

THEOPHYLLINE TOXICITY



Small Child During the "Hunger Winter", Amsterdam 1945, Black and white photograph, Emmy Andriess (1914 –1953)

“My country can never again afford the luxury of another Montgomery success”.

Prince Bernhard

In September of 1944 the Allies launched operation “Market Garden”. It involved an ambitious attempt to land 30,000 airborne troops behind German lines in Holland. It was the largest airborne assault in history. The plan called for the lightning capture of a series of bridges over major rivers within German occupied Holland. This would allow for the rapid entry of the British XXX corps into Germany itself and it was hoped thereby significantly shorten the war in Europe. The operation was successful up to the capture of the Rhine Bridge at Nijmegen. Overall, however it was a failure, as the final bridge at Arnhem was not held, due to a combination of strategic and intelligence bungling, resulting in the destruction of the British First Airborne division, and the loss of thousands of Allied lives. The war would go on for a further nine months.

The consequences of the failure of Market Garden would have fearful consequences for the Dutch people. The German Reichskommissioner, Seyss-Inquart was so infuriated with the active assistance the Dutch civilian population had given to the Allies during operations that he took severe reprisals. In addition to many random executions he issued a decree prohibiting the transport of food into the areas of the country still under German control. This was to have a devastating effect, particularly, on the densely populated cities of Amsterdam, Rotterdam, and The Hague. The ensuing winter of 1944-45 was the worst in over one hundred years. Many thousands of Dutch starved to death and infectious diseases that had not been known in Holland for centuries reappeared. The period has entered the Dutch historical consciousness as the “Hunger Winter”. Amsterdam in particular was hit hard and when Allied forces did eventually liberate the city they were met with pitiful scenes that would be forever etched in their memories, of a starving population, including many orphaned children roaming the streets, begging in rags.

Field Marshall Montgomery, years later in his memoirs, called operation Market Garden ninety percent “successful” and said:

“In my prejudiced view, if the operation had been properly backed from its inception, and given the aircraft, ground forces, and administrative resources necessary for the job, it would have succeeded in spite of my mistakes, or the adverse weather, or the presence of the 2nd SS Panzer Corps in the Arnhem area. I remain Market Garden’s unrepentant advocate.”

Dutch Prince Bernhard years later, however had this to say to say to Cornelius Ryan, the author of the international bestseller “A Bridge Too Far” which told the story of operation Market Garden:

“My country can never again afford the luxury of another Montgomery success!”

Operation Market Garden was one of the most ambitious campaigns of the Second World War in Europe. There was no margin for error as the success of the operation depended crucially on the allied taking of all the major bridges in Holland that would then enable the rapid entry of XXX Corps into the German homeland. As Field Marshal Montgomery pointed out the operation was “ninety percent successful”,

however in reality Market Garden was really a case of “all or nothing”. The last bridge at Nijmegen proved in the famous words of Cornelius Ryan, “A bridge too far”. The failure of the capture of the last bridge essentially meant that the gamble to quickly enter Germany and end the war was a failure. Additionally the allies suffered a serious setback with the decimation of the British First Airborne Division. Northern Holland as a consequence would remain under Nazi control for a further nine months. Nazi reprisals inflicted onto the Dutch, who had assisted the allied invasion were severe.

Emmy Andriess, who died of cancer at the age of just 39 years, was Holland’s most famous 20th century photographer. Her most famous works included photographs taken in Amsterdam during the last “Hunger Winter” months of the war. Her most poignant and haunting work was the image of a small orphan child found roaming the streets during this period.

When assessing patients with theophylline toxicity it must be remembered that its therapeutic index is extremely narrow. As it was with operation Market Garden, there is very little margin for error. Clinical toxicity will correlate well the blood levels of theophylline. As levels rise, a point is reached where things have gone a “bridge too far”, and the consequences, will be proportionately severe.



Grave of a British paratrooper killed during the battle of Arnhem September 1944. Tulips have been planted and the inscription, written in German says “Unknown English Soldier”.

THEOPHYLLINE TOXICITY

ACUTE THEOPHYLLINE OVERDOSE

Introduction

Theophylline (or **dimethyl-xanthine**) has a very narrow therapeutic index and there is great potential for both acute and chronic toxicity.

Both acute and chronic toxicity can be life threatening.

Hemodialysis is the definitive treatment in severe poisoning and should be instituted early in those at high risk, *before* life-threatening symptoms develop.

Aminophylline is a water-soluble form of theophylline molecules used for intravenous administration.

Pharmacokinetics

Absorption

- Theophylline is well absorbed following oral administration.
- Absorption is delayed with sustained release preparations, with peak levels being delayed up to **15 hours**.
- Aminophylline rapidly dissociates in vivo to release theophylline.

Distribution

- It is rapidly distributed within a small volume of distribution of 0.5 L/kg.

Metabolism and excretion

- It is metabolized by the cytochrome p450 system to active and inactive metabolites.
- Metabolism however is variable and is saturable.
- Elimination half-life may be greatly prolonged in severe intoxication.

Pathophysiology

- There are a number of theories regarding the predominant mechanism of toxicity. It may be inhibition of phosphodiesterase leading to raised intracellular levels of cAMP.
- It is also a competitive antagonist of adenosine.

Risk Assessment

- The most serious toxic effects include **tachyarrhythmias** and **seizures**.
- ♥ **These features occur late and indicate a poor prognosis.**
- *Elderly* patients with *co-existing medical conditions* tolerate theophylline toxicity poorly and have a correspondingly worse prognosis.

An age > 60 years is a significant predictor of severity and poor outcome in chronic toxicity (though not in acute toxicity.)

Severity of acute overdose correlates well with the ingested dose and to blood levels.

Dose related risk assessment:

Dose	Effect
5-10 mg/kg	Therapeutic loading dose.
10-50 mg/kg	Increasing toxicity.
>50 mg/kg	Potentially life threatening

For blood level related risk, see below.

Ingestion of just one 200 mg tablet of a slow release preparation can produce toxicity in a 10 kg child. Ingestion of multiple tablets can be life threatening in a child.

Other predictors of toxicity in theophylline (and caffeine) overdose include: ²

- Hypokalaemia - potassium concentration less than 3.0 mmol/L
- Blood glucose concentration greater than 10 mmol/L

Clinical Features

Note that most acute overdoses of theophylline will be of sustained release preparations and so clinical deterioration may be delayed for many hours.

These include:

1. GIT:

- Nausea, vomiting and diarrhoea.
2. CNS:
- Tremulousness.
 - Agitation/ restlessness.
 - **Seizures.**
3. CVS:
- Sinus tachycardia.
 - More serious tachyarrhythmias, including:
 - ♥ SVT
 - ♥ Atrial fibrillation/ atrial flutter
 - ♥ VT
 - Blood pressure:
 - ♥ Hypertension may be seen initially.
 - ♥ **Hypotension**, is seen later in severe overdose (possibly due to peripheral beta 2 effects). This can be very refractory to treatment.
4. Metabolic effects:
- Metabolic acidosis
 - **Hypokalaemia** (due to *stimulation* of the Na /K ATPase pump).
 - ♥ This can be severe and refractory.
 - Hypomagnesaemia
 - Hypophosphataemia
 - Hyperglycaemia

Investigations

1. FBE
2. U&Es/ glucose, (including an **urgent potassium level**).
3. **Serial serum theophylline levels:**

- These are extremely useful in predicting the risk of life threatening toxicity.

In acute overdose levels correlate well with clinical severity.

Levels should be repeated 2-4 hourly until falling.

4. Consider coingestion - blood alcohol/ paracetamol levels.

Level	Clinical Effect
55-110 micromols/ L	Therapeutic range.
110-220 micromols/ L	Minor toxicity.
220-440 micromols/ L	Moderate toxicity
440-550 micromols/ L	Severe toxicity.
> 550 micromols/ L	Potentially fatal without urgent intervention.

Levels > **330 micromols/L** may be associated with severe toxicity in the **elderly**.

Levels > **220 micromols/L** may be associated with severe toxicity in chronic poisoning.

4. ECG.

Management

The patient that presents with established severe toxicity (tachyarrhythmias/ seizures) has a poor prognosis and supportive measures alone will not ensure survival. **Hemodialysis will be needed.**

1. Immediate attention to any ABC issues:
 - IV access and take blood tests for urgent theophylline and potassium levels.
2. Continuous ECG monitoring.

3. Restlessness and agitation:

- Can be controlled with IV diazepam.

4. Seizures:

- Treat with IV benzodiazepines.

5. Hypotension:

- Fluids often give a good response
- If hypotension is refractory to fluids a vasopressors with selective alpha-agonist activity are recommended.²

Use:

- ♥ Initial bolus dosing with metaraminol
- ♥ **Noradrenaline infusion** should be commenced if metaraminol is not or only transiently effective.

6. Tachyarrhythmias:

These should be treated with IV **cardioselective** beta blockers.

- **IV metoprolol** 5 mg slowly, titrated to effect.

A repeat dose of 5 mg IV can be given after 5 minutes if the initial response is inadequate.

- **Esmolol infusion** is an alternative especially in those with severe airways (i.e asthma or COPD) disease.

7. **Charcoal:**

- Oral activated charcoal is indicated, in all patients with moderate to severe poisoning even in *delayed* presentations.
- If the patient's conscious state is compromised prior intubation will be necessary.
- Aggressive control of nausea and vomiting with IV ondansetron or similar may be necessary.
- **Repeat** activated charcoal will enhance elimination, (gut dialysing effect) but this does not replace the need for haemodialysis and should not delay the initiation of haemodialysis.

8. **Hypokalaemia:**

- Look for and treat any hypokalaemia.

This is a common problem and is due to a redistributive loss of potassium into the cells and not a whole body loss of potassium.

Hypokalaemia should be treated with caution as the potassium abnormalities will tend to self correct as the overdose is treated.

Note that other metabolic abnormalities do not usually require specific intervention and will resolve with treatment.

9. **Haemodialysis:**

This is the definitive life saving procedure in severe toxicity and is highly effective if initiated early.

Arrangements for haemodialysis should therefore be made early when life-threatening severe toxicity has occurred or is anticipated.

Patients at risk of death should be identified and dialyzed before clinical deterioration occurs.

Charcoal haemoperfusion is said to be the best modality, however, however it is not widely available and **standard haemodialysis** is still effective and usually able to be implemented more quickly.

Commonly accepted indications include:

- Serum theophylline level > 550 micromol/L in the setting of acute overdose.
- Clinical manifestations of severe toxicity such as arrhythmias, (including SVT), hypotension or seizures.

Disposition

Patients who have acutely ingested non-sustained release preparations and are asymptomatic at **6 hours** may be medically cleared.

Overdose of a **sustained release preparation** will require observation for **12 hours**, although serial theophylline levels may indicate earlier medical clearance in these cases.

CHRONIC THEOPHYLLINE TOXICITY

Introduction

Chronic toxicity is usually seen in elderly or infant patients.

This was a relatively common condition in the past when patients with airways disease were routinely treated with oral theophylline. Today however this treatment is very rare.

Risk Assessment

- Patients with chronic toxicity have a relatively worse prognosis than with acute overdose.
- This is often due to a failure to make the diagnosis or an under appreciation of the severity of the condition.

Clinical Features

In chronic theophylline toxicity the life threatening features of arrhythmias and seizures are seen as in acute overdose. These may however, occur at lower blood levels than seen with acute overdoses.

The commonest symptoms in chronic toxicity will be:

- Vomiting
- Tachycardia.

The prominent toxic features of *metabolic acidosis, hypotension and hypokalemia* that are seen in an **acute** overdose are **not** typical in a chronic toxicity setting.

Investigations

See for above in acute overdose, however in chronic intoxication severe toxicity can occur at levels > 220 micromols per liter.

Management

Management is along similar lines to acute toxicity however the threshold for dialysis is lower than for acute overdoses.

A serum theophylline level > 330 micromol/L in the setting of chronic toxicity indicates the need for dialysis.

References

1. Theophylline toxicity in Murray L et al. Toxicology Handbook 3rd ed 2015.
2. eTG - November 2015
 - Theophylline and Caffeine Toxicity.

Dr J Hayes
Reviewed May 2016