

**PRALIDOXIME**



"*The King's Daughter*" c. 1899 oil on canvas, Eduard Veith

*“Great by birth, greater by marriage, greatest in her offspring: here lies Matilda, the daughter, wife, and mother of Henry.*

*Tomb Epitaph of the Empress Matilda, First Lady of the English,  
Rouen Cathedral, 1167 A.D*

*In 1120 A.D, the twentieth year of the reign of the fourth and youngest son of the Conqueror, an unprecedented disaster struck the House of Normandy. King Henry received news that on the 25th of November, the “White Ship” had sunk in the English Channel just off the coast of Barfleur. The ship was crammed with 300 souls, among them many of the elite of the Norman nobility. There were only two survivors. Despite the entire crew having been roaring drunk, the ship had left in the middle of the night, in the face of stormy conditions. Not far out from France it ran up against some treacherous rocks, and quickly disappeared beneath the waves. Among the drowned was King Henry’s only legitimate son, the dashing William Adelin, heir to the Norman Kingdoms in France and in England. Henry was devastated not only on account of the loss of his son, but also on account of the threat this loss represented to the royal dynasty. His Queen, Matilda of Scotland, had died two years before, and Henry at the age of 52 years, was now considered, by the standards of the Twelfth century, to be an old man. Despite hastily remarrying an eighteen year old daughter of Godfrey I, Count of Louvain, he was unable to produce another male heir.*

*The situation remained uncertain in the extreme, as the laws of royal succession had not been established in such a young dynasty. There was no particular law against a woman succeeding to the throne, but then again the question had never arisen in the Norman Kingdoms of France. Henry decided that his heir would be his only daughter Matilda, and to secure her the succession he gathered all the great nobles of the Norman kingdoms on Christmas day 1126 and made them swear an oath of loyalty to her as his successor. Matilda had much to commend her. She had been married to the Holy Roman Emperor, Henry V, and as an Empress, she held enormous prestige, a prestige she retained even after the death of her husband, in 1125. But apart from this she was in her own right, every bit as head-strong, intelligent and capable a ruler, as her father, uncles and grandfather had been. As if these qualities were not enough it was also said that she was very beautiful - an arresting combination of qualities indeed, which threatened many males. She carried the royal bloodline of the Normans in her veins with every ounce of fire, determination, resilience and brilliance as befitted that of the Conqueror himself. All these traits would have been unhesitatingly admired in a male - there was really only one problem - she wasn’t a man. While Henry was alive, no baron or noble dared question his will, his daughter would succeed him as ruler of the Norman Kingdoms in England and in France. The problems began in 1135, when King Henry died. A period of great turmoil and civil war would ensue, that would become known in Norman history as the great “Anarchy”.*

*Not all the aristocracy or church were content for a woman to rule as monarch. The moment the old King died, many powerful barons, both in France and in England, divested themselves of their oath of loyalty to Matilda on the grounds that they had been coerced by Henry. They transferred their allegiance instead to Stephen of Blois, the cousin of Matilda, and grandson of the Conqueror via his mother. Apparently, in their opinion, a claim to the throne could be transmitted through the female line, but the*

*female herself had no right to it! Stephen and his supporters acted quickly. He reached London before Matilda and ensured that he was quickly crowned the new King of England, a great “fait accompli” ...or so he thought. But Matilda, daughter of King Henry, granddaughter of the Conqueror, Empress of the Holy Roman Empire, was not to be so easily dismissed. She had powerful supporters of her own, who had taken their oaths to King Henry seriously, and who saw in Matilda a more than qualified ruler, despite her gender. Among these powerful supporters were her second husband Henry of Anjou, one of the most powerful barons in Normandy, her half-brother, Robert of Gloucester, and her uncle, King David I of Scotland. By 1139 Matilda felt strong enough to challenge Stephen. Like her grandfather before her, she crossed the English channel at the head of a powerful army, while her husband Geoffrey of Anjou remained in Normandy to fight the supporters of King Stephen. Two years of hard fought bloody conflict followed in England until at the Battle of Lincoln in 1141 Stephen’s army was defeated and Stephen himself was captured and imprisoned. But Matilda’s efforts to be crowned at Westminster in London were met with fierce opposition from the people and the church. In consequence she was never crowned but rather ruled England as the “First Lady of the English”, from 7 April 1141 to 1 November 1141. Disaster struck for Matilda in late September 1141, when Robert of Gloucester was heavily defeated by forces still loyal to Stephen at the battle of Winchester. Robert himself was captured. With Stephen now a captive of Matilda and Robert, her chief lieutenant, a captive of forces loyal to Stephan an impossible stalemate ensued - the impasse only being broken when both sides agreed to exchange their prisoners. Stephen was released to his supporters and Robert was released back to Matilda. After this time neither side was strong enough to defeat the other, and for the next thirteen years each reigned in the regions where they held the strongest loyalty - Matilda in the south-west of England and Stephen in the south-east and the midlands. Meanwhile Matilda’s husband Geoffrey now aided by their son, yet another Henry, who had grown to become a brilliant soldier and leader, had managed to largely subdue Normandy, and that is where the situation remained until the death of Stephen in 1154. Tired of fighting, Matilda relinquished her right to the throne to her son. The people and the barons gave their allegiance to Henry rather than to Stephen’s son, William I, Count of Boulogne. Thus Matilda eventually won out over Stephan, her son becoming King of England, rather than Stephen’s. Henry II would prove to be a great King, and would father the legendary Richard Coeur de Lion, (the “Lionheart”).*

*Many when asked today “who was the first Queen of England?” would say Mary I. The more knowledgeable would say it was the unfortunate Queen Jane who ruled for just nine days before being beheaded. But the truth is, semantics aside, that the first Queen of England, was a Twelfth woman by the name of Matilda. Though Henry II is today remembered as a great King, his mother Matilda is largely unknown, on account of her gender. But to many of her contemporary supporters she was as every bit as great as her male Norman ancestors. Indeed her tomb epitaph records her greatness as being three times over - great by her birth to King Henry I, greater by her marriage to the German Emperor Henry V, but greatest of all by her son King Henry II, father and founder of the House of the Plantagenets.*

*The status of the drug pralidoxime remains uncertain. As with “Queen” Matilda during the time of the great Anarchy, it has both its supporters and its detractors.*

## **PRALIDOXIME**

### **Introduction**

**Pralidoxime** is an antidote used in Australia to reactivate acetylcholinesterase that has been inhibited by organophosphates.

It is an adjunctive agent to atropine in cases of organophosphate poisoning.

Its clinical efficacy is uncertain, but is usually still recommended in severe cases.

### **Chemistry**

**Pralidoxime** (2-pyridine aldoxime methyl chloride,) or **2-PAM**, usually as the chloride or methiodide salts, belongs to a family of compounds called **oximes** that bind to organophosphate-inactivated acetylcholinesterase.

### **Preparation**

**Pralidoxime iodide** as:

**Ampoules:**

- 500 mg/ 20 ml ampoules.

Note that Pralidoxime iodide is the only pralidoxime salt available in Australia.

It is not dose-equivalent to pralidoxime *chloride* (1 gram pralidoxime iodide = 0.65 gram pralidoxime chloride.<sup>5</sup>

### **Mechanism of Action**

Pralidoxime reactivates acetylcholinesterase that has been inhibited by binding to organophosphate or carbamate pesticides.

It is only effective if given before irreversible binding or “ageing” of the complex takes place.

Re-establishment of enzymatic function rapidly reverses the **nicotinic and muscarinic** effects of organophosphates poisoning.

Atropine is usually administered prior to pralidoxime and the effect at muscarinic receptors is synergistic. Note that atropine is *not* effective at nicotinic receptors.

An improvement in muscle strength is usually seen within 10-40 minutes of administration.

## **Pharmacodynamics**

It should be noted that while pralidoxime has been shown to reactivate red cell acetylcholinesterase in organophosphate poisoned patients, it has not been shown to improve survival or reduce the need for intubation.

## **Pharmacokinetics**

### Administration:

- Pralidoxime is administered IV.

### Distribution:

- Vd is 0.8 L/kg.
- Pralidoxime does not bind to human plasma proteins.
- It is unknown if pralidoxime can cross the human placenta
- It is unknown if pralidoxime is excreted into human breast milk.

### Metabolism:

- Around 80 % is excreted by the kidneys unchanged.
- The average elimination half life is around 75 minutes, though this is increased in poisoned patients and during continuous infusions.

## **Indications**

These include:

1. Organophosphate poisoning:
  - May be commenced as soon as immediate resuscitation and adequate atropinisation has occurred.
2. Carbamate poisoning:
  - Although not strictly indicated, it should *not* be withheld in cases of severe poisoning or where there is any doubt regarding the nature of the agent.
3. Nerve gas poisoning.

## **Contra-indications / Precautions**

There are no specific absolute contra-indications, other than prior severe allergic reactions.

### Pregnancy:

Safety in pregnancy has not been established, however administration should not be withheld where clinically indicated.

There is very limited information available describing the use of pralidoxime during pregnancy.

Due to the low molecular weight and negligible plasma protein binding of the medicine, placenta transfer is possible.

However, due to the relatively short half-life of pralidoxime, fetal exposure to the medicine is likely to be limited.

Case reports have described normal pregnancy outcomes following both intentional and inadvertent exposure to the medicine.

Therefore, if pralidoxime is the medicine of choice, monitoring of both maternal and fetal wellbeing is recommended.

### Breastfeeding:

Published reports following the use of pralidoxime during breastfeeding have not been located.

If pralidoxime is the medicine of choice, therapy should not be withheld.

However, monitoring of both maternal and infant respiratory function and wellbeing is recommended.

### **Adverse Reactions**

Usually these are minimal and non-specific nausea, headache, dizziness, blurred vision.

**Rapid administration** may be associated with more significant reactions including:

1. Laryngospasm
2. Muscle rigidity
3. Hypertension
4. Transient neuromuscular blockade

### **Dosing**

*The initial dose is:*

- **2 grams pralidoxime in 100 mls of normal saline IV over 15 minutes.**

*Then*

- **Commence a pralidoxime infusion at 500 mg per hour.**

**Children** are treated with an initial dose of 25 - 50 mg/kg, followed by an infusion of 10 - 20 mg/kg/hr.

The infusion may be ceased after 24 hours provided the patient is clinically well and remains under close observation.

In symptoms recur then the infusion should be recommenced for a further 24 hours. For severe poisoning with some organophosphate agents, many days of infusion (one week) may be required.

Administration beyond 24 hours may be ineffective, however it should still be given if clinically indicated.

The effectiveness of pralidoxime will depend not only in its timely administration, but also, on the agent that is being treated. Poisoning from certain organophosphates may be less responsive to pralidoxime than to others.

**Monitoring:**

If available, rapid red cell acetylcholinesterase activity assays may be done before the infusion is ceased and then repeated after 4 - 6 hours.

If activity is maintained, pralidoxime is no longer required.



*Henry I mourning the death of his son, (Detail), Illuminated Chronicle of England folio 6v, Royal MS 20 A ii. c. 1307- 27; British Library.*

## References

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