**DOSING AND ADMINISTRATION INSTRUCTIONS FOR INTRAVENOUS AMINOPHYLLINE IN ADULTS AND CHILDREN OVER 12 YEARS**

**\*IDEAL BODY WEIGHT SHOULD BE USED TO CALCULATE DOSES IN OBESE PATIENTS (BMI ≥30)**

**Ideal Body Weight** = IBW (male) = 50 + 2.3 x (each inch over 5 foot in height)

IBW (female) = 49 + 1.7 x (each inch over 5 foot in height)

**LOADING DOSE**

**PATIENTS ALREADY TAKING ORAL THEOPHYLLINE OR AMINOPHYLLINE MUST NOT BE PRESCRIBED A LOADING DOSE**

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| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Weight** | 30kg | 40kg | 50kg | 60kg | 70kg | 80kg | 90kg | ≥100kg\* |
| **Aminophylline loading dose** 5mg/kg  (maximum dose 500mg) | 150mg | 200mg | 250mg | 300mg | 350mg | 400mg | 450mg | 500mg |

***Administration Instructions***

*Dilute dose in 100ml sodium chloride 0.9% or 100ml glucose 5%, and infuse over 20 minutes. The infusion rate should not exceed 25mg/min.**If acute adverse effects occur, slow the rate or stop the infusion for 5-10 minutes.*

**Adverse effects:** Hypotension, arrhythmias, and convulsions especially if given rapidly. Hypersensitivity reactions, nausea, vomiting, dizziness, headache, CNS stimulation, insomnia.

**MAINTENANCE DOSE**

Prescribe the initial rate of infusion (mL/hour) from doses calculated in maintenance dose infusion rates table on page 2.

The initial maintenance dose for adults is 0.5-0.7mg/kg/hour (0.3mg/kg/hour in elderly patients).

Plasma-theophylline concentration is **increased** in **heart failure** and **hepatic impairment**, and is **decreased** in **smokers**, therefore these should be considered when prescribing the initial infusion.

***Administration Instructions***

*Dilute 1000mg aminophylline in 1000ml sodium chloride 0.9% or 1000ml glucose 5%, to make a concentration of 1mg per 1mL, and administer as a continuous intravenous infusion.*

*Maintenance doses should be administered immediately after the loading dose.*

**Expiry:** Once reconstituted, aminophylline has a 24 hour expiry.

**MONITORING**

**Monitor** ECG, heart rate, blood pressure. Serum potassium levels if therapy is on-going. Plasma-theophylline level, adjust the rate and duration of the maintenance infusion according to plasma-theophylline level.

Perform a 12 Lead ECG prior to loading dose. Consider continuous cardiac monitoring if there are risk factors for arrhythmias, for example concurrent medicines known to prolong QTc.

**AMINOPHYLLINE MAINTENANCE DOSE INFUSION RATES**

**Infusion rates based on a concentration of 1mg/mL**

|  |  |  |  |
| --- | --- | --- | --- |
| **Dose** | **ELDERLY**  **0.3mg/hr** | **NON-SMOKING ADULT**  **HEART FAILURE OR HEPATIC IMPAIRMENT**  **0.5mg/kg/hr** | **SMOKING ADULT**  **0.7mg/kg/hr** |
| **Patient Weight (kg)** | **Infusion Rate**  **(mL/hour)** | **Infusion Rate**  **(mL/hour)** | **Infusion Rate**  **(mL/hour)** |
| 35 | 10.5 | 17.5 | 24.5 |
| 40 | 12 | 20 | 28 |
| 45 | 13.5 | 22.5 | 31.5 |
| 50 | 15 | 25 | 35 |
| 55 | 16.5 | 27.5 | 38.5 |
| 60 | 18 | 30 | 42 |
| 65 | 19.5 | 32.5 | 45.5 |
| 70 | 21 | 35 | 49 |
| 75 | 22.5 | 37.5 | 52.5 |
| 80 | 24 | 40 | 56 |
| 85 | 25.5 | 42.5 | 59.5 |
| 90 | 27 | 45 | 63 |
| 95 | 28.5 | 47.5 | 66.5 |
| 100 | 30 | 50 | 70 |

N.B. Infusion pumps can only be set to one decimal place. If the calculation produces a figure to two decimal places, figures of 0.05 or above should be rounded UP to the next decimal place and figures below 0.05 should be rounded DOWN e.g. 2.33mL/hour should be rounded to 2.3mL/hour.

**EXAMPLE PRESCRIPTION**

For a 70kg non-smoking adult an initial aminophylline maintenance dose should be prescribed at 0.5mg/kg/hour. To administer this with an infusion concentration of 1mg/1mL, the initial infusion rate should be prescribed at 35mL/hour.

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| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **MAINTENANCE DOSE: To start immediately after loading dose** | | | | | | | | | | **ADMINISTRATION RECORD** | | | | | |
| Date  04/07/18 | **Aminophylline**  **1000mg in 1000ml** | **Sodium chloride 0.9% / Glucose 5%**  (circle as appropriate) | Dose  0.5  (mg/kg/hour) | | Infusion  Rate  35  mL/hour | Prescriber signature:  ADoctor | Prescriber name & Bleep:  A.Doctor  1234 | | | Pharmacist  Screen  A.Pharmacist | Time started:  09:30 | | | Time finished: | Nurse check  A.Nurse  A.Nurse |
| **THEOPHYLLINE LEVEL Date and time taken: 04/07/18 15:30 Level: 12 mg/L Continue Y/N** | | | | | | | | | | | | | | | |
|  | | | |  | | | |  |  | | |  |  | | |

**MINIMUM INFUSION VOLUMES**

In fluid restricted patients aminophylline infusion may be administered at a higher concentration.

**Discuss with pharmacy.**

**DRUG INTERACTIONS**

Theophylline is metabolised by the cytochrome P450 enzymes CYP1A2, CYP2E1 and CYP3A3; therefore drugs which induce or inhibit the action of these enzymes can decrease or increase theophylline plasma concentration respectively.

Common drugs that can affect theophylline clearance have been listed below;

|  |  |
| --- | --- |
| Plasma concentration  **increased** | Plasma concentration  **decreased** |
| Allopurinol (>600mg/day)  Cimetidine  Ciprofloxacin  **Erythromycin**  Fluvoxamine  **Pentoxifylline**  Propranolol  Verapamil | Carbamazepine  **Fosphenytoin**  **Phenobarbital**  Phenytoin  Rifampicin  **Ritonavir**  St. John’s Wort |

A comprehensive list of drug interactions can be found in the BNF.

**Smoking** induces the metabolism of theophylline, decreasing plasma theophylline concentration. In patients who stop smoking, a reduction in the **oral** theophylline/aminophylline dose of up to 25 to 33% might be needed starting the day after smoking is stopped and during the first week.

**Discuss with pharmacy**.

**ADMINISTRATION**

Modified release preparations should be swallowed whole. Do not chew, suck or crush capsules.

If symptoms are controlled, expected duration of impaired swallow/enteral feeding should be considered before making changes to treatment.

*Note: The rate of absorption from modified-release preparations can vary between brands. If brand/drug is switched, monitor symptom control and check plasma-theophylline level 3 days after switch.*

**SWALLOWING DIFFICULTIES**

Consider switching to Slo-Phyllin.

The contents of a capsule (enteric coated granules) may be sprinkled on to a spoonful of soft food, e.g. yoghurt, and swallowed without chewing. This method may not be appropriate for patients with limited understanding or impaired ability to follow instructions.

When switching oral aminophylline to oral theophylline, multiply total daily dose by 0.8 (adjust for salt correction factor). Round to the nearest practical dose.

Alternative formulations are available for short-term use.

**Discuss with pharmacy**.

**ENTERAL TUBE**

Modified release tablets are not suitable for enteral tube administration.

**1st Choice**

Give aminophylline injection enterally. Dilute prior to administration.

When switching from oral theophylline to oral aminophylline, multiply total daily dose by 1.25 (adjust for salt correction factor). Round to the nearest practical dose.

Aminophylline injection is an immediate release preparation, the **total daily dose** should be **split into four divided doses.**

Administration via this route is for short term use only.

**2nd Choice**

Consider switching to Slo-Phyllin.

Open a Slo-phyllin® capsule and pour the contents, (enteric-coated granules) through the feeding tube, flushing before and after with 15-30mL of water.

When switching oral aminophylline to oral theophylline, multiply total daily dose by 0.8 (adjust for salt correction factor). Round to the nearest practical dose.

**THERAPEUTIC DRUG MONITORING**

Aminophylline/theophylline treatment requires **therapeutic drug monitoring.**

Aim for serum theophylline level of **10-20mg/L.**

**INTRAVENOUS ROUTE**

Take aminophylline level **4-6 hours** after maintenance infusion starts, pausing infusion 20 minutes prior to taking level.

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

Monitor aminophylline levels daily if infusion continues for more than 24 hours.

**INTERPRETING LEVELS**

**Day 1**

|  |  |
| --- | --- |
| **Level** | **Action** |
| **<5mg/l** | Check for compliance with oral doses or that loading dose was given if clinically indicated.  Contact pharmacy for individual dosing advice. |
| **5-8mg/L** | Increase infusion rate by 25% then recheck levels in 24 hours |
| **8-10mg/L** | If symptoms are controlled, continue current infusion rate.  Check level in 24 hours if infusion continues |
| **10-20mg/L (target)** | Continue current infusion rate.  Check level in 24 hours if infusion continues |
| **20-25mg/L** | Decrease infusion rate by 25% then recheck levels in 24 hours |
| **25-30mg/L** | Stop infusion for 12 hours and then decrease rate by 25% |
| **>30mg/L** | Stop infusion and treat as overdose |

**Day 2 onwards:**

|  |  |
| --- | --- |
| **Level** | **Action** |
| **<5mg/l** | Check for compliance with oral doses or that loading dose was given if clinically indicated.  Contact pharmacy for individual dosing advice. |
| **5-10mg/L** | Increase infusion rate by 25% then recheck levels in 24 hours |
| **10-20mg/L (target)** | Continue current infusion rate.  Check level in 24 hours if infusion continues |
| **20-25mg/L** | Decrease infusion rate by 25% then recheck levels in 24 hours |
| **25-30mg/L** | Stop infusion for 12 hours and then decrease rate by 25% |
| **>30mg/L** | Stop infusion and treat as overdose |

Round infusion rate to nearest whole number of mL/hour once dose re-calculated.

**ORAL ROUTE**

Plasma-theophylline concentration is measured 5 days after starting oral treatment and at least 3 days after any dose adjustment.

Take level **4-6 hours** post dose for oral modified release preparations.

**INTERPRETING LEVELS**

|  |  |
| --- | --- |
| **Level** | **Action** |
| **<10mg/l** | Check for compliance with oral doses. If symptoms are not controlled and current dosage is tolerated, consider dose increase.  Recheck level in 3 days for further dosage adjustment |
| **10-20mg/L**  **(target)** | If symptoms are controlled and current dosage is tolerated, maintain current dose. |
| **20-25mg/L** | Decrease dose even if no adverse effects are present.  Recheck level after 3 days to guide further dosage adjustment. |
| **25-30mg/L** | Omit next dose and decrease subsequent doses even if no adverse effects are present. Recheck levels after 3 days to guide further dosage adjustment.  If symptomatic, consider whether overdose treatment is indicated. |
| **>30mg/L** | Stop Theophylline. Treat overdose as indicated.  If Theophylline is subsequently resumed, decrease dose and recheck level after 5 days to guide further dosage adjustment. |

**CONVERTING INTRAVENOUS AMINOPHYLLINE TO ORAL FORMULATIONS**

When converting from IV to oral therapy or making dose adjustments, it may not be possible to administer the exact dose calculated. Round to the nearest practical dose and adjust according to blood levels.

**Theophylline**

* Uniphyllin Continus® modified release tablets are available in 200mg, 300mg and 400mg.
* Slo-phyllin® modified release capsules are available in 60mg, 125mg and 250mg.

**Aminophylline**

* Phyllocontin® Continus® 225mg modified release tablets
* Phyllocontin® Forte Continus® 350mg modified release tablets (Reserve for smokers and other patients where theophylline half-life is shorter)

Patients should be establishedon **IV aminophylline for at least 48 hours** (to reach steady state) **before calculating the oral dose**. Check that the patient is on the correct IV aminophylline dose before converting to oral therapy.

Oral theophylline is the preferred oral switch and should be prescribed first line.

**Converting IV aminophylline to ORAL theophylline:**

1. Calculate the total amount administered in 24 hours by multiplying the hourly infusion rate by 24. This calculation assumes infusion concentration prepared is 1mg/ml.
2. Multiply the total aminophylline dose administered in 24 hours by 0.8, which is the salt correction factor.
3. Divide the total amount administered in 24 hours by the dosing interval for oral administration, e.g. divide by 2 for twice daily dosing.

**EXAMPLE CALCULATION**

1. For a maintenance rate running at 35ml/hr (~35mg/hr), the total daily dose is 840mg.
2. To convert to oral theophylline multiply 840mg x 0.8 = 672mg daily.
3. If the dosing interval for oral administration is every 12 hours i.e twice daily, divide 672mg by 2. This gives an oral dose of 336mg twice daily.
4. A suitable theophylline dosing regimen could be Uniphyllin Continus®, 300mg in the morning and 400mg in the evening.

**Converting IV aminophylline to ORAL aminophylline:**

1. Calculate the total amount administered in 24 hours by multiplying the hourly infusion rate by 24. This calculation assumes infusion concentration prepared is 1mg/ml.
2. Divide the total amount administered in 24 hours by the dosing interval for oral administration, e.g. divide by 2 for twice daily dosing. It is assumed that oral aminophylline has 100% bioavailability.

**EXAMPLE CALCULATION**

1. For a maintenance rate running at 35ml/hr (~35mg/hr), the total daily dose is 840mg.
2. If the dosing interval for oral administration is every 12 hours i.e twice daily, divide 840mg by 2. This gives the equivalent oral dose to be 420mg twice daily.
3. A suitable aminophylline dosing regimen could be Phyllocontin Continus® 225mg, 2 tablets (450mg) twice daily.

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| References  British National Formulary 76 (September 2018) [online] *BNF content published by NICE*. Available at: Bnf.nice.org.uk [Accessed 28 Nov. 2018].  **electronic Medicines Compendium (eMC) [online]**. Summary of Product Characteristics**;**  a) Hameln Ltd. Aminophylline injection. Last revised 23/01/2015.  b) Mercury Pharma International Ltd. Aminophylline hydrate 25mg/ml Solution for injection. Last revised 19/12/2015. **Available at https://www.medicines.org.uk/emc** [Accessed 15 Nov. 2018]  Martindale: The Complete Drug Reference. [online] Available at https://www.medicinescomplete.com/ [Accessed 15 Nov. 2018]  Medusa: Injectable Medicines Guide [online]. Available at <http://medusa.wales.nhs.uk> [Accessed 15 May 2018]  NEWT guideline. Available at: http://www.newtguidelines.com [Accessed 28 Nov. 2018].  Stockley's Drug Interactions [online] Available at <https://www.medicinescomplete.com> [Accessed 15 Nov. 2018] |