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Warfarin, phenytoin and thyroid hormones – a binding combination?

By Peter Tenni

The patient is a 72-year-old female resident of a nursing home. Her past medical history consists of osteoarthritis, type 2 diabetes mellitus, epilepsy and hyperthyroidism. In addition, she has had valvular heart disease, with a heart valve replacement in 1999.

Her current medications are:

- Carbimazole 10mg daily
- Phenytoin 300mg daily (was 400mg until 10 days before review, and was 300mg approximately a month ago; see laboratory tests)
- Warfarin 3mg daily (was 4mg daily until 10 days ago)
- Ranitidine 150mg twice-daily
- Recently ceased – *Oxycontin* 5mg twice daily, ceased 3 days before review).

A number of laboratory tests are available in the notes at the facility. These are shown below:

Test	Result		Normal range
	1 month ago	10 days ago	
Haemoglobin	132		115-155g/L
Mean cellular volume	88		80-100fL
White cell count	6.9		4-11/nL
Platelets	255		140-400/nL
INR	1.9	3.4	2-3
Warfarin dose	*4mg*	*Reduced to 3mg*	
Phenytoin	29	111	40-80mmol/L
Phenytoin dose	*Increased to 200mg twice-daily (from 300mg daily)*	*Reduced to 300mg daily*	
TSH	0.012	0.014	0.35-4.94
T3	4.9		2.5-5.5pmol/L
T4	10.7		10-24pmol/L

The medical notes at the facility are sparse, and are summarised below.

Date of entry	Comments
1 month ago	*Dilantin low, increase to 2bd* *Note TFTs, Leave as T3/T4 normal*
8 days ago	*Dilantin high, reduce to 300mg daily. INR high, reduce warfarin to 3mg daily*
3 days ago	*Very confused, no evidence of pain – cease* Oxycontin. *Repeat bloods.*

The lady has a moderate degree of cognitive impairment and requires the assistance of two people for her activities of daily living. The nurses arranged for the doctor to see her three days before your review, indicating that she was refusing her analgesics as she said: 'I have no pain and don't need the tablets'. Her blood pressure and heart rate were normal and the nurses indicate that, other than the fluctuating mild confusion, she is reasonably easy to manage and stable.

Clinical assessment

This is an interesting case of changes made to medications as a result of interpretation of laboratory tests. The tests from one month previously indicated a low phenytoin level and also a low TSH. At that time the medical practitioner increased the dose of phenytoin to 400mg (from 300mg daily) and did not change the carbimazole dose as the T3 and T4 were normal.

Phenytoin dose changes

As all pharmacists would know, a change in phenytoin dose of this magnitude is inappropriate and may result in an excessive increase in levels, as later occurs in this patient. This problem would need to be addressed with some explanation, especially, as when the level was later elevated, the doctor reduced the dose by 100mg to 300mg. Advice on this aspect of this case can be found in a previous medication review article addressing this issue.[1]

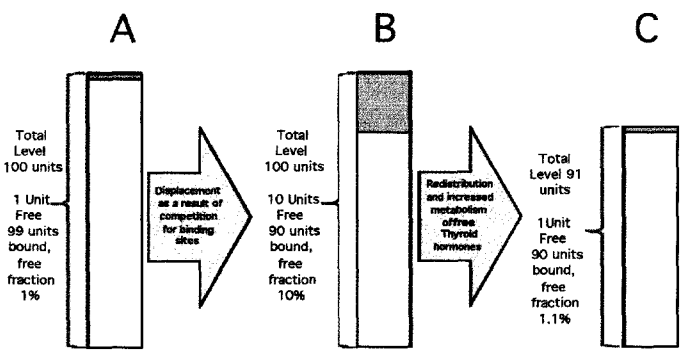
This patient is also taking warfarin, and the likely competition between this and the phenytoin would increase the free fraction of both drugs. It is interesting to consider the free fraction of the phenytoin related to the level taken one month ago, as it may well have been therapeutic. A serum albumin level would assist in the interpretation of this low phenytoin level. Depending on the clinical situation (for example the frequency of any seizures or the presence of any toxic symptoms) the dose increase in phenytoin may not have been necessary.

Interpretation of thyroid function tests

The thyroid function tests, however, require further discussion. As the doctor correctly pointed out, this lady's thyroxine (T4) and tri-iodothyroxine (T3) levels were normal, despite a thyroid stimulating hormone (TSH) level which was significantly inhibited, consistent with hyperthyroidism.

Thyroxine is highly bound (over 99%) to thyroid binding globulin and may be displaced from this protein by other highly protein bound drugs.[2] In this case, the presence of phenytoin and warfarin (both highly protein bound) may increase the free thyroxine and this would result in an increased uptake of thyroxine in the tissues, resulting in a reduced total serum level. Thus the use of highly protein bound drugs increases the 'free fraction' of both of the thyroid hormones, such that normal levels may be consistent with excessive thyroid hormone effects. This concept is shown in Figure 1.

Figure 1 Concept of increased free fraction



As can be seen from the concept outlined in Figure 1, a total level of 91 units (in situation C) would be biologically equivalent, in terms of free amount, to a total level of approximately 100 in situation A. In this case scenario, levels of thyroxine and T3 were normal, but could have provided a biologically increased free amount which was then responded to by a decrease in TSH. Thus, the patient's TSH provided the more appropriate or 'true' interpretation of the thyroid status, and hyperthyroidism should be suspected.

While there were no overt signs or symptoms of hyperthyroidism (the heart rate was only slightly elevated and the weight was stable), it is interesting to note the change in the patient's INR. There are two possibilities that may explain this increase in INR. Firstly, the increase in the phenytoin dosage may have increased the competition between the warfarin and phenytoin and resulted in a transient increase in free warfarin and therefore its effects. In contrast to this, the increased dose of phenytoin could induce the metabolism of warfarin and may result in a decreased warfarin effect.

The second possibility relates to the effect of the increased phenytoin dose on thyroid function. The increased dose may have resulted in an increased competition with thyroxine and T3 for thyroid binding globulin, resulting in an increased free level and a resultant hyperthyroid (at least biochemically) status. Hyperthyroidism could, in turn, have increased the catabolism of liver-synthesised clotting factors, increasing the sensitivity to warfarin.

Thus, in this case scenario, there is sufficient reason to suspect that the TSH levels obtained are representative of the true thyroid status, and some consideration of an increase in the dose of carbimazole should be undertaken. In addition, the significant changes in phenytoin dose may have contributed to changes in warfarin effects and thyroid status, in turn modifying the phenytoin free levels.

Actions and recommendations

It would be appropriate to discuss with the medical practitioner the possibility that this patient has a degree of hyperthyroidism, and also to outline appropriate dose modification of phenytoin and the potential impact of the multiple protein binding issues in the case. It would be useful to determine the current serum albumin, and also the current thyroxine and T3 levels. A Free Thyroxine Index and Thyroid Binding Globulin test may also assist with interpretation of the current thyroid status. As blood tests were ordered three days ago, some of these parameters may be available when the discussion with the doctor takes place.

It is important in this case (as in all cases) to consider the patient's current clinical status. The resident is described as relatively stable, and although the 'numbers' are a little abnormal, changes in medication should be undertaken with care.

In summary: The **one** circular, **ring**-like, relationship between the thyroid hormones, phenytoin and warfarin lead **to** a complex situation which does not clearly follow the **rule**s and where aspects of **them all** are important. Interpretation of the case should take into account the patient's clinical **and** symptomatic situation which could assist **in** overcoming **the darkness** in which the **bind**ing issues have placed **them**. (*Ed. Apologies to JRR Tolkien.*)

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References

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2. Hughes J (Ed.). Use of laboratory test data: process guide and reference for pharmacists. Pharmaceutical Society of Australia, 2004.