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This Medicines Information Leaflet is produced locally to optimise the use of medicines by encouraging prescribing that is safe, clinically appropriate and cost-effective to the NHS.

Guidelines for Prescribing and Administering Aminophylline and Theophylline in Adults

Aminophylline and theophylline are both xanthine derivatives (non-selective phosphodiesterase inhibitors), the primary effect of which are promoting bronchodilation through a reduction of the breakdown of cyclic AMP. Xanthines also stimulate respiratory effort.

When to use intravenous or oral therapy

Intravenous therapy

Asthma: Intravenous (IV) therapy is used in the treatment of acute bronchospasm in acute severe attacks of asthma that is not responding rapidly to the initial use of oxygen, short acting bronchodilators and IV magnesium.

Chronic Obstructive Pulmonary Disease (COPD): Xanthines may be used in the treatment of bronchospasm in severe exacerbations of chronic obstructive pulmonary disease (COPD) in patients who are not responding to oxygen therapy and nebulised short acting bronchodilators.

NB. IV therapy should **only** be started **after** consultation with an appropriate registrar or consultant.

Oral therapy

Asthma: Oral therapy has previously been used as long term prophylaxis in patients with asthma. However, it is no longer recommended in the latest update to the NICE guidance (NG245) in 2024[1] .

COPD: Xanthines can be used for the relief of reversible airways obstruction in patients with stable COPD with inadequate response to inhaled bronchodilators[2] or when patients cannot use inhaled therapies. The use of xanthines in this situation is limited in their effect as the reversible component of this disease is often small.

The decision to add in oral theophylline as regular treatment should be made by an appropriate registrar or consultant.

Contraindications and cautions

- **Cardiac disease:** Xanthines can cause cardiac arrhythmias.
- **Epilepsy:** Xanthines lower the seizure threshold. If necessary to use, patients should be carefully observed for possible signs of CNS stimulation.
- **Hepatic insufficiency:** Xanthines are metabolised by the liver, therefore a dose reduction is needed.
- **Pregnancy and breastfeeding:** Avoid usage unless benefits outweigh risks.
- **Renal insufficiency:** No specific dose reduction is required, but caution is advised if severe impairment as these patients are at a higher risk of seizures.

Caution should be taken with patients with the following medical conditions: hypertension, hyperthyroidism, peptic ulcers.

Interactions with other medicines

Xanthines have the potential to interact with many medicines. The main interactions are as follows:

Drugs causing an **INCREASE** in xanthine plasma concentration	Drugs causing a **DECREASE** in xanthine plasma concentration
Allopurinol **Antiarrythmics:** Amiodarone **Antibacterials:** Macrolides, isoniazid, quinolones **Antidepressants:** Fluvoxamine **Antifungals:** Fluconazole, ketoconazole **Antiviral:** Aciclovir **Calcium channel blockers** **Ulcer healing drugs:** Cimetidine	**Antibacterials:** Rifampicin **Antidepressants:** St John's Wort **Antiepileptics:** Carbamazepine, phenytoin, primidone **Antivirals:** Ritonavir Tobacco

Dose and administration

Because the metabolism of xanthines varies greatly from person to person, it is not possible to establish a single dosage regimen for xanthines that will suit all patients. This variation is reflected in its elimination half life, which varies from 4 hours in healthy adult smokers to about 25 hours in patients with hepatic cirrhosis[3].

Please note: Aminophylline is a mixture of theophylline with ethylenediamine, which is 20 times more soluble than theophylline alone and the reason it is given via IV

Intravenous therapy

Prior to prescribing IV aminophylline, please ensure the patients weight has been documented – Do NOT estimate weight

When prescribing in EPMA use the powerplan

IV Aminophylline in adults

Loading dose

Loading dose for patients with BMI greater than 30 should be based on **ideal body weight (IBW)**

For patients NOT already taking oral xanthines:

- Give a loading dose of aminophylline at 5mg/Kg (usual doses is between 250 – 500mg)

The loading dose should be given in 100ml of infusion fluid over 20-30 minutes – the rate of administration should NOT exceed 25mg per minute.

For patients ALREADY TAKING oral xanthines:

- Stop oral xanthine therapy
- Do **NOT** give a loading dose

Maintenance infusion

Maintenance infusions should be prescribed as 500mg of aminophylline in 500ml of infusion fluid (Sodium chloride 0.9% or glucose 5%)

The initial maintenance infusion should be started immediately after loading and is based on the patients weight (***Table A***) –In patients with BMI greater than 30 **ideal body weight should be used when calculating the initial infusion rate (*Table B*).**

- In adult patients, **without heart failure**, start the maintenance infusion at **500microgram/Kg/hour.**
- **In patients with heart failure**: A reduced infusion rate of **300microgram/Kg/hour** may be used.
- The maintenance infusion rate may be adjusted according to plasma theophylline levels up to a maximum rate of **700microgram/Kg/hour.**

Subsequent maintenance infusions should be based on levels – see recommended monitoring.

Please note: to avoid excessive dosage in patients with a BMI greater than 30, the dose should be based on IBW – ***Table B or use IBW calculator***

Gender of patient	Calculation using patients height in feet and inches	Calculation using patients height in centimetres
Male	50 + (2.3kg for each inch over 5 feet)	[(height (cm) – 154) x 0.9] + 50
Female	45.5 + (2.3kg for each inch over 5 feet)	[(height (cm) – 154) x 0.9] + 45.5

Table B: Ideal body weight calculations

Oral therapy

These recommendations are only for patients who are coming off an aminophylline infusion and requiring oral therapy as maintenance treatment (NB: no longer recommended in patients with asthma[1]).

When treatment is changed from IV to oral therapy, the maintenance infusion should be stopped and oral therapy started immediately.

The aim of converting from IV to oral therapy is to achieve a dosage regimen that is likely to maintain theophylline concentrations within a range that is safe and effective for the individual.

1. Convert the hourly infusion rate to the total amount administered in 24 hours by multiplying the hourly dose by 24.
2. Convert to oral theophylline by multiplying the total amount of aminophylline (mg) by 0.8.
3. Divide this total amount by 2 for twice daily dosing interval. Uniphyllin Continus® is a 12 hourly preparation.

For example:

If the IV aminophylline dose was 20mg/hr:

(20mg x 24 x 0.8) / 2 = 192mg every 12 hours.

A suitable theophylline dosing regimen would be Uniphyllin Continus® 200mg twice daily. **For patients taking oral therapy prior to starting the infusion:**

Restart oral therapy at the dose the patient was taking prior to having the aminophylline infusion.

Oral preparations of theophylline (Uniphyllin Continus®) are available as 200mg, 300mg and 400mg tablets. Aminophylline tablets (Phyllocontin®) have been discontinued and are no longer recommended.

For patients starting oral therapy for the first time:

For safety, it is recommended to start patients in the OUH on the same brand of xanthine: The first line brand used within the OUH is Uniphyllin Continus®, which is a brand of theophylline.

Recommended monitoring

There is a relationship between the dose of xanthine and the reduction in airways resistance achieved. This relationship is shown to be linear and can be measured by taking a plasma theophylline level.

The recommended plasma theophylline concentration range / level for an optimum effect in the absence of complicating factors is **10-20 mg/litre.** Although a lower concentration of 5-15mg/L may still be effective.

Intravenous therapy

If the patient already takes oral xanthine therapy, a plasma theophylline level should be taken prior to an infusion being started. It is not necessary to wait for the results of this prior to starting the infusion.

Once the infusion has been started, an initial level should be taken 4-6 hours after starting the aminophylline infusion.

Do not adjust the dose/frequency if the first level is between 8-10mg/L. Re-check level after a further 24 hours.

For further advice on interpretation of plasma theophylline levels see Appendix 1.

Monitor aminophylline levels daily if infusion continues for more than 24 hours provided the patient's clinical condition is stable and the dosage remains unchanged, otherwise more frequent levels are advised.

In exceptional circumstances it may be appropriate to exceed the maximal infusion rate. This decision must be made and documented by a respiratory specialist and continuous cardiac monitoring should be under taken while the patient is on these high infusion rates

Serum potassium levels should also be monitored daily during IV aminophylline therapy.

Oral therapy

A theophylline plasma level should be taken 4 – 6 hours after an oral dose of a xanthine.

The level should be taken at least 5 days after starting therapy and at least 5 days after any change in dosage or any medications have been started / stopped that may alter the theophylline plasma level.

Adverse effects

Many patients experience gastrointestinal symptoms when their plasma concentration is within the therapeutic range, but minor adverse affects do not always precede major ones. Several of the adverse effects (such as; nervousness, tachycardia, arrhythmias and cardio-respiratory arrest) can be features of an acute attack of asthma. It may become impossible to distinguish between features of the underlying disease and those attributable to theophylline toxicity without measuring the plasma theophylline concentration.

Minor adverse affects, such as nausea, insomnia, nervousness and headache are common if the plasma theophylline concentration is rapidly increased above 10 mg/litre.

Most patients will tolerate the drug better if the dose is gradually increased in order to attain maintenance plasma concentrations in the middle or upper part of the therapeutic range.

Serious adverse effects are as follows: persistent vomiting, gastrointestinal bleeding, seizures, cardiac arrhythmias and cardio-respiratory arrest which can often occur at concentrations above 20mg/litre.

Frequency and severity of adverse effects increases at concentrations less than 20mg/L.

Toxicity

Treatment of toxicity is supportive.

Clinical features rather than theophylline levels should guide treatment.

Seek specialist advice for the management of serious side effects.

References

1. National Institute for Clinical Excellence. Asthma: diagnosis, monitoring and chronic ashma management (BTS, NICE, SIGN). November 2024. Available from: Overview | Asthma: diagnosis, monitoring and chronic asthma management (BTS, NICE, SIGN) | Guidance | NICE
2. National Institute for Clinical Excellence. Chronic Obstructive Pulmonary Disease in over 16s (NG115) – Diagnosis and Management. 2018 (updated July 2019). Available from: https://www.nice.org.uk/guidance/NG115
3. Monographs on Aminophylline and Theophylline from: Sweetman SC (ed), *Martindale: The Complete Drug Reference.* [online] London: Pharmaceutical Press http://www.medicinescomplete.com
4. British National Formulary (BNF) 82. British Medical Association & the Royal Pharmaceutical Society of Great Britain. September 2024 – March 2025.
5. Brighton & Sussex University Hospital Guideline: Dosing and Administration Instructions for Intravenous Aminophylline in Adults and Children Over 12 years. (Reviewed Dec 2020)

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Flowchart for Prescribing Intravenous Aminophylline - Prescribe on EPMA using IV Aminophylline in

Is the patient obese (BMI greater than 30)?

YES

Use **IDEAL** body weight for calculations

Gender	Calculation using patients height in feet and inches	Calculation using patients height in centimetres
Male	50 + (2.3kg for each inch over 5 feet)	[(height (cm) – 154) x 0.9] + 50
Female	45.5 + (2.3kg for each inch over 5 feet)	[(height (cm) – 154) x 0.9] + 45.5

Or ***IBW calculator***

NO

Use **ACTUAL** body weight for calculations

Does the patient usually take an oral Xanthine e.g. Uniphyllin Continus?

YES

Stop oral theophylline

Take an aminophylline level then start aminophylline infusion at the **maintenance dose** (No loading dose required).

NO

Prescribe a **loading dose** of intravenous aminophylline at 5mg/kg as a stat dose – Usual dose range 250 – 500mg. (Use IBW if BMI greater than 30). *The loading dose should be given in 100ml sodium chloride 0.9% over 20 - 30 minutes (do not exceed a rate of 25mg/min)*

Maintenance Infusion Dosing

Aminophylline 500mg in 500ml of sodium chloride 0.9% (or glucose 5% if preferred) Intravenously

Prescribe the initial maintenance rate following the table below (**Table A**):

		Patients weight (kg) – IBW if BMI greater than 30											
Patient	**Dose**	40 - 44kg	45 – 49kg	50 – 54kg	55 – 59kg	60 – 64kg	65 – 69kg	70 – 74kg	75 – 79kg	80 – 84kg	85 – 89kg	90 – 94 kg	95 – 100 kg
Patient with heart failure	300 microgram / kg / hour	12	13.5	15	16.5	18	19.5	21	22.5	24	25.5	27	28.5
Adult (Initial infusion rate)	500 microgram / kg / hour	20	22.5	25	27.5	30	32.5	35	37.5	40	42.5	45	47.5
Adult (Maximum infusion rate)	700 microgram / kg / hour	28	31.5	35	38.5	42	45.5	49	52.5	56	59.5	63	66.5
		Maintenance infusion rate (ml / hour)											

Levels

Levels should be taken after the first **6 hours** of the infusion starting and then every 24 hours thereafter.
The optimum therapeutic drug level range is **10-20mg/L**.
If the patient's level is outside this range, see **Appendix 1** for support in interpreting levels or contact a senior doctor / pharmacist for further guidance in adjusting the rate of infusion.

Stopping the Infusion

Restart oral theophylline in patients who were previously on this medicine 1 hour prior to the infusion stopping.
If the patient was aminophylline naïve prior to having the aminophylline infusion, review whether maintenance oral therapy is required – please see 'Oral therapy' section.

Appendix 1. Intravenous Aminophylline Infusion Dose Titration Using Plasma Theophylline Levels

Plasma theophylline level (mg/L)	Symptoms and dose tolerance	Action required
8 - 9.9	**Symptoms controlled** Current dose tolerated	No change to infusion rate, re-check levels in 24 hours.
	Symptoms not controlled Current dose tolerated	INCREASE infusion rate by 25% if patient is still symptomatic. Re-check levels in 4-6 hours.
10 - 14.9	**Symptoms controlled** Current dose tolerated	Maintain rate of infusion, re-check levels in 24 hours.
15 - 19.9	**Symptoms controlled** Current dose tolerated	Consider DECREASING rate of infusion by 10% to provide greater margin of safety even if current dosage is tolerated. Recheck levels in 4-6 hours. Decision to maintain infusion rate instead of decreasing should be made by a senior doctor.
20 - 24.9	**High levels** (Signs of toxicity may be absent)	Stop infusion. Recheck level after a minimum of 6 hours. If restarting, ensure level is less than 15mg/L and DECREASE previous infusion rate by at least 25%. Recheck levels 4-6 hours after restarting.
Greater than 25	**High levels**	Stop infusion for 24 hours. Consider if supportive management of toxicity is required (See 'Toxicity'). If restarting, check levels and once less than 15mg/L can restart but DECREASE previous infusion rate by at least 50%. Recheck levels 4-6 hours after restarting.