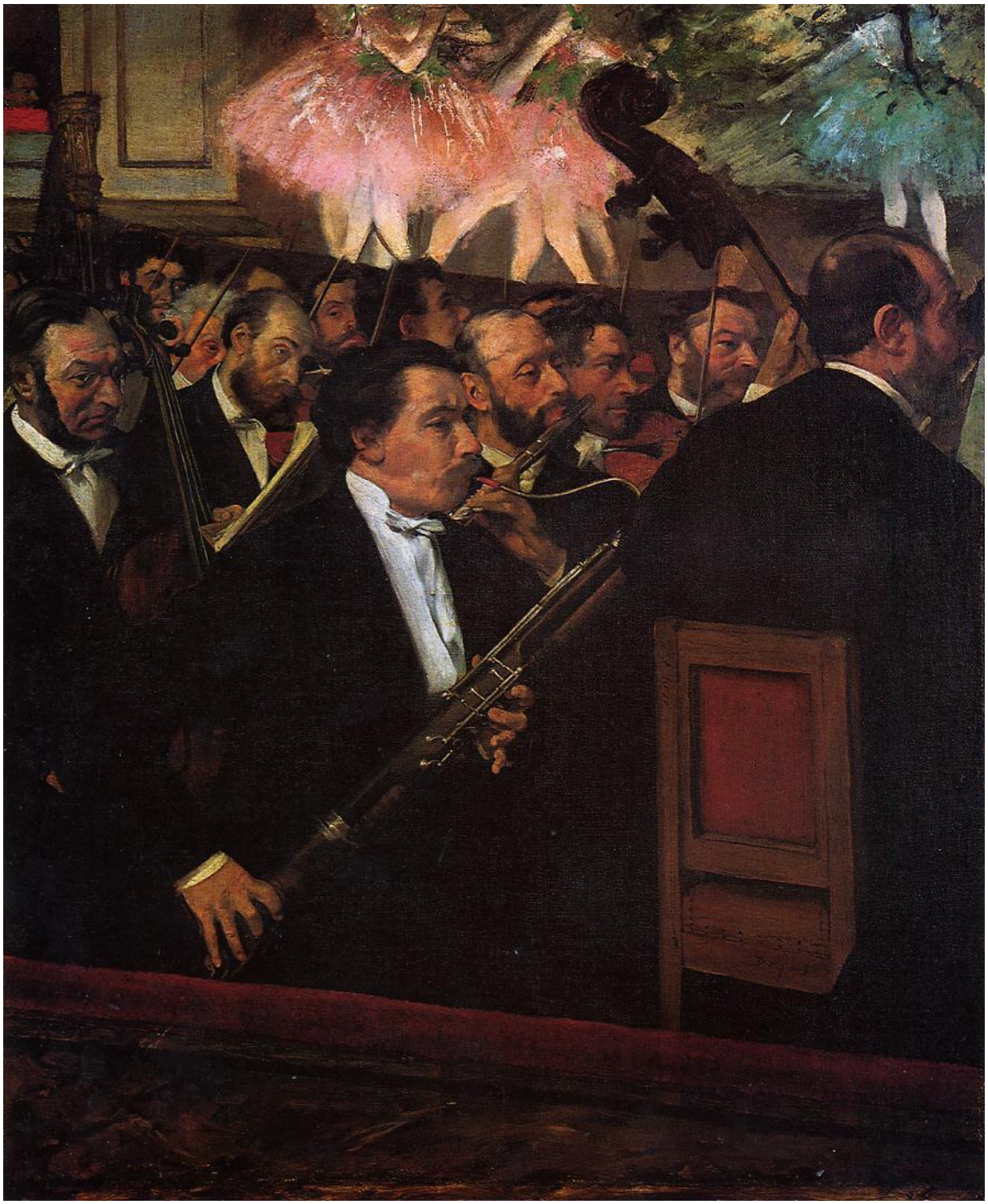
THE NORTHERN HOSPITAL

CEPHALOTHIN



"The Orchestra at the Opera House" oil on canvas, 1868-69, Edgar Degas, Musee d'Orsay.

"In art you love and you produce only what you are used to. Novelty captivates you and then bores you"

Edgar Degas

By the late 1860s Edgar Degas had fully developed his "Realism" oeuvre, and increasingly he was becoming well noted and admired for his works, which had, along with others, such as Courbet, gone some way to breaking the power of the great Academies of Art and their "Salons". Around 1868, Degas's good friend, Desire Dihau, a bassoonist in the Paris Opera, commissioned him to do his portrait. Degas agreed, and immediately went about depicting his friend not as a traditionally staged immobile statue, but rather in the full heat and passion of his profession. "I do portraits of people in typical and familiar positions, above all giving their faces the same choices as the expression of their bodies", he recorded in one of his sketchbooks. The result would be a priceless masterpiece, which would also immortalise his friend, Desire. It is priceless on a number of different levels, not immediately apparent to the thousands of casual observers who today stream past it daily at the Musee D'Orsay.

The musicians are depicted with great skill, in the manner of the Realists of the mid-Nineteenth century and as such the work provides an important example of the genre's aim to depict the lives of real and contemporary people of a modern metropolis. But Degas also achieves this in his own unique way. Of course Desire is at the forefront of the action playing his bassoon; it is after all meant to be his portrait. However we do not see him necessarily as the "main attraction" or the "star" of the show, but rather within his natural environment, practicing his Art as an integral member of a highly skilled, focused and professional group. Degas loved to depict movement and dynamic interaction, capturing subjects unawares as they went about their routine businesses. The musicians around Desire are scarcely less individually displayed, and though not occupying the foreground, anyone one of them may become the focus of our intention, stealing the show. Desire is merely a part of an overall whole. Any of this would make "The Orchestra at the Opera House" a masterpiece, of the Realism genre in Degas's style, and yet this is not why the work has become priceless, there is far more at play here than at first meets the eye.

Though our eye is not as immediately drawn to it, look closely at the top quarter of the work, it is utterly and radically different in style compared to rest of the scene. Almost incidentally we see the stage performers in the background. In contrast to the subdued tones of the orchestra pit, the stage is ablaze with strong light. We see the legs of the dancers up-lit by the glare of blazing gas lamps. In comparison to the sharp edged realistic definition of the musicians, the dancers are far less distinct, however there is a movement and energy reflected in the glowing metallic iridescence of their skirts that makes the musicians appear muted by comparison. "The Orchestra at the Opera House " is the very first work Degas produced of ballerinas of the Paris Opera. Here we are seeing evolution in progress. From this point on, Degas becomes increasingly enraptured by the dancers and their world. He begins to leave the audience behind and increasingly we see greater and greater percentages of his canvas filled with dancers, until the audience disappears off the scene all together. This work marks the beginning of Degas' obsession with ballerinas, a subject for which he is most remembered today. At his death

in 1917, over 1200 paintings and sculptures were found in his studio, and fully one quarter of his total oeuvre related to ballerinas. Though Degas always refused the label "Impressionist" there is of course no question he was profoundly influenced by their vibrant style. He once recorded, "In art you love and you produce only what you are used to. Novelty captivates you and then bores you". He was always on the lookout for new means of creativity. Having found Realism, he for w while produced only what he was used to, however, he soon became bored and looked for other avenues of expression, eventually finding it in Impressionism, which allowed him to express his own version of "Realism" in a fantastically novel way, released from the restricting bonds of traditional ideology.

"The Orchestra at the Opera House" today reads like a layered section of a geological strata of the visual Arts. At the lower sedimentary level we see the older Age of Realism, which is sharply divided off from the sudden "catastrophe" of Impressionism that would overwhelm and replace the earlier age. "The Orchestra at the Opera House" depicts two genres, and in the process records not only the personal evolution of Degas' work but also the evolution of the history of Art in general; and it is this which makes the work unique and great.

Though today Edgar Degas is known as one of the greatest Impressionists, its a label he did not much care for - he would always consider himself a "Realist" painter. In "The Orchestra at the Opera House" the paleontological strata are not strictly separated- as if to demonstrate the fact that his Realism would always remain a part of him, we see the handle of a cello reaching into the new age and linking them together.

In a later work, "Ballet Scene from Robert Le Diable", 1871, Degas would similarly record an even earlier geological strata, when he depicted the new Realism in the image of his audience and simultaneously the death of the older Age of Romanticism depicted by performers of that outdated genre on stage. Ironically in his "Orchestra at the Opera House" he also records the demise of his own beloved Realism, at least in the sense of what we call Realism today, at the expense of the new Impressionism.

The antibiotic cephalothin was the first cephalosporin antibiotic introduced into clinical practice in 1964. Like Degas' "Orchestra at the Opera" it marked the dawn of a new age and the demise of an older one. Today the penicillins are much less effective beta - lactam agents than they were in the 1940s when they were introduced, though they still retain an important role. The cephalosporins on the other hand continued to evolve, with "fifth generation" versions at last count and have become one of a range of new and powerful broad spectrum antibiotics by which we fight the good fight against ever more dangerous bacterial pathogens.

CEPHALOTHIN

"…I will argue that every scrap of biological diversity is priceless, to be learned and cherished, and never to be surrendered without a struggle….We should preserve every scrap ….while we learn to use it and come to understand what it means to humanity".

Edward O Wilson.

A plate culture of the fungus Acremonium falciforme. The cephalosporin antibiotics were first isolated from fungi of the genus acremonium.

Introduction

Cephalothin (or cephalotin - trade name **Keflin)** is the archetype cephalosporin beta lactam antibiotic.

The cephalosporins are moderate to extended range antibiotics.

They have *variable* resistance to bacterial beta-lactamases.

The widespread use of cephalosporins across the world has been linked with the increasing prevalence of infections caused by multiresistant organisms including: [1]

- Methicillin-resistant *Staphylococcus aureus* (MRSA)
- Vancomycin-resistant enterococci (VRE)

- Other multiresistant Gram-negative organisms
- Clostridium difficile.

Cephalothin is a moderate spectrum cephalosporin.

In general, **cephalothin** has higher activity against **Gram positive** than Gram negative organisms, the latter *varying* greatly in their sensitivity to the drug.

Cephalothin has until recently been largely replaced by **cephazolin** because the short half-life of cephalothin makes it inadequate for the treatment of Gram-negative infections.

However, there have been reports of clinical failures with cephazolin for staphylococcal infections. These may be due to methicillin-susceptible *S. aureus* (MSSA) isolates carrying inducible enzymes that hydrolyse cephazolin but not cephalothin.

The prevalence of such isolates in Australia is unknown.

Because of this, in some patients with *severe staphylococcal infections*, cephalothin may now be preferred. [1]

Cephalothin's principle current use is in those with mild - moderate staphylococcal or streptococcal infections in people with mild to moderate penicillin allergy, (but *not* with severe/ life threatening reactions to beta lactams).

History

The cephalosporin antibiotics were first isolated from the fungus ***Cephalosporium acremonium.***

They were discovered by **Giuseppe Brotzu** (1895 - 1976) an Italian pharmacologist (and politician) in 1948 in Sardinia.

Cephalothin was the first cephalosporin antibiotic introduced into clinical practice in 1964.

Chemistry

Cephalothin is a semisynthetic cephalosporin beta lactam antibiotic.

The **beta-lactam antibiotics** are structurally related via their central **beta lactam** moiety. Side chains determine antibacterial, pharmacological and pharmacokinetic properties.

The beta-lactam antibiotics include:

1. Penicillins

2. Cephalosporins

3. Carbapenems

4. Monobactams

Classification

The cephalosporins can be classified into **5** principle groups or "generations": [1]

1. **First Generation**:

   Moderate-spectrum cephalosporins

   Principally gram positive activity, but with some limited gram negative activity.

   - Cephalothin
   - Cephalexin
   - Cephazolin.

2. **Second Generation**

   Slightly less gram positive cover than first generation agents, but extended activity against gram negatives and anaerobes.

   Moderate-spectrum cephalosporins with **anti-Haemophilus** activity:

   - Cefaclor
   - Cefuroxime

   Moderate-spectrum cephalosporins with **anti-anaerobic** activity:

   - Cefoxitin

4. **Third Generation**

   Reasonable gram positive cover, and further extended activity against gram negative agents.

   Broad-spectrum cephalosporins:

   - Ceftriaxone
   - Cefotaxime

5. **Fourth Generation**

Good gram positive cover and good gram negative cover

Broad-spectrum cephalosporins with **antipseudomonal** activity:

- Cefepime
- Ceftazidime

6. **Fifth Generation**

Newer very broad spectrum agents.

Broad-spectrum cephalosporins with **anti-MRSA** activity:

- Ceftaroline
- Ceftolozane (& Tazobactam)

Preparations

Ampoules:

- Cephalothin 1 gram (as powder for reconstitution).

Mechanism of Action

The cephalosporins are **bactericidal** agents.

They interfere with **bacterial cell wall peptidoglycan** synthesis during the stage of active multiplication, thereby leading to cell lysis and death.

The cephalosporins have *variable* resistance to bacterial beta-lactamases. [1]

Some organisms (e.g. *Serratia*, *Citrobacter* and *Enterobacter* species) have chromosomal resistance in the form of **cephalosporinase** enzymes, and resistance can develop during treatment. [1]

Pharmacodynamics

In general, cephalothin has higher activity against **Gram positive** than Gram negative organisms, the latter *varying* greatly in their sensitivity to the drug.

Cephalothin, cephalexin, and cephazolin all have a similar range of antimicrobial activity.

They are *active* against:

- Streptococci and staphylococci, including beta lactamase producing staphylococci
- A limited range of Gram-negative bacteria (including *Escherichia coli* and some *Klebsiella* species).

They are *inactive* against:

- Enterococci and *Listeria monocytogenes.*
- Gram-negative anaerobic organisms (including *Bacteroides fragilis* and related species).

Pharmacokinetics

Absorption:

- Cephalothin is **not** absorbed significantly following oral administration.

  It is administered parenterally, i.e **intramuscularly** or **intravenously.**

  Intravenous administration is the preferred route.

Distribution

- Cephalothin passes readily into many body fluids including:
  - ♥ Pleural
  - ♥ Joint
  - ♥ Ascitic
  - ♥ Aqueous humour
  - ♥ Bile.
- Cephalothin crosses the placental barrier.
- CSF levels of cephalothin are **low** and **unpredictable.**

Metabolism and excretion:

- About 70 % is excreted in the urine
- About 30 % is metabolized in the liver to the O-desacetyl metabolite.

- Cephalothin has a serum half-life of approximately 50 minutes in those with normal renal function.

- Probenecid slows tubular excretion and almost doubles peak blood levels.

Indications

Infections due to susceptible / likely susceptible bacterial organisms.

Conditions include:

1. Staphylococcal and streptococcal infections in people with mild to moderate penicillin allergy, (but *not* severe/ life threatening reactions).

2. UTI, (though cephalexin is now generally preferred).

Note that, as for all antibiotics, the prevalence of bacterial resistance may vary geographically and over time for selected species and local information on resistance is also important, particularly when treating severe infections.

Contra-indications/precautions

These include:

1. Contraindicated with a history of severe or immediate allergic reaction to cephalothin.

2. Caution in those with a history of an allergic reactions to other beta lactam antibiotics:

    - As cross-reactivity between penicillins, cephalosporins and carbapenems can occur.

3. Caution in significant renal impairment (Cr Cl < 20 mL/minute).

    - As a **class** the cephalosporins can occasionally cause neurotoxicity in patients with significant renal impairment; usually when administered too rapidly IV and in high doses

      Neurotoxicity may manifest as confusion, seizures, encephalopathy.

Pregnancy

Cephalothin is classified as a class A drug with respect to pregnancy.

Class A drugs are those drugs which have been taken by a large number of pregnant women and women of childbearing age without any proven increase in the frequency of

malformations or other direct or indirect harmful effects on the fetus having been observed.

Breast feeding

Safe in breast feeding.

Adverse Effects

All the beta lactams including the cephalosporins have a **wide therapeutic index** and are not associated with significant adverse effects, apart from hypersensitivity reactions..

Adverse reactions include:

1. GIT upset, (as with most antibiotics).

2. Allergic reactions:

    - Including serious and *fatal* **anaphylactic** reactions.

      Anaphylaxis is more frequent following **parenteral** therapy, but it has also occurred in patients on oral therapy

3. Dermatological:

    - Occasionally severe reactions such as Stevens-Johnson syndrome.

4. Pseudomembranous colitis:

    - Pseudomembranous colitis has been reported with nearly all antibacterial agents, including the cephalosporins, and may range in severity from mild to life-threatening.

      Therefore, it is important to consider this diagnosis in patients who present with diarrhoea subsequent to the administration of antibacterial agents.

Dosing

Exact doing and the duration of dosing depends on the condition being treated as well as the severity of the condition and illness.

In *general* terms:

- **Cephalothin 1 - 2 grams IV 4 -6 hourly**

  Children: 50 mg/kg (up to 2 grams) IV 4 -6 hourly

See latest Antibiotic Therapeutic Guidelines for full prescribing details.

References

1. eTG Complete - November 2016

    - Antibiotic Therapeutic Guidelines, 15th ed 2014.

2. Cephalothin in Australian Medicines Handbook, Accessed February 2015.

3. Cephalothin in MIMs 1 June 2009.

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