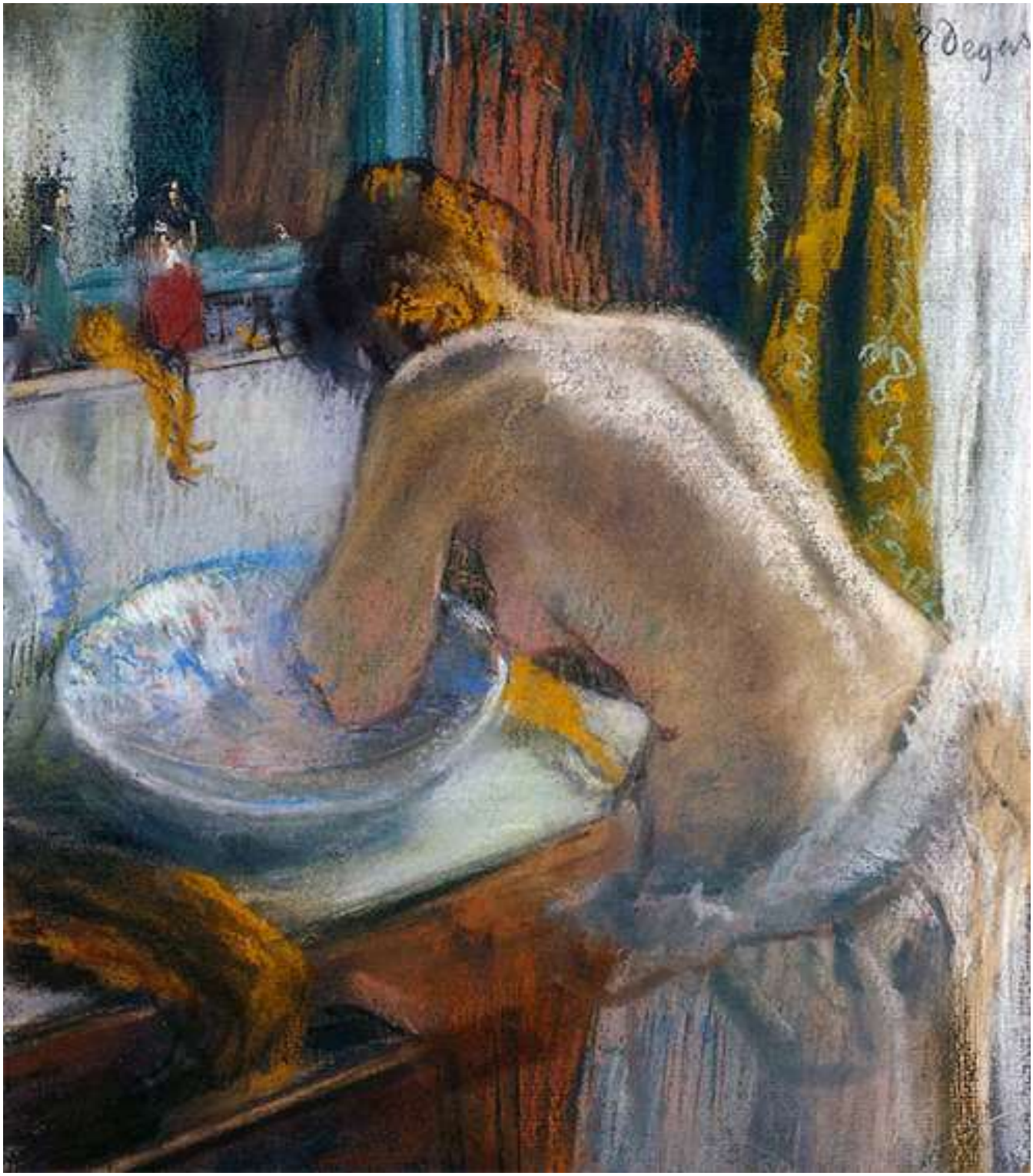
THE NORTHERN HOSPITAL

LINEZOLID



"Bather", pastel on paper, Edgar Degas.

...The flaky textures of pastel chalk are subtly used to suggest a dry glow of almost symbolic quality in the women's bodies. Employing a blatantly colourful hatching technique, Degas no longer uses the lines to define form (unlike Ingress) or indeed volume but rather amasses lines to lend colourful vitality to entire visual zones. "I am a colourist with lines", asserted Degas; and the dictum had a precise meaning if we consider the shimmer of hatched zones in these works. Skin gleams as pure colour, embedded in a radiant surround. Degas was open to technical experiments of any kind to achieve his ends. He cursed the "diabolical work of taking the brightness out of pastel colours, I wash them time after time". He changed the technique radically and fundamentally, making it an invention all his own.

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John Kear, "Edgar Degas, his life and works", Lorenz, 2015.

Edgar Degas idolized the Neoclassicist, Jean Auguste Dominique Ingres. As a young man of just 21 years, in 1855 visiting Jean Auguste, he had warily confessed that he wished to become an Artist. He never forgot the words of advice that the great man had given him; "Draw lines young man...a lot of lines, whether they're from memory or from Nature". This was good advice....for a Neoclassicist. Though Degas would become a passionate Realist and Impressionist, he never forgot the advice of Ingres. Like Ingres he was interested in depicting form and volume, but he would achieve this in a radically different way to his boyhood hero. He used pastel chalk shading and soft imperceptible lines to achieve his affects of not only form and volume but also of movement. He was interested in the flesh and blood physical presence of women - and their dynamic movements - not an idealized Neoclassical frozen facsimile statue in marble so much beloved by the Neoclassicists. The new Impressionism allowed him the creativity achieve movement. His works even today remain arresting; beautiful and visually stunning.

In the modern struggle against the microbial pathogenic world, one strong word of advice has been to "attack the bacterial ribosome". To stay ahead of the arms race we must be as creative and innovative as Edgar Degas! In the antibiotic agent, linezolid, we have just such an innovative approach. This agent is a completely novel class of synthetic antibiotic, known as the oxazolidinones. It should only be used for serious or life-threatening infections from multiresistant organisms and not for patients who are simply colonized with these.

LINEZOLID

Introduction

Linezolid (trade name in Australia, "**Zyvox**") is a is a novel synthetic antibacterial agent belonging to a new class of antibiotics, the **oxazolidinones.**

Linezolid is indicated for the treatment of suspected or proven infections due to Gram positive organisms resistant to multiple classes of antibiotics, including **methicillin resistant Staphylococcus species** and **vancomycin resistant enterococcus species.**

Linezolid should only be used for serious or life-threatening infections from multiresistant organisms and not for patients who are simply colonized with these.

It can be given orally or intravenously.

History

The oxazolidinones had been known as **monoamine oxidase inhibitors** since the late 1950s.

Their antimicrobial properties were discovered by researchers at E.I. DuPont de Nemours in the 1970s.

In 1987, DuPont scientists presented a detailed description of the oxazolidinones as a new class of antibiotics with a novel mechanism of action, however early compounds were hepatotoxic and development was discontinued.

Pharmacia & Upjohn (now part of Pfizer) recommenced oxazolidinone research in the 1990s which led to the development of safer analogues.

The U.S. Food and Drug Administration (FDA) approved linezolid on April 18, 2000

Chemistry

Linezolid is an antibacterial agent of the **oxazolidinone** class.

Classification

Linezolid is a is a novel synthetic antibacterial agent belonging to a new class of antibiotics, the **oxazolidinones.**

Preparations

Linezolid as:

Tablets:

- 600 mg

Oral liquid:

- 20 mg/mL (powder for reconstitution), 150 mL

Ampoules:

- 2 mg/mL, 300 mL (so total of 600 mg per 300 mls)

Mechanism of Action

Linezolid selectively inhibits bacterial protein synthesis via a mechanism of action different from that of other antibacterial agents.

It binds to the **23S** ribosomal RNA segment of the **50S subunit** of the bacterial ribosome and prevents the formation of a functional **70S initiation complex** which is an essential component of the bacterial translation process.

The unit of measurement for ribosome subunits is the **Svedberg unit,** which is a measure of the rate of sedimentation in centrifugation rather than size. This accounts for why fragment names do not add up: for example, prokaryotic 70S ribosomes are made of 50S and 30S subunits.

Note that linezolid is also a weak, **reversible, nonselective MAOI.**

Pharmacodynamics

Linezolid is active against **Gram positive bacteria** only.

Linezolid is indicated for the treatment of suspected or proven infections due to **Gram positive organisms resistant to multiple classes of antibiotics**, including:

- **Methicillin resistant Staphylococcus species (MRSA)**
- **Vancomycin resistant enterococcus species, including E. faecalis and E. faecium**
- **Streptococci (including penicillin-resistant S. pneumoniae)**

Linezolid is bacteriostatic against Enterococci and Staphylococci.

Linezolid is bactericidal for the majority of strains of Streptococci

Linezolid has *no* clinical activity against *Gram negative pathogens*. Specific Gram negative therapy is required if a concomitant Gram negative pathogen is documented or suspected.

Pharmacokinetics

Absorption:

- Linezolid can be given orally or intravenously.

  Linezolid is rapidly and extensively absorbed following oral dosing

  Absorption from the oral suspension is similar to that achieved with the film coated tablets.

- Maximum plasma concentrations are reached within two hours of dosing and the absolute bioavailability is approximately 100%.

Distribution:

- Linezolid is readily distributed to well perfused tissues.
- Its volume of distribution at steady-state averages at about 40 to 50 L in healthy adults and approximates to total body water.
- Plasma protein binding is moderate at about 30 %
- Human placental transfer is thought likely to occur.
- Linezolid is excreted into breast milk

Metabolism and excretion:

- Linezolid is only metabolized (around 70 %) and partly renally excreted (around 30 %)
- Half - life is around 5 - 7 hours

Indications

Linezolid is indicated for the treatment of suspected or proven infections due to Gram positive organisms resistant to multiple classes of antibiotics, including **methicillin resistant Staphylococcus species** and **vancomycin resistant enterococcus species.**

Linezolid may be used as a second line alternative to vancomycin for MRSA infection.

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. Hypersensitivity to linezolid

2. As linezolid has MAO inhibiting activity:

   - Avoid foods rich in tyramine (e.g. mature cheese, soy sauce, yeast extracts) that may result in elevations in blood pressure.

   - Avoid concurrent use with MAOIs

   - Avoid concurrent use with serotonergic agents.

3. Renal impairment:

   - Adverse effects such as thrombocytopenia and anaemia may be more frequent in renal impairment; monitor complete blood count each week.

     Linezolid's metabolites accumulate when Cr Cl is < 30 mL/minute (though the clinical significance of this is unknown).

Pregnancy

Linezolid is a category B3 drug with respect to pregnancy.

Category B3 drugs are those 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.

There is very limited information available following the use of linezolid during human pregnancy.

A single case report has described the delivery of a healthy infant following maternal use of linezolid in the second trimester of pregnancy.

However, due to a lack of safety information, consider an alternative medicine during pregnancy if possible.

Consultation with an Infectious Diseases Specialist or Clinical Microbiologist for further advice is recommended.

Breast feeding

Published reports describing the use of linezolid during breastfeeding have not been located.

Linezolid, and the metabolites, are excreted into breast milk, but the effects in the breastfed infant are still unknown.

Therefore, due to a lack of safety information, consider an alternative medicine where possible.

In circumstances where linezolid is the medicine of choice, linezolid therapy should not be a reason to discontinue breastfeeding.
However, observe the breastfed infant for potential adverse effects such as vomiting, diarrhoea, tongue discoloration and rash.

Adverse Effects

1. Allergic reactions

2. Hypersensitivity skin reactions

3. GIT upset

    - Including clostridium difficile associated enteritis

4 Raised liver enzymes

5. Drug interactions:

    MAOIs:

    - Caution with concurrent treatment with inhibitors of MAO A or B or within 2 weeks of such treatment.

    Serotonergic agents:

    - Treatment with drugs that may contribute to serotonin toxicity increases the likelihood of serotonin toxicity again due to linezolid being a weak MAOI; avoid these combinations or monitor carefully.

6. Uncontrolled hypertension:

    - Including conditions of phaeochromocytoma and thyrotoxicosis - hypertension may be induced; avoid use or monitor carefully.

Rarely:

7. Mitochondrial effects

    - Linezolid inhibits mitochondrial protein synthesis, which is thought to result in adverse effects such as **optic** and **peripheral neuropathy, anaemia** and **lactic acidosis.**

      These usually resolve after stopping linezolid, but there may also be permanent damage, e.g. blindness.

Long courses of treatment, particularly **> 28 days**, increase the risk as may some mitochondrial DNA mutations.

8. Myelosuppression

- This is reversible, and includes anaemia (common), thrombocytopenia, leucopenia, neutropenia, rarely pancytopenia; occurs particularly in people treated for >10 - 14 days or with other risk factors.

Dosing

Treatment for > 28 days is not recommended.

When infused IV this should be over **30 - 120 minutes.**

Adult, child >12 years:

- Oral, 400 - 600 mg every 12 hours.
- IV, 600 mg every 12 hours.

Child 1 month - 12 years:

- Oral / IV, 10 mg / kg (maximum 600 mg) every 8 hours.

References

1. eTG - July 2017
2. Linezolid in Australian Medicines Handbook, Accessed December 2016.
3. Linezolid in MIMs Website, 1 February 2014.
4. Linezolid in RWH Pregnancy and Breastfeeding Guidelines, 3 March 2015.

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