

BETA BLOCKER OVERDOSE



“The Three Magi”, oil on wooden panel, Nineteenth Century Italian, artist unknown,

“The Magi, were of Chaldea, where astrology was born, of which this is a dictum: Great conjunctions of planets in cardinal points, especially in equinoctial points of Aries and Libra, signify a universal change of affairs, and a cometary star appearing at the same time tells of the rise of a great King”.

Johannes Kepler, Astronomi Opera Omnia, 16th /17th Century.

*For millennia speculation has existed as to the nature of the Biblical account of the Star of Bethlehem. The star was said to have guided three Magi, or wise men, from the East, to the birthplace of Christ. Ever since the mysterious account given in both Luke and Mathew, believers have attributed the star to a miraculous event, others to it merely being a symbolic apocryphal religious story. In the modern age our understanding of Astronomy has progressed, “light years” from what it was in the First Century A.D, and necessarily explanations of the Star of Bethlehem have become far more sophisticated. Was the “star” a true Astronomical event that happened around the time of the birth of Christ? Twenty First Century explanations for the miraculous apparition, have largely now settled on the possibility - or even probability - depending on one’s level of faith - of the star being a supernova, a comet or a meteor. Most recently however Michael Molnar, a renowned Astronomer and former head of the Physics Laboratory of Rutgers University has argued that there is another intriguing possibility that may explain the true nature of the Star of Bethlehem. He argues passionately and convincingly that to understand what the star was, one has to leave behind anachronistic 21st century high-end ideas of Astrophysics and instead see through the eyes of an Astronomer of the First Century B.C. - a perspective almost unimaginably different to that of Astronomers of our own time. He gives a fascinating, and compelling argument, that the Star of Bethlehem was neither a comet, a meteor, nor even a type Ia supernova - but rather it was a very rare **Astrological** event, and one that had profound importance in the context of Roman occupied Judea in the First Century B.C.*

*In the ancient world, an Astronomer and an Astrologer was one and the same thing. Those trained in the art of Astronomy struggled to make meaning of their observations of the heavens, and this understanding in large part took the form of Astrology. It cannot be overemphasized enough, that an Astrologer of those times was very different to the television charlatans and confidence tricksters of the gullible that call themselves “astrologers” in the 21st Century. Astrologers in the ancient world - given the context of their state of technology - were also brilliant observational Astronomers and Mathematicians. They could chart the paths of the stars and planets across the heavens with startling accuracy. The differences from Astronomers of today was of course not only of a lack of advanced technology, but also one of the **interpretation** of astronomical observations, brilliant as these often were. In a Religious age, it is easy to see how the interpretation of the Heavens became intimately connected with the affairs and fate of humanity. Astrologers looked to the stars to try and understand the world they lived in, and made predictions based on these truly scientific observations. An important task of the Astrologer was the construction of the horoscope, a map of the heavens that charted the exact position of the stars at the exact time as well as exact location that a person was born. As Astrologers could accurately predict the future pathway of the stars, then it followed that because the stars had divine influence over the affairs of humanity, predictions could also be made for the future life path of an individual if it was known under what star alignments they had been born. Horoscopes were taken so seriously that the Emperor Augustus decreed the death penalty for anyone who divulged the information they contained on any living Emperor, as this information could possibly be used against the Emperor.*

Most Astrologers of the ancient world were Persian or Hellenistic, i.e. “wise men from the East”. To understand why the astrological portent of the Star of Bethlehem was so important to those of the First century AD, one has to understand the politics of the day. Judea had been under brutal Roman rule and sacred scripture had long predicted the rise of a powerful King that would one day free the people from Roman oppression. Who else

better to search for a powerful portent of a Messiah, than a learned Astrologer, and indeed this is exactly what happened. Learned men would vigilantly scan the heavens for any sign of a regal birth. And it happened that in 6 B.C a once in a lifetime astrological conjunction arose in the sign of Aries the Ram - the Zodiacal sign of Judea! The signs were multiple and powerful, a lunar occultation of Jupiter, which had arisen in the East, and occurred in the sign of the Ram were just the most important of a host of regal portents, that all came together in the year 6 BC. Fascinatingly, modern 21st Century computers not only confirm this stellar arrangement for 6. BC, they also do it with a precision that gives a precise day on which this alignment would have occurred - April 17th! Molnar argues that three Zoroastrian astrologer - priests from the East (now known to history as the "Magi") were so startled by this event, they thought it important enough to report it to the Roman client King of Judea of the time - King Herod. Herod, like all others of the day implicitly believed in the power of astrology. When told that a future great King had been born somewhere in Judea he ordered the wise men to seek this child out. Realizing they had been somewhat naive in reporting this event to Herod - whose only intention in seeking out the child could have been to eliminate a potential rival, (indeed Augustus himself famously remarked that it was safer to be Herod's pig than one of his sons, as Herod had executed three of his sons on the mere suspicion they were planning usurpation of his throne) - promptly fled back to the East and disappear from history as rapidly and as mysteriously as they had entered it. In frustration Herod in 4 BC is said to have ordered the immediate execution of all children under the age of 2 years - an age of birth which correlates well with the astrological event in Aries in 6 BC, (the current best guess for the birth of Christ!). Molner goes on to explain that a mortal fear pervaded the Roman overlords of Judea during these years as they could never be certain that the child born under the sign of Aries in 6 BC (by our reckoning) had survived Herod's sickening massacre of the innocents. As the astrological sign of the royal birth was disputed by no one of the day, Molnar then further explains that Rome, rather than trying to deny the event had occurred, tried to put a different interpretation on it to oppose the one widely held view that had caught the popular imagination i.e. of the birth of a Messiah. Around 5 AD bronze coins began to be minted in Antioch that depicted the "Star in Aries", but its meaning had been appropriated from that of a regal birth to that of Roman conquest over Judea. As an interesting postscript to these events, one notes that Tiberius (who employed his own personal astrologer) - the successor to Augustus, spent the final years of his life hidden away on the Isle of Capri. Was this perhaps because he still lived in fear of the momentous prediction made in 6 BC of the birth of an all powerful King of Judea? The Star of Bethlehem appears to have been a true event, but not in the sense of any modern understanding of astronomy. It was an event that in the minds of those of the First Century B.C was even more powerful than that- a foretelling of the future given to humanity from heaven itself. Although this prediction did not come true in the sense of a temporal King of Judea, it did happen to coincide with a particular birth in Judea that could by any criteria be said to have been one of the most (if not the most) influential in history. Perhaps there is something after all in the very ancient Persian wisdom, "...it is so, for it is written in the stars!"

It appears that when it comes to the treatment of beta blocker overdose, we have been looking in the wrong place. Although based on sound theory, like the supernova, or comet or meteor theories for the Star of Bethlehem, there is in fact no good evidence for the efficacy of glucagon. Indeed a more sophisticated understanding of this condition has provided us with an alternative answer from a most unexpected source - insulin!

BETA BLOCKER OVERDOSE

Introduction

Propranolol and **sotalol** are the two beta blocking agents that are most likely to cause significant and potentially life threatening toxicity in overdose.

Most other beta-blockers do not result in significant toxicity.

Propranolol is treated predominantly as a **class I sodium channel blocking agent**, rather than as a beta blocker.

Insulin-dextrose euglycemia therapy is the best pharmacological inotrope therapy.

Lipid emulsion therapy may be a further option in refractory cases of propranolol toxicity.

See also separate documents on:

- **Insulin-dextrose euglycemia therapy (in Drugs folder).**
- **Lipid emulsion therapy (in Drugs folder).**

History

Glucagon had been traditionally put forward on reasonable theoretical grounds as a specific antidote to beta blocker poisoning; however it offered no advantages over standard inotropes or chronotropes. In large doses it also had a propensity to cause nausea and vomiting, which was problematic in unwell patients with reduced conscious states.

Current expert opinion has now abandoned this agent, in favour of conventional inotropes and Insulin-dextrose euglycemia therapy

Preparations

Current beta -blocker agents include:

- **Propranolol**
- **Sotalol**
- **Atenolol**
- **Bisoprolol**
- **Carvedilol**
- **Pindolol**
- **Esmolol**
- **Metoprolol**
- **Oxprenolol**

Pharmacokinetics

Absorption

- Beta blockers are rapidly absorbed from the GIT with peak levels occurring within 1-3 hours post ingestion.

Distribution

- There is rapid distribution with variable volumes of distribution depending on the agent.
- Propranolol is especially lipophilic.

Metabolism and excretion:

- This is variable depending on the agent.
- The half-life of propranolol is 12 hours but this can be longer in overdose.

Toxicology

There is competitive antagonism at:

- Beta 1 receptors
- Beta 2 receptors

Excessive blockade leads to a fall in intra-cellular cAMP levels with resulting diminution of the chronotropic, inotropic and metabolic effects of catecholamines.

Added features of **propranolol** toxicity include:

- High lipid solubility allows for CNS penetration
- Class I **sodium channel blocking** effects with prolongation of the QRS.

Added features of **sotalol** toxicity include:

- **Blockade of K channels** interfering with cardiac repolarization (class III activity) leading to significant **QT prolongation** and the potential for torsades de pointes.

Risk Assessment

The response to overdose with beta blockers can be highly variable.

Factors that affect toxicity include:

- The dose taken.
- **The agent taken.**
- Co-morbidities, (cardiac and respiratory)
- **Co-ingestion:** calcium channel blockers, digoxin.
- Elderly

The most toxic agents in isolation are:

- **Sotalol**
- **Propranolol**

Other beta blockers are relatively less toxic *unless taken with other cardiovascular-acting agents*, (e.g calcium antagonist or digoxin), where severe toxicity can occur.

No clear toxic dose of beta blockers has been identified except for **propranolol**, where ingestions of as little as **1 gram** can be associated with significant toxicity, which includes depressed conscious state, seizures and sodium channel blockade. ²

Toxicity usually manifests within 2 hours, though this can be delayed with sotalol or controlled release preparations.

PR prolongation on ECG even in the absence of bradycardia is an **early sign** of toxicity.

Children:

Any ingestion of propranolol or sotalol is potentially serious in children.

Clinical Features

Signs of toxicity generally occur within **4 hours**.

1. Cardiovascular:

This represents the most serious toxic effects and include:

- Bradycardia
- Hypotension
- Conduction delays:
 - ♥ **PR prolongation** on ECG even in the absence of bradycardia is an **early sign** of toxicity.
- Myocardial depression
- **Propranolol** may also cause **QRS** widening, a predictor of ventricular arrhythmias.
- **Sotalol** may also cause **QT** widening leading to torsades de pointes.

2. CNS:

- **Propranolol may cause delirium, coma and seizures.**

3. Respiratory:
 - Bronchospasm
 - Cardiogenic pulmonary edema
4. Metabolic:
 - Hyperglycaemia or hypoglycaemia

Investigations

1. FBE
2. U&Es/ glucose
3. Consider coingestion:
Blood alcohol and paracetamol levels.
4. ECG:
 - PR prolongation, even in the absence of bradycardia this is a sign of early toxicity.
 - Prolongation of QRS (propranolol) or QT (sotalol)
5. CXR:
 - Pulmonary edema/ aspiration.

Management

1. Attend to any immediate ABC issues.
 - Close observation and **continuous ECG monitoring** is mandatory.
2. Charcoal:
 - This may be given within **2 hours** of ingestion if the patient is stable and alert.
 - When **propranolol** or **sotalol** has been taken it is probably best avoided unless the patient is intubated, due to the potential for sudden coma and arrhythmias.
3. CNS toxicity:

- In the case of **propranolol** CNS induced toxicity, treat seizures, delirium with IV benzodiazepines along usual lines.

Then for hypotension/ bradycardia:

4. Fluids
 - An initial fluid bolus.
5. Atropine:
 - 1.2 mg - 2.4 mg IV
6. Inotropes:
 - Isoprenaline/ adrenaline infusion.
7. Arrhythmias:

Widened QRS due to propranolol:

- **This should be treated as a class I anti-arrhythmic effect and sodium bicarbonate should therefore be given.**

Torsades de pointes due to sotalol:

- MgSO₄:

For Torsades de pointes:

 - ♥ **Magnesium sulphate 50% 2 to 4 mL (= 1 to 2 g or 4 to 8 mmol) IV as a slow injection over 10 to 15 minutes.**²
- The background bradyarrhythmia should receive atropine/ isoprenaline as a temporizing measure to pacing.
- The torsades rhythm itself should be cardioverted/ defibrillated if prolonged

See also Prolonged QT syndromes and torsades de pointes (in CVS folder).

8. **Insulin-dextrose euglycemia therapy:**

- This is a technique used primarily in **calcium channel blocker** overdose.
- It has been advocated also in cases of severe **beta blocker** overdose.

For details of the technique see Document, Insulin-Dextrose Euglycemia, (Drugs Folder).

9. Lipid Emulsion Therapy:

- The role of this therapy is not well defined.
- It may be considered in life-threatening toxicity where there has been an inadequate response to other therapies.

10. Mechanical myocardial assist devices:

In severe cases refractory to all medical and pacing treatments mechanical cardiac assist devices may be tried where available.

Options here include:

- Aortic balloon pump.
- ECMO

11. Hemodialysis:

- Is *not* effective for beta blocker overdose.

Disposition:

Close clinical observation and continuous ECG monitoring should occur for at least **6 hours**.

Patients with ECG changes or symptoms will require monitoring in a critical care (ICU/HDU) setting.

Patients who remain asymptomatic and have a normal ECG at 6 hours post ingestion may be medically cleared.



“The Star of Bethlehem Coin” The first bronze coins of Antioch depicting Aries were issued in c. 5-11 AD in the then Roman province of Syria - (Molnar Collection - RPC 4265).

The Ram representing Aries, the Constellation of Judea, in the pre-Roman annexation period, is seen looking back towards the “star”, Jupiter. The normal momentary retrograde motion of the planets, due to the uneven orbital speed of the Earth with respect to the outer planets as they are observed as they move across the sky, provides an intriguing explanation for the Biblical account of the miraculous movements of the Star of Bethlehem.

References

1. Beta Blockers in L Murray et al. Toxicology Handbook 3rd ed 2015.
2. eTG - July 2016
 - Beta Blocker Overdose in eTG, Toxicology and Wilderness, 2nd ed 2012.

Further Reading:

Molnar M.R, “The Star of Bethlehem”, The Legacy of the Magi, Rutgers University Press, 1999.

Dr J. Hayes

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