

Adjusting phenytoin doses in a patient with co-morbidities

This article describes the application of therapeutic drug monitoring to achieve optimal dosing of phenytoin in an elderly patient with co-morbid conditions. By David Jones.

The case

Mrs JW is a 73-year-old woman admitted to hospital following a fall resulting in right hip pain. This was followed by a range of medical problems including congestive cardiac failure, urinary sepsis, atrial fibrillation, seizures, abnormal liver function tests, poor urine output, a gastrointestinal bleed and *Clostridium difficile*-associated diarrhoea.

Medical and drug history

Mrs JW's previous medical history included epilepsy, osteoarthritis, monoclonal gammopathy and thrombocytopenia.

She normally receives her medication in a dosette box and was taking the following medicines before admission (confirmed by the ward pharmacist):

- Amiloride 5mg OD
- Bumetanide 3mg OD
- Phenytoin sodium 100mg OM and 325mg ON
- Simvastatin 40mg ON

On admission, her electrolyte levels were as follows:

• Sodium	138mmol/L
• Potassium	3.9mmol/L
• Urea	11.5mmol/L
• Creatinine	113µmol/L
• Alkaline phosphatase	350 IU/L (chronic)
• C-reactive protein	67mg/L
• White cell count	7.9 x 10 ⁹ /L
• Platelets	74 x 10 ⁹ /L (chronic)

The initial diagnosis was a mechanical fall (i.e. not leading to loss of consciousness), following a number of previous falls, which may have been caused by confusion resulting from a urinary tract infection or urinary sepsis.

Plan

The immediate plan was to: obtain lying and standing blood pressures, seek physiotherapy input, perform urinalysis, start calcium supplements (Adcal D3; Prostraken, 1 tablet BD) for bone protection, stop the diuretics (the patient was showing clinical signs of dehydration) and take a phenytoin level.

Following a discussion between the medical staff and the pharmacist, it was decided not to prescribe a low molecular weight heparin for prophylaxis of venous

thromboembolism because of Mrs JW's low platelet count.

The junior doctor asked the ward pharmacist for advice about taking a phenytoin level and was advised to take a trough level in line with standard practice.

The trough phenytoin level was 3mg/L. The usual therapeutic range is 10–20mg/L, so a dose adjustment was required. The pharmacist provided support in calculating the maintenance dose that would achieve a mid-range, steady-state concentration close to 15mg/L.

Calculating phenytoin doses

When calculating a phenytoin dose for a patient, three main factors must be considered: serum albumin status, renal function and the non-linear metabolism of phenytoin.

Serum albumin status Phenytoin is usually highly bound to serum albumin. Hypoalbuminemia (low serum albumin) increases the proportion of unbound ('free') phenytoin that is able to exert a pharmacological effect. There is a formula which can be applied to calculate the adjusted phenytoin concentration that would be observed if the patient had a normal serum albumin concentration, using the patient's observed phenytoin level, the abnormal serum albumin concentration and the normal albumin concentration (40g/L).

Renal function Patients with renal failure have an increased proportion of unbound phenytoin. This is partly attributable to the decrease in serum albumin associated with advanced renal failure and the change in binding affinity of phenytoin to serum albumin.

Phenytoin metabolism For most drugs, the rate of metabolism is proportional to

the plasma concentration. This follows the principles of first-order kinetics (i.e. doubling the dose of the drug results in an approximate doubling of the plasma concentration). However, the rate of phenytoin metabolism approaches its maximum at therapeutic concentrations. This is described as capacity-limited metabolism, which follows the principles of zero-order kinetics. Increasing the maintenance dose of phenytoin results in disproportionate rises in plasma concentration, which can make dose adjustment difficult.

As a general rule, when steady-state phenytoin concentrations exceed 12mg/L, a daily dose increase should not exceed 25mg — but any increase should be tailored to the individual patient's parameters and potential changes in binding.

The half-life of phenytoin is sometimes reported as 22 hours but, since it increases as the plasma concentration increases, it may be between seven and 42 hours. Many other drugs reach steady state concentrations in four to five half-lives, but with phenytoin this can take much longer, so the time at which a phenytoin level is taken is not crucial. In clinical practice, a trough level (pre-dose) is usually considered acceptable for routine monitoring.

Dose calculation

A graphical method was applied, as shown in Figure 1. This is referred to as an orbit graph or Vozeh plot. The graph is divided into two sections; on the left hand side, a steady-state phenytoin concentration can be plotted along the x-axis (C_p) against the corresponding dosing rate of phenytoin base in mg/kg/day on the y-axis (V_m). The right hand side of the graph can be used to estimate the most likely values of V_m and K_m (the plasma concentration at which the rate of metabolism is exactly half the maximum rate), based on population pharmacokinetic studies.

The orbits represent the fraction of the sample patient population whose V_m and K_m values are within that orbit (innermost orbit = 50%, next orbits = 75%, 90% and 95%, respectively, outermost orbit = 97.5%).

On admission Mrs JW was taking 425mg of phenytoin sodium daily (100mg OM and 325mg ON), resulting in a steady-state phenytoin concentration of 3mg/L. She weighs 75kg. A new maintenance dose was derived using the following standard method:

1. Calculate V_m , the dosing rate of phenytoin, and plot on the y-axis. This should be calculated using the salt fraction of phenytoin sodium capsules, which is 92% of the actual dose (the percentage of the administered salt that is the active constituent).

425mg phenytoin sodium \equiv 391mg phenytoin base

Therefore the dosing rate (V_m) of phenytoin is: $\frac{391\text{mg}}{75\text{kg}} = 5.2\text{mg/kg/day}$

2. Obtain the steady-state phenytoin concentration (C_p) corresponding to the above dosing rate and plot on the x-axis. In this case, the steady-state phenytoin level obtained for this dosing rate was 3mg/L.

3. Decide on a target phenytoin concentration. In most cases, the target concentration is taken to be the average of the therapeutic range, in this case 15mg/L.

4. Connect the two points from parts (1) and (2) above. This is done by drawing a

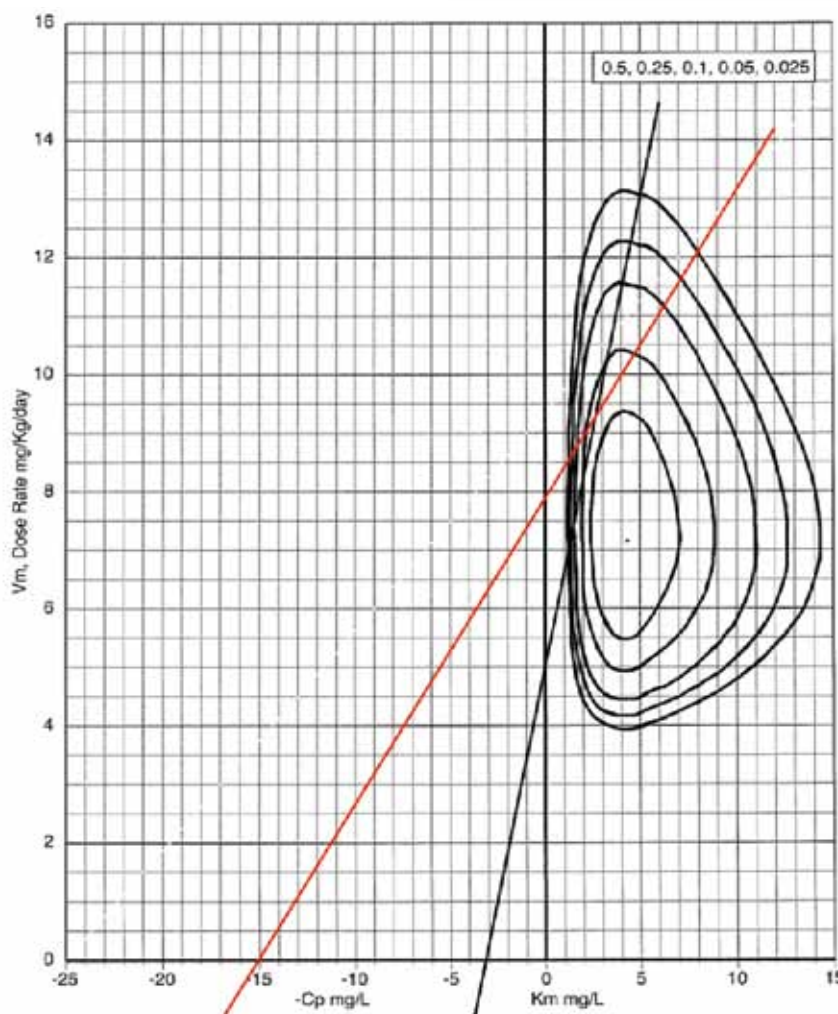


Figure 1: Vozeh plot showing calculation of a new phenytoin maintenance dose to correct a phenytoin level of 3mg/L

straight line, passing through the orbits to the right of the graph (the black line in Figure 1).

5. Calculate the new maintenance dose. The new maintenance dose is calculated by drawing another straight line from the middle of the line crossing the innermost orbit, to the new, desired steady-state phenytoin concentration. The point, at which the new line crosses the y-axis, is the new dosing rate of phenytoin base required to achieve the desired phenytoin concentration (the red line in Figure 1).

In this case, the new dose rate was 7.8mg/kg/day. The new maintenance dose for Mrs JW was therefore:

7.8mg x 75kg = 585mg/day phenytoin base (equivalent to 635mg/day phenytoin sodium). For ease of administration, the pharmacist suggested rounding down the dose to 600mg/day.

Antibiotic complications

Over the next week or so, Mrs JW was treated for urinary sepsis. She received intravenous piperacillin with tazobactam (Tazocin; Lederle) 4.5g TDS, and her renal function was monitored regularly. This was later changed to oral ciprofloxacin 500mg BD, following advice from the microbiologist. Quinolone antibiotics such as ciprofloxacin are known to lower a person's seizure threshold and should be avoided in patients with epilepsy. Unfortunately, the switch from IV to oral antibiotics took place over the weekend, when the hospital does not operate a clinical pharmacy service, and during this time Mrs JW suffered a number of seizures. The on-call doctor presumed that the seizures were due to the effect of the quinolone, as opposed to a sub-therapeutic phenytoin concentration.

Ongoing monitoring of the patient identified *Clostridium difficile*-associated diarrhoea, which was thought to be

secondary to successive antibiotic treatments. This caused changes in Mrs JW's biochemistry — her potassium level fell to 2.9mmol/L (and was treated with oral potassium supplements) and her creatinine rose to 219µmol/L due to dehydration.

The pharmacist advised that Mrs JW's phenytoin level should be checked again and monitored closely. The next day her phenytoin level was reported to be 19mg/L. Since this level is at the top end of the therapeutic range and in light of Mrs JW's worsening renal function and reports that she was becoming increasingly drowsy (presumed to be secondary to the phenytoin dose increase), the pharmacist suggested a phenytoin dose review.

Dose adjustment

The Vozech plot was used again to calculate a new dose based on Mrs JW's phenytoin concentration of 19mg/L and her recent dose of phenytoin sodium 600mg/day (Figure 2).

600mg phenytoin sodium \equiv 552mg phenytoin base.

The corresponding dosing rate was therefore: $\frac{552\text{mg}}{75\text{kg}} = 7.4\text{mg/kg/day}$

As shown in Figure 2, the point at which the red line crosses the y-axis (the new dosing rate of phenytoin base) was 7mg/kg/day. The new maintenance dose was thus calculated as:

7mg x 75kg = 525mg/day phenytoin base (equivalent to 570mg/day phenytoin sodium). This was rounded down to 550mg/day for convenience.

Further monitoring

Following this dose reduction, the plan was to monitor Mrs JW closely and check her phenytoin level in five to seven days time. Mrs JW remained seizure free and was not showing any signs of phenytoin toxicity. However, after six days Mrs JW's steady-state phenytoin level was reported to be 23mg/L. This was due to ongoing (but improving) renal impairment and an acute reduction in serum albumin (to 27g/L).

Once again, a new maintenance dose was determined, using the same

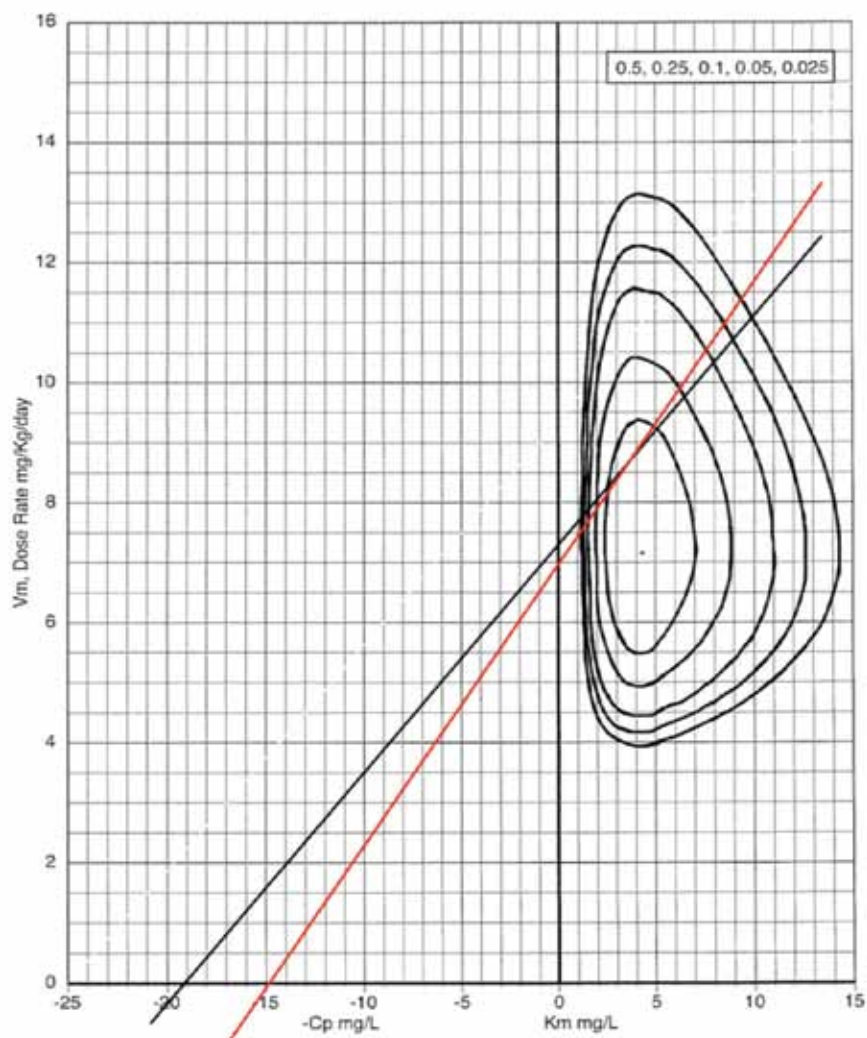


Figure 2: Vozech plot showing calculation of a new phenytoin maintenance dose to correct a phenytoin level of 19mg/L

method and a phenytoin concentration of 23mg/L at a dosing rate of 6.75mg/kg/day phenytoin base. The new dosing rate was found to be 6.25mg/kg/day. The new maintenance dose was therefore:

6.25mg x 75kg = 469mg/day phenytoin base (equivalent to 509mg/day phenytoin sodium), rounded down to 500mg/day.

The remainder of Mrs JW's hospital stay involved rehabilitation and mobilisation, and titration of carvedilol and furosemide doses, which were newly prescribed for her ongoing congestive cardiac failure.

Mrs JW continued to take 500mg phenytoin sodium and remained seizure free. Ongoing monitoring was carried out by the pharmacist and, before the patient was discharged, two steady-state phenytoin levels were taken seven days

apart, recording 17mg/L and 15mg/L, respectively.

The pharmacist arranged a new dosette box for Mrs JW which contained the following medicines:

- Furosemide 80mg OM and 40mg at lunch
- Paracetamol 1g QDS
- Senna 2 tablets ON
- Sodium docusate 200mg BD
- Carvedilol 6.25mg BD
- Phenytoin sodium 250mg BD

Mrs JW was discharged, and a routine follow-up appointment at the intermediate care outpatient clinic was scheduled for six weeks time.

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