

DIGOXIN FAB FRAGMENTS



“Abandon all hope, you who enter here”, woodcut print, Gustave Dore, 1865.

*Through me the way to the city of woe
Through me the way to eternal pain
Through me the way among the lost*

*Justice moved my maker on high
Divine power made me
Wisdom supreme, and primal love*

*Before me nothing was
And I endure eternally.
Abandon all hope, you who enter here*

*These words, dark in hue, I saw inscribed
over an archway. And then I said:
"Master, for me their meaning is hard".*

*And he, as one who understood:
"Here you must banish all distrust,
here must all cowardice be slain.*

*"We have come to where I said
you would see the miserable sinners
who have lost the good of the intellect".*

*And after he had put his hand on mine
with a reassuring look that gave me comfort,
he led me toward things unknown to man.*

*Now sighs, loud wailing, lamentation
Resounded through the starless air,
so that I too began to weep.*

*Unfamiliar tongues, horrendous accents,
words of suffering, cries of rage, voices
loud and faint, the sound of slapping hands...*

*all these made a tumult, always whirling
in that black and timeless air,
as sand is whirled in a whirlwind.*

*And I, my head encircled by error, said:
"Master, what is this I hear, and what people
are these so overcome by pain?"*

*And he to me: "This miserable state is born
by wretched souls of those who lived
without disgrace yet without praise.*

*They intermingle with that wicked band
Of angels, not rebellious and not faithful
to God, who held themselves apart.*

*"Loath to impair its beauty, Heaven casts them
out and depth of Hell does not receive them
lest on their account the evil angels gloat".*

*And I: "Master, what is so grievous to them,
that they lament so bitterly?"
He replied, "I can tell you in few words.*

*"They have no hope of death,
and their blind life is so abject
that they are envious of every other lot.*

*"The world does not permit report of them,
Mercy and justice hold them in contempt.
Let us not speak of them - look and pass by".*

*And I, all eyes, saw a whirling banner
that ran so fast it seemed as though
it never could find rest.*

*Behind it came so long a file of people
that I could not believe
death had undone so many.*

*After I recognized a few of these,
I saw and knew the shade of him
who, through cowardice, made the great refusal.*

*At once with certainty I understood
this was that worthless crew
hateful alike to God and to His foes.*

*These wretches, who never were alive,
were naked and beset
by stinging flies and wasps.*

*that made their faces stream with blood,
which, mingled with their tears,
was gathered at their feet by loathsome worms...*

**Dante Alighieri,
The Inferno, III, 1-69
(1306-1317)**

On the 4th of July 2010, Pope Benedict XVI visited the tomb of one of his most revered predecessors, an obscure Thirteenth century Pope by the name of Celestine V. Celestine reigned for less than five months, and yet today he is revered as the patron Saint of L'Aquila in Ambruzzo, and pilgrims still visit his tomb. In a public audience at Sulmona, Pope Benedict praised Celestine as a role model for humility. So endeared to Celestine, was Benedict that he proclaimed the "Celestine year" from 28 August 2009 through 29 August 2010, to celebrate the 800th year since his birth. Celestine was most definitely famous for at least one thing - he was the first Pope in history to abdicate the Papacy - and the only one until, poignantly, Benedict himself abdicated on 28th February 2013. No doubt Benedict got his precedent and inspiration from Celestine in this regard! So today Celestine is considered a Saint of great humility, but just what did his contemporaries think of him? It comes as quite a shock to learn that Dante Alighieri, in his Divine Comedy, places Celestine in the very first part of Hell! The first part of Hell, is the "zone of the neutrals" - it's the least bad part, not quite Hell, not even Limbo. Dante had no hesitation in placing Popes whom he considered were deserving of eternal punishment into Hell, and a number are found there. To understand this extraordinary situation with respect to Celestine V, so at odds with current day perception, we need to understand the history of Celestine himself and the politics of his day.

In the late Thirteenth century the Papacy was a highly political office. The Royal houses of Aragon and Anjou constantly struggled for supremacy, which was reflected by their Cardinals' sympathies whenever it came to the election of a new Pope. In 1292 Pope Nicholas IV died and a titanic political struggle began among Europe's cardinals as to who should succeed him. The papacy remained vacant for twenty seven months, and no decision could be reached. Finally out of desperation, a compromise Pope was elected, one who was, not politically aligned and elderly and so not expected to reign long, thus ensuring more time for manoeuvre and the finding of an eventual "right" Pope. The choice however was almost comically farcical, if it wasn't so disastrous! It fell to a certain Pietro del Morrone, an octogenarian who had spent the previous six decades of his life, as a hermit in the Abruzzi! A solemn delegation from the Cardinals delivered the "good news" to Pietro, who instantly recoiled in terror. After much prayer and deliberation on Pietro's part, he was finally coerced into accepting the highest office in all of Christendom. The agonized old man was then led on a donkey to L'Aquila for his consecration, where he became Pope Celestine V. He immediately became the puppet of Charles II who took him to Naples. So terrified was Celestine of his worldly and sophisticated cardinals, he refused to speak to them, instead having a small wooden cell built to withdraw from the world and make him feel safe. On the rare occasion the Cardinals did talk to him, they had to abandon their sophisticated Latin for his crude vernacular Italian, the only language he understood. Celestine completely ignored all political, administrative and diplomatic duties, and happily bestowed favours on anyone who asked for them, just to be left in peace. Clearly the situation was a complete disaster, and something had to be done to get rid of him. This task was enthusiastically taken up by a certain Cardinal Benedetto Caetani.

It was said that Cardinal Caetani began whispering through a "speaking tube" at night to Celestine, pretending to be the voice of God, telling him that unless he abdicated the Papacy, he would surely go to Hell. The simple and gullible Celestine, in a panic, was easily persuaded that he should abdicate. On Christmas eve, 1294, the new Pope was elected - somewhat unsurprisingly, it turned out to be Cardinal Benedetto Caetani, who took the name of Boniface VIII. In complete contrast to Celestine, Boniface was a supremely worldly sophisticate, intelligent well educated, well connected, ruthlessly ambitious and greedy. His intention was

to use his office to his fullest advantage - he would increase the power of the Papacy against the Monarchs of Europe and in the process would also make himself extremely wealthy to boot! In order to celebrate the dawn of the new century, Boniface declared that the year 1300, would be a Jubilee year, for pilgrims to come to Rome from all over Europe. It is estimated that over 200,000 pilgrims attended Rome for the Jubilee celebrations. One of those pilgrims was a certain Dante Alighieri, and what he witnessed in Rome truly shocked him! He quickly saw that the entire episode appeared to be nothing more than a massive money making enterprise. Offices and indulgences were being sold to the highest bidders on a massive scale. So disillusioned did Dante become that when he commenced writing the *Inferno* a few years later, he placed the, by now deceased Celestine, (possibly murdered on the orders of Boniface) in the twilight world of the "neutrals" - a "vestibule" region lying between the gates of Hell, and Hell proper. This was a place reserved for the "fence sitters" or "ditherers" - those who did not make a stand on any issue in life. He condemns Celestine as the ultimate ditherer, the one who did not make a stand against Boniface, (who he condemned to the Eighth Circle of Hell) - "I saw and knew the shade of him who, through cowardice, made the great refusal". Celestine abdicated the chair of St Peter and so by his decision, Dante's arch enemy Boniface would usurp the Papacy. The neutrals are condemned to an eternity of regret for not taking a stand on anything one way or another - a sin for which Dante considered a great many would end up in Hell, - "I could not believe death had undone so many..." In this zone of the "neutrals" the ditherers and fence sitters, those who wasted their lives are forced to follow a great whirling banner for all eternity as a reminder of their not following any cause whatever in life - "And I, all eyes, saw a whirling banner that ran so fast it seemed as though it never could find rest. Behind it came so long a file of people....." All the while they are pursued by stinging insects to increase their torment - "This miserable state is born by wretched souls of those who lived without disgrace yet without praise... The world does not permit report of them, Mercy and justice hold them in contempt. Let us not speak of them - look and pass by..."

When we assess our patients who have acutely overdosed on digoxin or who may be suffering from inadvertent chronic toxicity, we must carefully assess the risk profile. Early and accurate risk assessment, in cases of both acute and chronic toxicity, allows for the administration of digoxin immune fragments before life threatening toxicity develops. There must be no dithering or fence sitting due to underestimation of potential lethality or concerns about cost - we must make an early and decisive decision, lest we find ourselves in a special place reserved for the ditherers - the zone of the Neutrals within the vestibule of Hell!



Left: Document declaring the election of Pope Celestine V, 1294, Vatican Archives.

DIGOXIN FAB FRAGMENTS

Introduction

Digoxin Fab fragments (trades names “**Digibind**” and “**Digifab**”) are specific **anti-digoxin antibodies**.

The affinity of these for Digoxin is greater than that of digoxin for its receptor.

These antibody fragments will quickly and safely reverse the toxicity of digoxin and other cardiac glycosides.

Early and accurate risk assessment, in cases of both acute and chronic toxicity, allows for the administration of digoxin immune fragments BEFORE life threatening toxicity develops.

FAB fragments should not be withheld in acute or chronic toxicity due to underestimation of potential lethality or concerns about cost.

See also separate document on:

- **Digoxin Toxicity (in Toxicology folder)**

Presentation

Digoxin Fab fragments as:

Ampoules:

- 38 mg Digibind per vial.

Digoxin Fab fragments are derived from an ovine source, i.e immunoglobulin fragments from sheep that have already been immunized with a digoxin derivative, DDMA, (Digoxin-dicarboxy-methoxylamine).

Supply of Digibind:

Supplies of Digibind should be stocked in the Emergency Department fridge for immediate access.

In high risk or unstable patients every effort must be made to secure further stocks of FAB fragments if needed.

Mechanism of Action

Digibind binds with free intravascular and interstitial digoxin molecules, making them unavailable for binding at their site of action on cells in the body (the sodium-potassium ATPase receptor).

A concentration gradient develops and intracellular digoxin dissociates from tissues and moves to the intravascular space where binding to immune Fab continues.

One ampoule of 38 mg Digibind will bind 0.5 mg digoxin

Pharmacodynamics

Mean-time to initial response (from end of infusion) is 20 minutes, (0-60 minutes)³

Meantime to complete response (from end of infusion) is 90 minutes, (30-360 minutes)³

Pharmacokinetics

Absorption:

- Digoxin antibody fragments are administered IV.
- IM or SC administration is **not** recommended.

Distribution:

- Both Digibind and Digifab have similar volumes of distribution - (0.3 L/kg and 0.4 L/kg for DigiFab and Digibind, respectively)
- Both have extensive penetration from the circulation into the extracellular space.

Metabolism and excretion:

- Half-life of Fab fragments is about 12 hours.¹
- Digoxin bound to Fab fragments is excreted in the urine with an elimination half life of 16-30 hours.¹

Indications

Early and accurate risk assessment, in cases of both acute and chronic toxicity, allows for the administration of digoxin immune fragments BEFORE life threatening toxicity develops.

Acute Digoxin Overdose:

1. Tachyarrhythmias with toxic digoxin levels.
2. Bradyarrhythmias with toxic digoxin levels.
3. Cardiac arrest.

4. Serum Potassium levels > 5 mEq/L in the setting toxic digoxin levels.
5. Serum digoxin level > 15nmol/L (12 ng/ml)
6. Confirmed oral overdose: > 10 mg digoxin in adults, and 4 mg digoxin in children.

Consider:

7. Any toxic digoxin levels in the presence of significant renal impairment.
8. Serum Digoxin levels > 10 ng/ml.

Chronic Digoxin Toxicity:

1. Tachyarrhythmias with toxic digoxin levels.
2. Bradyarrhythmias with toxic digoxin levels.
3. Cardiac arrest.
4. Moderate to severe GIT symptoms
5. Any symptoms in the presence of impaired renal function

See also Risk assessment chart in chronic toxicity in Digoxin Toxicity Document.

Other life-threatening cardiac glycoside toxicities:

1. Oleander poisoning
2. Cane toad poisoning (bufotoxin)
3. Some Chinese medicines (e.g. Chan Su, Dan Shen and Lu-Shen-Wan)

Contraindications

There are no *absolute* contraindications.

Adverse Reactions

1. Allergic reactions, (very rare)

Others secondary to withdrawal of digoxin and its effects, (and not due to any direct effect of digibind). These include:

2. Hypokalaemia.
3. Loss of inotropic action, with worsening of cardiac failure.

4. Loss of control of AF.

Dosing

Dosages are calculated on the basis that one ampoule of Fab binds 0.5mg of digoxin.

Cardiac monitoring is mandatory in all patients who require Fab fragments and until toxicity is reversed.

Note that early and accurate risk assessment allows for the administration of digoxin immune fragments BEFORE life threatening toxicity develops.

The calculated dose is diluted in 100 mls of normal saline and administered IV over 30 minutes.

This dose can be given more rapidly in more urgent situations; e.g. if cardiac arrest is imminent inject over 3 - 5 minutes.

Following adequate dosing a response is normally apparent by 20 minutes and is maximal by 4 hours.

Acute Digoxin Overdose

1. **Known dose:**

The total body load of digoxin (in mg) = the dose ingested (in mg) X 0.8

(Multiply by 0.8 to allow for a bioavailability of 80%)

Each vial will bind 0.5 mg of digoxin

Therefore:

Number of vials needed = The total body load of digoxin (in mg) / 0.5

Alternatively use the following formula:

Number of Ampoules = Ingested dose (mg) x 0.8 (bioavailability) x 2

2. **Unknown dose, (Emergency Empirical Dosing):**

If a patient presents with serious digitalis toxicity from an **acute ingestion** and neither serum digitalis concentration, nor an estimated ingestion amount is available:

- **Give 5 ampoules initially if the patient is hemodynamically stable and 10 vials initially if unstable.**

- Repeat doses of 5 ampoules should be given every 30 minutes until reversal of digoxin toxicity is achieved.
- In **cardiac arrest** give **20** vials (760 mg).

Chronic Digoxin Toxicity

1. **Number of ampoules = $\frac{\text{serum digoxin (ng/ml)} \times \text{body weight (Kg)}}{100}$**

Worked approximations using this formula are as follows:

| Adult Dose Estimate of Digibind (in # of vials) From Steady State Serum Digoxin Concentration (i.e. 6 or more hours after last dose). | | | | | | | |
|---|-------------------------------------|-----|-----|-----|------|------|------|
| Patient Weight (kg) | Serum Digoxin Concentration (ng/ml) | | | | | | |
| | 1 | 2 | 4 | 8 | 12 | 16 | 20 |
| 40 | 0.5 v | 1 v | 2 v | 3 v | 5 v | 7 v | 8 v |
| 60 | 0.5 v | 1 v | 3 v | 5 v | 7 v | 10 v | 12 v |
| 70 | 1 v | 2 v | 3 v | 6 v | 9 v | 11 v | 14 v |
| 80 | 1 v | 2 v | 3 v | 7 v | 10 v | 13 v | 16 v |
| 100 | 1 v | 2 v | 4 v | 8 v | 12 v | 16 v | 20 v |
| Where v = vials | | | | | | | |

Note that many laboratories now measures serum digoxin levels in nmols/L. The conversion factor is $\text{ng/ml} \times 1.28 = \text{nmols/L}$

Alternatively:

2. **Empiric dosing:** ¹

Give 2 ampoules and observe for clinical response.

If toxicity remains after 30 minutes give a further 2 ampoules.

Therapeutic End Points

These are:

- Restoration of normal cardiac rhythm and conduction.
- Resolution of nausea and vomiting.

Rarely digoxin toxicity may recur **beyond 24 hours**, necessitating further treatment with digoxin immune Fab fragments.

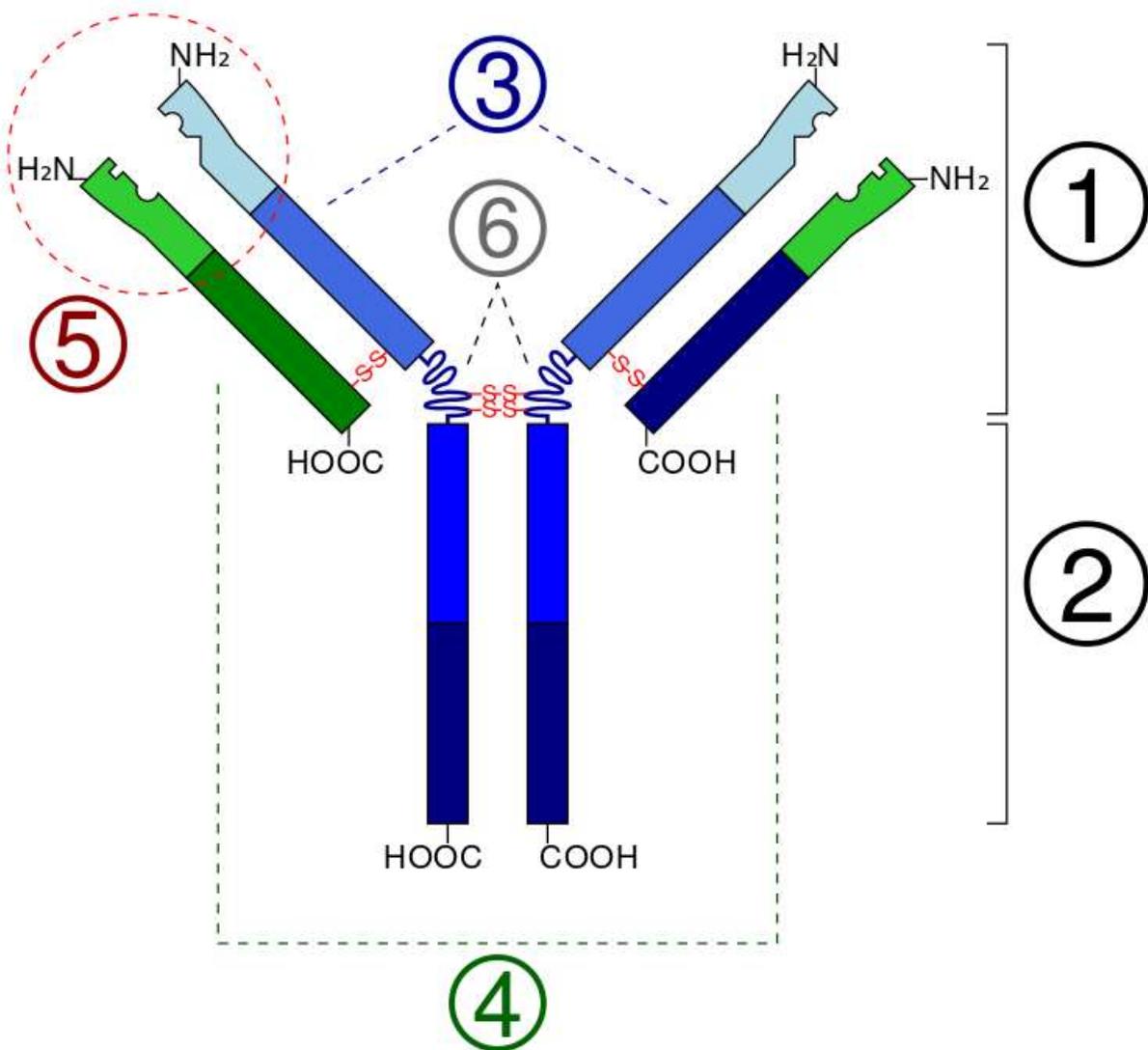
It is not necessary to bind the **total** body digoxin load to control toxicity. The administration of less than the calculated dose of digoxin immune Fab may still be sufficient to control toxicity.

Measured serum digoxin levels increase dramatically after Fab fragment administration as digoxin is pulled from cardiac sites and bound to antibody in the blood. This is the case because most serum digoxin assays will measure both free and Fab bound digoxin.

Monitoring of digoxin levels after antibody administration is therefore unnecessary, as these levels cannot be interpreted for up to 3 weeks, (unless the laboratory is able to measure free digoxin levels)

Appendix 1

Basic Structure of an Antibody: (<https://en.wikipedia.org/wiki/Antibody>)



1. *Fab region:*

- The **antigen-binding fragment** (or **Fab**) is the region on an antibody that binds to specific antigens.

2. *Fc region:*

- The **fragment crystallizable region** (or **Fc region**) is the tail region of an antibody that interacts with cell surface receptors called Fc receptors and some proteins of the **complement system**.

3. *Heavy chain (blue) with one variable (VH) domain followed by a constant domain (CH1), a hinge region, and two more constant (CH2 and CH3) domains*
 - *There are five types of mammalian immunoglobulin heavy chain: γ , δ , α , μ and ϵ .*

These define the 5 classes of immunoglobulins: IgG, IgD, IgA, IgM and IgE, respectively.
4. *Light chain (green) with one variable (VL) and one constant (CL) domain:*
 - *In mammals there are two types of immunoglobulin light chain, which are called **lambda** (λ) and **kappa** (κ)*
5. *Antigen binding site (paratope)*
6. *Hinge regions*

By using just the Fab fragment of the anti-digoxin antibody, (which is what is important for digoxin binding) the molecule is rendered less immunogenic to humans than it would otherwise be with the entire molecule intact. Hence there is a very low to negligible risk of allergic/ anaphylactic reactions.



“...I saw and knew the shade of him who, through cowardice, made the great refusal...”, (Dante)

St Celestine, fresco, Fourteenth, century, Niccolò di Tommaso, Castel Nuovo Naples.

References:

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