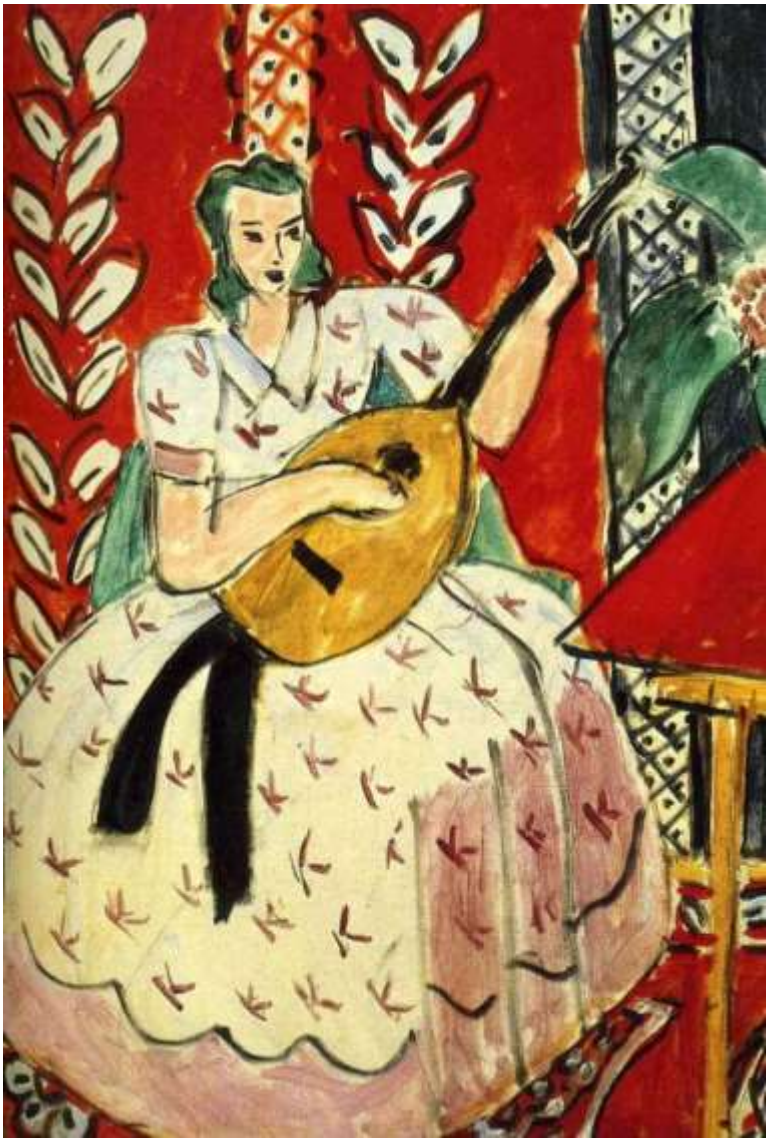
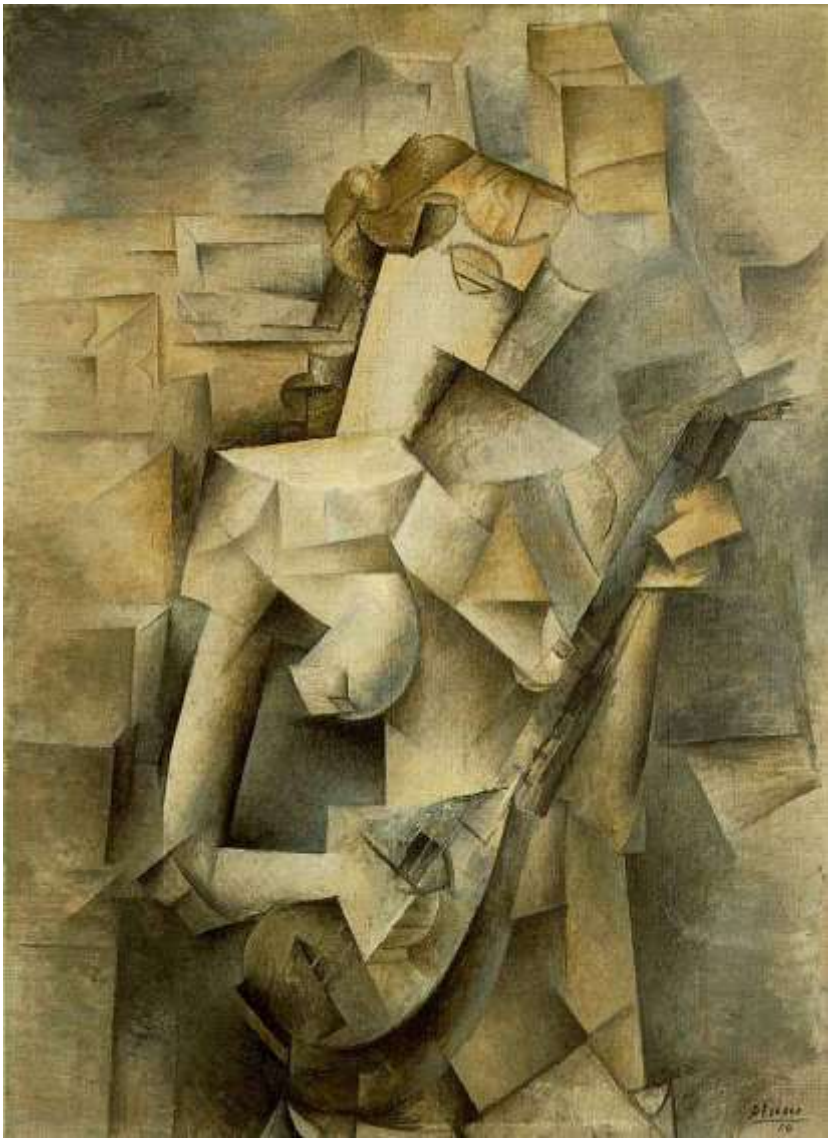
THE NORTHERN HOSPITAL

CO-TRIMOXAZOLE (TRIMETHOPRIM AND SULFAMETHOXAZOLE)





Left: "The Lute", (Detail), oil on canvas, 1943 Henri Matisse.

Right: "Girl with a Mandolin" (Fanny Tellier), Cubist, 1910. Pablo Picasso. Museum of Modern Art Ney York.

My choice of colors does not rest on any scientific theory; it is based on observation, on feeling, on the very nature of each experience. I… …merely try to find a color that will fit my sensation. There is an impelling proportion of tones that can induce me to change the shape of a figure or to transform my composition. Until I have achieved this proportion

in all the parts of the composition I strive towards it and keep on working. Then a moment comes when every part has found its definite relationship, and from then on it would be impossible for me to add a stroke to my picture without having to paint it all over again.

Henri Matisse, 1908.

The goal I proposed myself in making cubism? To paint and nothing more... with a method linked only to my thought... Neither the good nor the true; neither the useful nor the useless….

When we discovered Cubism, we did not have the aim of discovering Cubism. We only wanted to express what was in us.

Pablo Picasso

In the decade before the Great War, Henri Matisse and Pablo Picasso, though respectful of each other's work had become intense professional rivals. Henri, older than Pablo by a decade had led the avant-garde of modern Art with his Fauvist works, but the younger man now seriously threatened to take this mantel from him with the stunning Cubist works, both he and Georges Braque were producing. Then Pablo just after the death of his father, became seriously ill with a fever, and the doctors were at a complete loss as to what was the matter with him. Henri, became seriously concerned for his rival and one afternoon visited Pablo to find him in a terrible state. He took pity on the young man and began to take care of him. Every day he visited, bringing him fresh oranges and flowers and ensuring that Pablo ate and drank and kept up his spirits. Eventually Pablo recovered, from whatever it was that had afflicted him, and by this time the two had become friends. Pablo invited Henri to come horse riding with him in what amounted to a public display of friendship and reconciliation. It was quite an amazing show given their recent bitter rivalry, and their friends were quite at a loss as to what was going on. The two men had clearly decided to forget the past, and began discussing their works and ideas on Art. Rather than rivals they quickly came to be seen by the wider public as the joint leaders of avant-garde Twentieth century Art. It was around this time that history records that one or the other - it remains unclear which - commented to the other, that they were not so different after all, "We are both searching for the same thing, only by opposite means".

Henri Matisse and Pablo Picasso, were two of the giants of Twentieth century Art. Both strove to express what they felt within them in their own way, Henri with his Fauvism and Pablo through his Cubism, but both also continued to evolve and adapt in the years to come. Despite the oceans of ink that have been spent in explaining and analysing their works, neither were overly concerned with elaborate theories and philosophies, rather their work spontaneously came from their hearts.

In our ongoing battle with the microbial world, one group of agents that are most useful are the antifolate antibiotics - trimethoprim and sulfamethoxazole. Like Henri Matisse and Pablo Picasso they both work to achieve the same ends, though they do so by different means.

CO-TRIMOXAZOLE (TRIMETHOPRIM AND SULFAMETHOXAZOLE)

Introduction

Co-trimoxazole (**TMP/SMX -** trade name in Australia, **"Bactrim"**) is a combination antibiotic that consists of:

- **Trimethoprim**

And

- **Sulfamethoxazole**

Both these drugs are **bacterial folic acid inhibitors.**

Trimethoprim and sulfamethoxazole have a synergistic action. They have a greater effect when given together than when given separately, because they inhibit successive steps in the bacterial folate synthesis pathway.

The greatest potential for adverse reaction comes from **sulfamethoxazole.**

Co-trimoxazole is on the World Health Organization's List of Essential Medicines, the most important medications needed in a basic health system.

Classification

Folic acid inhibitors include:

1. Trimethoprim
2. Sulfonamides:
    - Sulfamethoxazole
    - Sulfadiazine/ Silver sulfadiazine

With the exception of sulfamethoxazole, the sulfonamide antibiotics have a limited role in practice, in part due to their unfavorable adverse effect profile (including frequent hypersensitivity reactions).

Preparation

Tablets:

Formulation is trimethoprim and sulfamethoxazole, in a ratio of 1 (trimethoprim) to 5 (sulfamethoxazole) as:

- **Trimethoprim + sulfamethoxazole 160 mg + 800 mg.**

Liquid:

- **Trimethoprim 8 mg/mL, sulfamethoxazole 40 mg/mL, 100 mL**

Ampoules:

- **Trimethoprim 16 mg/mL and sulfamethoxazole 80 mg/mL, 5 mL.**

Mechanism of Action

Sulfamethoxazole and trimethoprim are both **bacteriostatic** antibiotics.

They both *competitively* inhibit **bacterial folate metabolism** that is essential for bacterial growth.

Trimethoprim and sulfamethoxazole have a greater effect when given together than when given separately, because they inhibit successive steps in the bacterial folate synthesis pathway.

Human tetrahydrofolate synthesis:

Dietary Folate → Dihydrofolate → Tetrahydrofolate

↑

Dihydrofolate reductase

Bacterial tetrahydrofolate synthesis:

Dihydropteroate diphosphate + p-aminobenzoic acid (PABA)

Dihydropteroate synthase → ← Sulfonamides

↓

Dihydropteroic acid

↓

Dihydrofolic acid

Dihydrofolate reductase → ← Trimethoprim

↓

Tetrahydrofolic acid

Tetrahydrofolic acid, or tetrahydrofolate, is a folic acid derivative.

Tetrahydrofolate is essential for normal purine and hence DNA and RNA synthesis.

Many **bacteria** use dihydropteroate synthetase to produce dihydropteroate, a molecule without function in humans. This makes it a useful target for the **sulfonamide** antibiotics, which inhibit dihydropteroate synthase (by competing with the **PABA precursor).**

Trimethoprim is an inhibitor of the enzyme **dihydrofolate reductase.**

Pharmacodynamics

The following organisms are usually susceptible: [4]

- Escherichia coli
- Klebsiella species
- Enterobacter species
- Morganella morganii
- Proteus mirabilis.
- Indole-positive Proteus species including Proteus vulgaris.
- Haemophilus influenzae (including ampicillin-resistant strains)
- Streptococcus pneumoniae
- Shigella flexneri and Shigella sonnei.

Pharmacokinetics

Absorption:

- Co-trimoxazole can be given orally or IV.

  Co-trimoxazole is rapidly absorbed on oral administration.

  it reaches peak blood levels after 1 - 4 hours, which corresponds to those achieved when each component is given alone.

Distribution:

- The volume of distribution of trimethoprim is about 130 litres

The volume of distribution of sulfamethoxazole is about 20 litres.

- About 45% of trimethoprim is bound to plasma proteins

  About 65 % of sulfamethoxazole is bound to plasma proteins

  The free forms of trimethoprim and sulfamethoxazole are considered to be the therapeutically active forms.

- Trimethoprim and sulfamethoxazole both cross the placenta

Metabolism and excretion:

- Approximately 50-70 % of the trimethoprim dose is excreted unchanged in the urine, the rest is metabolized in the liver.

  Approximately 10-30 % of sulfamethoxazole is excreted unchanged in the urine, the rest is metabolized in the liver.

- The mean serum half-live of trimethoprim is 10 hours

  The mean serum half-live of sulfamethoxazole is 8 - 10 hours

Indications

Indications include: [2]

1. Infections caused by *L. monocytogenes* (as an alternative to ampicillin or benzylpenicillin)
2. *Nocardia* spp., *Stenotrophomonas maltophilia*
3. Melioidosis (with other agents)
4. Shigellosis
5. PCP
6. Pertussis
7. Prevention therapies:
   - Primary prevention of cerebral toxoplasmosis in HIV patients
   - Prevention of pertussis (if a macrolide unsuitable)
   - Primary and secondary prevention of PCP

- Secondary prevention of spontaneous bacterial peritonitis.

In the past cotrimoxazole was commonly used to treat UTI, however **trimethoprim** is now used alone for common infections in adults (particularly UTI) as sulfamethoxazole offers no advantage in these situations and there is a higher incidence of adverse effects. [2]

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. Allergic reactions; to sulfonamides in particular, (contraindicated).

2. States of folate deficiency:

    - **Contraindicated in megaloblastic** anaemia *due to folate deficiency*.

    - Folate deficiency in general may worsen, increasing risk of blood dyscrasias; consider using calcium folinate supplement.

      Groups at risk for possible folate deficiency include:

      ♥ The elderly

      ♥ Patients with malnutrition states, including chronic alcoholics

      ♥ Patients receiving anticonvulsant therapy

      ♥ Patients with malabsorption syndromes

3. Sulfonamides increase the risk of haemolysis in G6PD deficiency.

4. Blood dyscrasias:

   Including serious/ life-threatening conditions such as:

    - Neutropenia

    - Aplastic anemia

   Other reactions can include:

    - Megaloblastic anemia

- Hemolytic anemia
- Thrombocytopenia

5. Liver impairment

6. Renal impairment:

   - Contraindicated by the manufacturer if Cr Cl < 15 mL/minute.

7. Systemic lupus erythematosus (SLE):

   - This condition may worsen with sulfonamide use.

8. Slow acetylator phenotype:

   - There is a greater risk of adverse effects with sulfonamides.

9. Elderly:

   - Avoid use in the elderly, there is an increased risk of severe adverse effects (particularly blood dyscrasias and skin disorders).

10. Neonates:

    - Sulfamethoxazole is contraindicated in preterm infants and neonates < 4 weeks old due to an increased risk of kernicterus, as sulfonamides displace bilirubin from plasma albumin).

Pregnancy

Trimethoprim and sulfamethoxazole is classed as category C with respect to pregnancy.

Category 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.

Trimethoprim *in isolation* is classed as category B3

Sulfamethoxazole *in isolation* is classed as category C

Breast feeding:

Compatible in infants 1 month or older; may cause diarrhoea in infant. Other antibiotics preferred in younger or preterm neonates

Adverse Effects

Co-trimoxazole, in particular sulfamethoxazole, can occasionally cause serious adverse effects.

1. GIT upset

2. Allergic reactions:

   - Sulfonamides in particular can cause serious allergic and hypersensitivity reactions

   - Note that **HIV infection** increases frequency of allergic reactions to drugs; these are often intolerable and may require use of an alternative.

   - Sulfamethoxazole + trimethoprim **IV** infusion contains **sodium metabisulfite**, a sulfite that may cause allergic-type reactions, including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people.

     The overall prevalence of sulfite sensitivity in the general population is unknown and probably low.

     Sulfite sensitivity is seen more frequently in asthmatic than in non-asthmatic people.

3. Dermatological:

   Again the sulfonamides in particular can cause serious dermatological hypersensitivity reactions including:

   - Stevens- Johnson syndrome

   - TEN

   - DRESS

   Treatment should be ceased at the first sign of a skin rash.

4. Methaemoglobinaemia:

   - Sulfamethoxazole can induce methaemoglobinaemia.

5. Liver impairment:

   - Including fulminant liver failure.

   - Elevation of serum transaminase and bilirubin/ cholestatic jaundice.

6. Renal impairment:

    - Interstitial nephritis

7. Crystalluria:

    - Sulphonamides may *rarely* cause this.

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 oral dosing is: [1]

- **Trimethoprim and sulfamethoxazole 160 + 800 mg orally, 12 hourly for 5 days.**

- **Child 1 month or older: 4 + 20 mg/kg up to 160 + 800 mg**

See latest Antibiotic Therapeutic Guidelines for doses in specific conditions.

References

1. eTG - November 2015.

2. Co-trimoxazole in Australian Medicines Handbook Website Accessed July 2015.

3. Co-trimoxazole in MIMs Website, 1 June 2015.

4. Co-trimoxazole in Critical Care Drug Manual, Dr Paul Young Wellington Hospital Intensive Care Unit, NZ 2010.

Dr J. Hayes
Reviewed May 2016.