

SGLT2 INHIBITOR (GLIFLOZIN) INDUCED - EUGLYCEMIC DKA



“All Good Things”, Star Trek, the Next Generation, Final Episode, May 1994.

Earth - Archean Eon, 3.5 billion years ago.

Q: *Welcome home.*

PICARD: *Home?*

Q: *Don't you recognise your old stomping grounds? This is Earth, France, about, oh, three and a half billion years ago, give or take an eon or two. Smells awful, doesn't it? All that sulphur and volcanic ash. I really must speak to the maid.*

PICARD: *Q, is there any point to all this?*

Q: *Look.*

(A purple sky - dominated by a massive glowing spiral light)

PICARD: *So the anomaly is here too, at Earth!*

Q: *At this point in history the anomaly fills your entire quadrant of the galaxy.*

PICARD: *The further back in time, the larger the anomaly.*

Q: *Come here. There's something I want to show you. You see this?*

(Points to a primal slime filled pond)

Q: *This is you. I'm serious. Right here, life is about to form on this planet for the very first time. A group of amino acids are about to combine and form the first protein, the building blocks of what you call life. Strange, isn't it? Everything you know, your entire civilisation, it all begins right here in this little pond ofgoo. Appropriate, somehow, isn't it? Too bad you didn't bring your microscope. It's really quite fascinating. Oh, look, there they go. The amino acids are moving closer ...and closer....and closer. Oh! Nothing happened. See what you've done?*

PICARD: *Are you saying that I caused the anomaly, and that the anomaly somehow disrupted the beginnings of life on Earth?*

Q: *...Congratulations.*

At the end of the 24th century Humanity stands at the threshold of conquering the tyranny of inter-stellar distance. The most complex and powerful starship ever built - Galaxy class - is constructed. With its staggering ability to travel at warp factor 9.8 - with a theoretical barrier of warp factor 10 being a limit to what the laws of physics say is possible - the whole Milky Way now seems within Humanity's grasp. The Enterprise D, named for its five predecessors, is about to embark on a 7 year mission of previously unimagined possibilities. But Captain Jean-Luc Picard and his senior officers hold a terrifying secret - a secret so deeply shocking that only the highest levels of Starfleet Command and the Federation of Planets are privy to it. An alien intelligence of unimaginable power had appeared to the senior crew barely after the mission had begun. It seemed that it could take any form it chose - communicate in any way or language it

desired. Taking a human form, suddenly it appeared out of nowhere on the bridge of the Enterprise and announced that the mission was not permitted to proceed, apparently unimpressed with Humanity as a species, especially one that now seemed poised to dominate the Galaxy. Previously Humanity, held no interest for it, but now on the verge of breaking out into the Milk Way, its attention has been caught.

It appeared to be an immaterial intelligence of electromagnetic energy permeating space, but existing within planes of dimensions beyond normal human experience or even comprehension. Just as a three dimensional being would appear to have miraculous powers of movement in space to a creature that inhabited only two dimensions, it seemed to hold powers truly miraculous to humans and all other sentient species of the galaxy existing within the perceived - "normal" confines of space and time. As best as can be determined it exists outside of normal "space" and "time" - but can readily move within any of the 26 dimensions now theoretically described by 24th century physics. Its abilities and powers seem unlimited. It is unclear whether the entity is one or part of many - some of the Federation's most brilliant Physicists regard it as a sentient energy form of some kind of electromagnetic "continuum" beyond what is known. So alien a life form, it is unclassifiable by any convention previously established. It is given a top-secret "species" designation of simply "The Q Continuum"

Its power is incomprehensibly God-like, but this is not what is shocking. There was some initial hope that such a vast, cool intelligence, would share the best of noble human values. But it soon becomes apparent that it is not a benevolent or nurturing "god". It is vengeful, jealous, petty, spiteful, arrogant beyond measure, without any regard for any life form other than its own. If it is a god then it is akin to the terrifying Yahweh of ancient's Earth's Old Testament or of the thunderbolt hurling Zeus of the Classical Age of Greece. It is clear that the entity's powers are unchallengeable - a cross roads in Human civilization has been reached. Will Humanity grow and evolve by exploring the Universe - or will it be forced to retreat back to its small speck of dust - the Earth - from which it emerged, to slowly stagnate, exhaust its planetary resources and then inevitably die. The honour, the dignity, the very survival of Humanity is at stake

Captain Picard, decides to test the full capacity of 24th century technology at his command, by ordering a quick get away from the entity now suspended in space before the Enterprise. They flee at a velocity, never before travelled by any Human. Exceeding maximum engineering specifications, the Enterprise engages at warp factor 9.9, it is uncertain they will survive. The Intelligence is momentarily taken off guard, perhaps surprised that the species it so belittles, holds such capacity at the very limits of physics. It soon recovers however from its momentary lapse in arrogant assuredness, chases after the Enterprise and immobilizes it. Its interest now piqued, it seems almost curious, though its arrogance remains unabated. Perhaps it senses some kind of threat. It reappears on the deck and lists numerous examples of Humanity's barbarism over the course of its history, then announces that Humanity will be put "on trial" for its worthiness to exist. Captain Jean-Luc Picard now desperate, concedes that in the past Humanity was indeed a brutal species, but he argues desperately and passionately that this is no longer true - and that such an Intelligent being should test his claim for itself. Intrigued, the entity agrees. Humanity will be given a test. Then it vanishes just as suddenly as it had appeared. Over the next few weeks, Jean-Luc saves a remarkable

animal from the torments of its captors, an alien, humanoid species who exploit it ruthlessly for its abilities to covert energy into material goods upon which they grow rich. The Q suddenly reappears, explaining that this was the test it had alluded to. It is grudgingly respectful for the first time. Humanity will be spared, it announces. Then it vanishes again.

Captain Jean-Luc Picard, leads his crew on the planned mission - seven years of fabulous exploration of the Alpha Quadrant of the Milky Way follows - but all the time he knows that the "Q entity" is watching. Indeed from time to time it reappears and sneers and torments Jean-Luc and his crew, putting them in life threatening situations and watching to see how they respond like some spoilt personality disordered child who enjoys tormenting defenseless animals. The 7 year mission ends, a stunning success - the frontiers of the Federation have not been so enormously expanded since the time of Captain James T. Kirk. The Enterprise begins its return voyage home, but a remarkable and deeply puzzling phenomenon or "anomaly" of sub-space is then reported to have been picked up by long range sensors. It appears to have originated in the distant Devron System. But then a miraculous thing happens. Jean-Luc begins to experience disorientating episodes of "time shifting". One minute he is reliving the past in the full vigor of his youth - the next he is an old man in the distant, future, very frail and suffering the effects of an early form of rare dementia known as Irumodic Syndrome. Then suddenly he is back to the present.

PICARD: (in dressing gown) Counselor! What's today's date? **The date!**

WORF: Stardate 47988.

PICARD: 47988.

TROI: Captain, what's wrong?

PICARD: 47988. I'm not sure. I don't know how or why, but I'm moving back and forth through time!

As Jean-Luc becomes more accustomed to the time shifts, he begins to remember more and more of each episode - moving easily from time frame to time frame. A pattern soon emerges - in each of the three time periods - the past, the present and the future, the mission of the Enterprise is the same - the investigation of a mysterious space - time "anomaly" in the Devron System. In each time period Jean-Luc orders a novel method of scanning the anomaly in order to investigate its nature - an inverse tachyon beam. In the present he begins the scan - in the past he also scans - but the anomaly seems very much larger - hundreds of millions of kilometers in diameter; but in the future, it is so small as to be undetectable by normal scanning methods. Again Jean-Luc orders an inverse tachyon scan - not to examine it - but merely to find it! Then in the present suddenly the Q appears! It shockingly announces that the "trial" had never really ended. After 7 years the Q have reached a verdict - Humanity does not deserve to survive - it will fail its final test. Humanity will be wiped entirely from existence, to make way for some other more "worthy" species to dominate the Galaxy. Jean-Luc is desperate and pleads with Q to spare humanity. The Q sneers and tells him, that it is not the Q who will exterminate

Humanity - rather it will be Jean-Luc himself! Then something remarkable happens. The Q momentarily seems to soften. It is as if the spoiled child, suddenly has grown up. It feels sorry for the “pet” it has been brutalizing. It is a poignant moment between a tearful Jean-Luc and the Q. “Would it help to have a different perspective?” the Q quietly whispers.

Jean-Luc is transported back to the fiery origins of a primal Archean Earth, billions of years ago. Even though there is no oxygen on Earth at this time, he seems unaffected. The Q draws his attention to an alien purple sky. He is staggered to see the “anomaly” from Earth - and it fills half the sky! Q draws Jean-Luc’s attention to a tiny slimy pond under his feet. He explains that he is about to witness the very moment that life first formed on Earth - the one in virtually infinite chance that life began is about to happen right now - a critical nanoscopic conjunction of certain groups of amino acids, will form the first protein. But the anomaly stops it from happening - life never starts on planet Earth. Jean-Luc now understands - the anomaly is essentially an explosion of anti-time, the result as Data of the future will tell him of a meeting of time and anti-time. Just as matter and anti-matter - if they meet - will annihilate each other so will time and anti-time; but here the result is not a stupendous explosion of matter - it is an explosion of anti-time that originated in the distant future. Back as far as the Archean Eon the explosion fills a quarter of the Milky Way - life on Earth never happens - humanity never comes into existence.

Jean-Luc next finds himself back in the distant future. He explains his experiences to Commander Data, who realizes that it is the inverse tachyon beams from the three different time periods that is sustaining the anti-time explosion. By ordering the scans in all three time periods Jean-Luc will indeed be the cause of the non-existence of humanity. Data determines that the way to repair the rupture in time is for the inverse tachyon beam in all three time periods to be stopped to shrink the anomaly and then, again in all three time periods, the Enterprise must enter the very center of the collapsing anomaly and seal the original rupture via the formation of a containing warp bubble. This is all very fine in the future where the anomaly is very small, but in the present and the past especially, where the anomaly is very much larger and more powerful, it will result in suicide missions. Jean-Luc with Irumodic syndrome in the future must convince his senior officers of this course of action, while in the present and past he must convince the crew of the need for a suicide mission in order to save humanity. With supreme leadership in all three time periods Jean-Luc manages to convince his crew and so achieves the task, even though two of the Enterprises are destroyed in the process. The anomaly is repaired, the anti-time explosion never happens in the future.....

(Picard sits with his head in his hands)

Q: *The Continuum didn’t think you had it in you, Jean-Luc, but I knew you did.*

PICARD: *Are you saying that it worked? We collapsed the anomaly?*

Q: *Is that all this meant to you? Just another spatial anomaly? Just another day at the office?*

PICARD: *Did it work?*

Q: *Well, you're here, aren't you? You're talking to me, aren't you?*

PICARD: *What about my crew?*

Q: *The anomaly. My crew. My ship. I suppose you're worried about your fish, too. Well, if it puts your mind at ease, you've saved humanity...once again.*

PICARD: *Thank you.*

Q: *For what?*

PICARD: *You had a hand in helping me get out of this.*

Q: *I was the one that got you into it. A directive from the Continuum. The part about the helping hand, though, that was my idea.*

PICARD: *I sincerely hope that this is the last time that I find myself here.*

Q: *You just don't get it, do you, Jean-Luc? The trial never ends. We wanted to see if you had the ability to expand your mind and your horizons. And for one brief moment, you did.*

PICARD: *When I realised the paradox.*

Q: *Exactly. For that one fraction of a second, you were open to options you had never considered. That is the exploration that awaits you. Not mapping stars and studying nebulae, but charting the unknowable possibilities of existence.*

PICARD: *Q, what is it that you're trying to tell me?*

(Q leans towards Picard and makes to whisper in his ear - but then suddenly stops, and withdraws)

Q: *You'll find out. In any case, I'll be watching. And if you're very lucky, I'll drop by to say hello from time to time.....See you out there!*

When we prescribe our patients a Gliflozin, we must always keep our minds open to options never considered - that in the patient with ketoacidosis, it may be that we ourselves are to blame for this anomaly - we may be the cause of the very condition which we seek to prevent!

SGLT2 INHIBITOR (GLIFLOZIN) INDUCED - EUGLYCEMIC DKA

Introduction

Sodium-glucose co-transporter 2 (SGLT2) inhibitors (also known as **Gliflozins**) are an increasingly prescribed class of medication for type 2 diabetes mellitus.

These agents **reduce glucose reabsorption** in the kidneys.

An important, but **underappreciated** adverse effect of these agents is **Euglycemic Diabetic Ketoacidosis**, which can be **life-threatening**.

DKA occurs when there is insufficient insulin for suppression of lipolysis, leading to the generation of ketone bodies.

Insulin deficiency typically results in hyperglycaemia; thus, DKA is usually seen only when glucose is ≥ 14 mmol/L.

It is postulated that by reducing the circulating glucose load, **SGLT2 inhibitors** lead to **reduced stimulation of endogenous insulin secretion** (or reduced dosing of exogenous insulin), resulting in DKA despite euglycaemia - as there is insufficient insulin to prevent lipolysis.

SGLT2 inhibitors may also contribute to **euglycemic diabetic ketoacidosis** by promoting **renal tubular absorption of ketone bodies** (thus, **urine ketone measurement is not reliable in diagnosing DKA in this setting**) and **increasing glucagon secretion**.

There should be a high index of suspicion for diabetic patients who are taking a gliflozin and who present “unwell”. Look for ketoacidosis with only mildly elevated or normal blood glucose levels.

Management of euglycemic diabetic ketoacidosis involves:

1. Cessation of the gliflozin agent.
2. Rehydration
3. Insulin and dextrose infusion.
 - It may be necessary to deviate from usual DKA protocols by administration of a higher rate of dextrose in order to deliver sufficient insulin to **clear the ketoacidosis**.
4. Treatment of any precipitating pathology

Preparations

Currently available Sodium-glucose co-transporter 2 (or SGLT-2) inhibitors (or “Gliflozins”) in Australia include:

1. Dapagliflozin
2. Empagliflozin

Toxicology

The gliflozins are reversible competitive inhibitors of the protein sodium-glucose co-transporter 2 (SGLT-2).

SGLT- 2 is the predominant transporter for the reabsorption of glucose from the glomerular filtrate back into the circulation.

The SGLT-2 inhibitors as a group reduce glucose reabsorption in the kidney and so increase its excretion in the urine.

DKA occurs when there is insufficient insulin for suppression of lipolysis, leading to the generation of ketone bodies.

Ketosis results from restriction of carbohydrate usage with increased reliance on fat oxidation for energy production.

Insulin deficiency typically results in hyperglycaemia; thus, DKA is usually seen only when glucose is ≥ 14 mmol/L.

DKA was traditionally thought to occur exclusively in type 1 diabetes (T1DM), but it is now recognized that it may occur in some patients with T2DM. This most commonly occurs in the setting of acute illness (associated with increased secretion of counter-regulatory hormones such as cortisol and catecholamines), or at time of diagnosis of diabetes.

As glucose is the chief stimulus for insulin release under all circumstances, plasma insulin levels will fall with reduced blood glucose levels.

It is postulated that by *reducing the circulating glucose load*, **SGLT2 inhibitors** may lead to **reduced stimulation of endogenous insulin secretion** (or reduced dosing of exogenous insulin), resulting in DKA despite euglycaemia - as there is insufficient insulin to prevent lipolysis.

SGLT2 inhibitors may also contribute to **euglycemic diabetic ketoacidosis** by promoting **renal tubular absorption of ketone bodies** (thus, **urine ketone measurement is not reliable in diagnosing DKA in this setting**) and **increasing glucagon secretion**.

Risk assessment

Cases may be precipitated by

1. Metabolically stressful situations such as:
 - Surgery
 - Trauma
 - Infection
 - ACS
2. Other risk factors for ketosis including:
 - Low carbohydrate diet
 - Excess alcohol intake.
3. Missed insulin doses

Clinical features

There should be a high index of suspicion for diabetic patients who are taking a gliflozin and who present “unwell”

Look for ketoacidosis with only mildly elevated or normal blood glucose levels.

Most cases occur in **insulin-deficient patients** i.e., type I diabetics or long-standing type II diabetics.

Clinical symptoms may be the result of :

1. Those of an underlying precipitant condition, (when present).
2. The resulting ketoacidosis:

These symptoms are non-specific, but can include

- Lethargy/ malaise
- Delirium/ confusion
- GIT upset
- ♥ Nausea / vomiting / abdominal pain.

Investigations

Blood tests:

1. FBE
2. U&Es/ glucose
 - Glucose may be **mildly elevated** or may be **normal**
3. VBGs / ABGs:

There will be a high anion gap metabolic acidosis

 - Acidosis: pH < 7.35 (can be severe, and life-threatening).
 - PCO₂ Low
 - HCO₃⁻ Low
 - Base excess < -2 mmol/L
4. Lactate
 - Not typically elevated per se, unless secondary to hypovolemia/ hypoxia
5. LFTs
6. Troponin

Ketones:

Blood capillary ketone testing:

- These will be elevated

Measured blood ketones:

- Elevated b-hydroxybutyrate levels (normal < 0.30 mmol/L)

Urinary ketones:

- SGLT2 inhibitors may contribute to euglycemic diabetic ketoacidosis by promoting **renal tubular absorption of ketone bodies** and thus, **urine** ketone measurement is **unreliable** in diagnosing DKA in patients taking gliflozins.

Septic work up:

Look for a source of sepsis

- Urine for M&C
- Blood cultures
- CXR

ECG:

To help exclude ACS

Management

Prevention:

The American Association of Clinical Endocrinologists and American College of Endocrinology recommend that SGLT2 inhibitors be ceased pre-operatively or in other physically stressful situations, such as severe infection or excessive exercise.¹

SGLT2 inhibitors should be used with caution in the acute care hospital setting, and that they should be prescribed only to patients with adequate carbohydrate intake, after resolution of acute illness. In many cases, this may not be until patients are close to discharge.

Treatment:

Management of euglycemic diabetic ketoacidosis involves:

1. Cessation of the gliflozin agent.
2. Rehydration
3. Insulin and dextrose infusion.
 - Note that **unlike** the situation with DKA or HHS (and *like* the situation with alcoholic DKA) dextrose must be commenced simultaneously with insulin. The aim is not to normalize glucose levels, (which may already be normal), but rather to clear the **ketoacidosis**.
 - It may be necessary to deviate from usual DKA protocols by administration of a higher rate of dextrose (e.g. 10% dextrose as opposed to 5% dextrose) in order to deliver sufficient insulin to **clear the ketoacidosis**.
4. Treatment of any precipitating pathology

Disposition

Very unwell patients may require admission to a HDU or ICU

Referral to:

- Endocrinology
- Clinical Toxicologist
- ICU, as required



The Enterprise scans a mysterious spacial anomaly in the Devron System, by use of an inverse tachyon beam.



You just don't get it, do you, Jean-Luc? The trial never ends!



“.....I’ll be watching. And if you’re very lucky, I’ll drop by to say hello from time to time.....See you out there!”

References

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