

PENICILLAMINE



"Emerald", print, Romain de Tiroff Erte.

Preface:

*Says Moshe, the servant of God from Cordova: The beneficence of our master, the noble and mighty Vizier, may God grant him a long life, has been acclaimed far and wide, in this country as well as in numerous foreign lands. His highness has made it his life's work to share in the good which God has bestowed upon him with **all** people, to keep them from harm, forever intent on assisting them in a useful way, whether by means of his riches and exalted rank or with judicious advice and intervention....*

On Simple and Compounded Remedies, Effective Against All Kinds of Poison:

1. Says the author: Both the simple and compounded remedies which possess a specific power against poison of all kinds and origins are called by the general name of antidote or life-savers, eventually Bezeheriye, derived from the Persian word, bezoar. Well known is the best of all compounded remedies against deadly poison, the great theriac of the 4 ingredients (diatessaron). The foremost of all simple remedies is the emerald, which acts as an antidote, both against swallowed poison and against the bites of poisonous animals. In addition to that, it is specifically adapted to strengthen the heart when put it in the mouth. All this is mentioned and confirmed by Ibn Zohr, the master of years-long experience, the greatest experimenter in drugs, who applied himself to such research more than anybody else and was able to engage in it by dint of his great wealth and exceptional knowledge in the art of medicine. His pupils, friends, and colleagues of mine who came to see me, told me that he never went about, either on a journey or at home, without a silver vessel containing the great theriac and a piece of fine emerald, because - God bless his memory - he was much afraid of deadly poisons...

*On Poisons and their Antidotes; A Treatise to the Honoured One,
Vizier Kadi Abd el-Rahim ibn Ali al- Bishani - Al-Fadhiliye*

Maimonides 1198 A.D.

The densest of the medieval centuries, the six hundred years between, roughly, A.D 400 and A.D. 1000, are still widely known as the Dark Ages. Modern historians have abandoned that phrase, one of them writes, "because of the unacceptable value judgment it implies." Yet there are no survivors to be offended. Nor is the term necessarily pejorative. Very little is clear about that dim era. Intellectual life had vanished from Europe. Even Charlemagne, the first Holy Roman Emperor and the greatest of all medieval rulers, was illiterate...

A World Lit Only By Fire, William Manchester, 1992.

Moshe ben Maimon, better known to history as Maimonides, was a brilliant, quintessential Renaissance man. Only thing is the Renaissance had not yet really happened! The West (or those within its culture who are so inclined to political incorrectness) speaks of the "Dark Ages" - the period of the fall of the Western Roman Empire to around the late Thirteenth Century. Very little learning came from this period when compared to the periods that preceded it and that followed it. But Dark Age is a relative term. While it can most certainly be applied to the West, (in a manner of speaking) for the period 476 to around 1250 AD (or CE if one prefers), when it comes to the Arabic and Persian worlds, it is quite a different matter altogether. For the period of the Seventh to Twelfth centuries, the Islamic world had become a shining beacon for the arts, culture and science, while the West wallowed in relative darkness and ignorance. The principle city of the of the Islamic world, during this golden age was Baghdad, but in 1258 disaster struck. A terrifying Mongol hoard suddenly

emerged from the far East. Bagdad was attacked. It fell to the Mongols and was raised to the ground - a disaster for the Islamic world akin to the fall of Rome for the West. Whilst Rome would rise again under the Christian Papacy, Baghdad would never again regain its former preeminence. The Thirteenth century marked a watershed period. The light of learning would pass from a Mongol ravaged East, back to the West, who was then undergoing its first tentative steps towards rediscovering the glories of its distant past.

Maimonides strikes a fascinating figure. He bridged the two worlds of the East and the West just at the time of these momentous changes. He represented the brilliance of the eastern polymath of a world rapidly disintegrating, but also heralded the brilliance of the Renaissance scholar of the age about to emerge in the West. True to his Jewish heritage he had to learn to continually adapt and survive within foreign cultures. But not only could he adapt, he positively thrived within each, so much so that he became personal physician to the Sultan of Egypt, having turned down an offer from the Christian King, Richard the Lionheart, to be his personal physician!

Maimonides was born in Islamic Cordova in 1135. In his early years he studied not only the Talmud, but also the Bible. He studied also across the board range of all sciences and humanities as known in his time. Cordova allowed him to do this at first, but then a far more warlike and fanatical faction, of the ruling Almohades took control, offering all a choice between conversion to Islam or death. Maimonides fled, and Cordova became the poorer for it. In the year 1165, he went into exile in Crusader held Israel, where he was tolerated and well respected. In the following year he accepted an offer to go to Egypt, where he became personal physician to the Sultan of Egypt, a more enlightened Islamic ruler, than the Almohades. He died in 1204, the same year that Christian crusaders sacked the great city of Constantine.

Maimonides provided many bridges - not only between his own Jewish culture, and Islam and Christianity, and also between the old passing medieval world and the emerging one of the Renaissance, but also within his own culture itself. Solomon Schimmel well articulated these bridges when he wrote in 1964, "Jewish theological tradition boasts many thinkers who felt the need to integrate the latest scientific and philosophical knowledge of their age with the teachings of Judaism. From Philo of the Hellenistic period to Samson Raphael Hirsch of (more) modern times there is a long chain of such men, each in quest of the underlying unity longed for by the religious soul. The most prominent link in this chain is Moshe ben Maimon, or Maimonides".

It is intriguing to consider the possibility that potent medicines were once known to humanity but then lost. A number of precedents of this are well documented, the discovery by Jesuit priests of quinine being used by South American tribes people or more recently the stunning rediscovery by Youyou Tu of a potent group of anti-malarial agents first documented in traditional Chinese herbal medicine handbooks of the Third century AD.

Apart from his many treatises, on philosophy and theology, Maimonides also left major works on medicine. His particular interest was in the field of toxicology. He described intriguing antidotes to poisons, the most interesting of which he records include the all purpose antidotes of the mysterious great theriac and a fabulous concoction of crushed emeralds. Perhaps our lesson from Maimonides is to keep an open mind and to broaden our bridges with the past and with other cultures in order to enrich our own. Today we do have multi-purpose antidotes such as charcoal and penicillamine - but perhaps we should not ignore the distant past. What miraculous medicinal agent may have lurked among the hundreds of components of the great theriac. Could there even be a possible medical benefit in crushed emeralds waiting to be rediscovered?

PENICILLAMINE

Introduction

Penicillamine is a chelating agent, useful for the *second* line treatment of many heavy metal poisonings.

Although a good chelator it has frequent side effects, and there are more efficacious and better tolerated agents available.

It is also used to treat chronic copper toxicity, (Wilson's Disease)

History

Dr. John Walshe first described the use of penicillamine in Wilson's disease in 1956.

He had discovered the compound in the urine of patients (including himself) who had taken penicillin, and experimentally confirmed that it increased urinary copper excretion by chelation.

In the past was also used for the treatment of Rheumatoid arthritis.

Chemistry

Penicillamine is an α -amino acid metabolite of penicillin.

Preparation

Tablets:

- 125 mg
- 250 mg.

Mechanism of Action

The pharmaceutical form is **D**-penicillamine, as L-penicillamine is toxic (it inhibits the action of pyridoxine)

It is an α -amino acid metabolite of penicillin, although it has **no** antibiotic properties of its own.

It binds heavy metals with variable efficacy forming soluble complexes which are then excreted into the urine.

Pharmacokinetics

Absorption:

- Penicillamine is given orally. It is well absorbed.

Distribution:

- Penicillamine is distributed throughout the body water.
- Penicillamine can cross the human placenta

Metabolism and excretion:

- Penicillamine is metabolized to sulfate conjugates and these are excreted in the urine.
- Elimination half-life is around 90 hours.

Indications

Toxicological indications for penicillamine include:

1. Chronic copper toxicity, (Wilson's Disease)
2. A second line agent for the chelation of heavy metals including:
 - Arsenic
 - Iron
 - Lead
 - Mercury
 - Zinc

Contra-indications/ Precautions

These include:

1. Known hypersensitivity.
 - Including a history of penicillin allergy - *cross-sensitivity* to penicillamine may occur. ³
2. Renal failure (unable to excrete the chelates)
3. Pregnancy, (penicillamine is teratogenic) - see below

Pregnancy

Penicillamine is a category D drug with respect to pregnancy.

Category D drug are those drugs which have caused, are suspected to have caused or may be expected to cause an increased incidence of human fetal malformations or irreversible damage. These drugs

may also have adverse pharmacological effects. Specialised texts should be consulted for further details

Breast feeding:

Reports describing the use of penicillamine during breastfeeding have not been located, and the effects on the breastfed infant are unknown. Adverse effects have not been noted in the breastfed infants of mothers taking penicillamine for Wilson's disease. However, the concentration of zinc and copper in the mother's milk was found to be reduced. Therefore, due to the potential risk of severe adverse reactions in the breastfed infant, avoid breastfeeding during penicillamine treatment.

Adverse Reactions

Adverse effects are diverse and relatively frequent and often require cessation of therapy.

They can include:

1. Allergic reactions
2. Dermatological hypersensitivity reactions.
3. Systemic hypersensitivity reactions:

- Goodpasture's syndrome.

4. Hematological effects:

Variable bone marrow cell line depression including:

- Thrombocytopenia
- Leucopenia/ agranulocytosis.

5. Neurological:

- Peripheral neuropathy
- Myasthenia gravis.

5. Renal:

Nephrotoxicity:

- Glomerulonephritis
- Nephrotic syndrome.

6. GIT:

- Hepatotoxicity
- Pancreatitis.

Dosing

Penicillamine is an uncommonly used drug and so should only be used under the direction of a specialist Toxicologist.

In *general terms*:

- **Give 4-7 mg/kg orally 4 times a day, (with a maximum adult daily dose of 2 grams).**

Monitoring:

Monitoring is important:

- Second weekly FBE and FWT
- Weekly urine and/or blood testing for the toxic heavy metal.

The exact duration of therapy will depend upon any developing toxicity as well as the rate of elimination of the toxic heavy metal.

Months of therapy may be required.

Therapeutic end point:

The therapeutic end point is generally taken as the lowering of metal concentrations in the blood to non-dangerous levels.

References

1. Penicillamine in: Murray L et al. Toxicology Handbook 3rd ed 2015.
2. RWH Pregnancy & Breastfeeding Guidelines, 27 August 2015.
3. Penicillamine in Australian Medicines Handbook, Accessed May 2016.

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