Phenytoin intoxication: A case presentation

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Summary

A case history of a patient with Phenytoin toxicity on an "average" adult dosage, is presented, and the possible reasons are discussed.

The pharmacokinetic variability demonstrated by Phenytoin, due to variations in its absorption and metabolism, leading to a variation in serum concentration for a specific dosage, is outlined. Its variable end-organ effect for a specific serum concentration (pharmacodynamic variability), is also mentioned, as well as the effect of drugs and diseases on these two variables.

The importance of monitoring serum concentrations in problem cases, and of single drug therapy, is discussed, and a few side-effects, including the "acute cerebellar syndrome", are mentioned.

A regime for treatment to minimise side effects is suggested.

This is not supposed to be a dissertation by an expert on epilepsy, or even on pharmacology. It is an attempt by a general practitioner to explain an interesting phenomenon observed in a patient seen during the humdrum of a busy casualty session.

Case history

On the 6th of September, 1981, an adult male aged 34 years, was brought into our casualty department on a stretcher, accompanied by his relatives. It was a Sunday morning, busy as always, and I was in a hurry.

I spent a little more time than usual on this man, however, since he caught my interest.

The complaint was that the man had been unable to walk for a week. Further questioning revealed that he was an epileptic, on treatment at a neighbouring hospital for the past three years (since 1978).

His treatment consisted of one red and white capsule three times a day. He hadn't had any fits during these three years apparently, except for the previous Monday (a week before). He hadn't had any fits since then.

He also complained of not being able to see very well with his left eye.

On questioning later on, it became clear that he was a rather heavy drinker, especially over week-ends. He smoked about five cigarettes per day, and was unemployed and unmarried.

On examination his blood pressure was 150/105, his pulse was 72/min, and he was a fully conscious fit looking chap. He did appear to be rather dull though, and most of the talking was done by his brother. If he could understand what one was asking him, he could answer quite clearly, and did not appear to be particularly sedated.

He had good motor function in his arms and legs, and only when attempting to stand, or sit upright, did it become clear that he was markedly ataxic - he couldn't stand up, he simply lost his balance and fell over.

He also had a marked bilateral horizontal nystagmus, to both sides, and very brisk tendon reflexes -especially of his lower extremities.

I couldn't find anything wrong with his eyes. He could perform the finger-nose test reasonably well, although a degree of past pointing was present. The heel-shin test was also done moderately well.

The patient was then admitted to the medical wards, with the provisional diagnosis of Phenytoin toxicity. In the ward he was taken off the Phenytoin (for that was what the red and white capsules turned out to be), and blood was sent to the laboratory the next day for determination of his serum Phenytoin concentration. It turned out to be (34 u g/ml 136 u mol/1) which is well above the therapeutic range.

While in the ward he improved gradually, and was discharged after nine days, completely recovered, on Phenytoin 100 mg bid but unfortunately he never came back for follow up.

Discussion

Phenytoin (structurally related to Phenobarb)[4], is probably the most widely used anti-epileptic drug.[5] It has been in use for epilepsy since 1938[1], and gradually therafter people became aware of its side-effects. It is only relatively recently, however, that its interesting metabolism has been understood, and that some of its previously unknown side-effects were discovered.[6]

Lately the trend has been more and more towards single (or at the most two) drug therapy.

If Phenytoin is going to be used for this — as it often is, because of

its low cost — one has to know its characteristics well.

Metabolism and elimination

The metabolism of Phenytoin demonstrates a wide pharmacokinetic variation - ie a variation in serum concentration on a given oral dosage of the particular drug. This can cause toxicity on a dosage that would be a normal maintenance dosage for many others.

Richens[5] describes a similar patient, who developed toxicity on a dosage of 300 mg/day. Many other examples also exist.[3,8]

Conversely, this can also lead to people needing much more than this average maintenance dosage - ie as high as 500 mg/day (or up to 600 mg,[5], though few will tolerate more than 500 mg/day[1]). On an adult dosage of 4 - 5 mg/Kg, one can get as much as a 50-fold variation in serum concentration for a given dosage!

The reason for this lies mainly in the liver. The hepatic hydroxylation enzymes metabolise 98%[1,12] of the Phenytoin, before excretion and elimination via the kidneys. Some people are slow metabolisers of DPH (Diphenyl Hydantoin = Phenytoin) due to a familial enzymatic defect,[1,3,5,8, etc] and others, are fast metabolisers.

Extrinsic factors that can affect this metabolic rate are: drugs (that can inhibit/stimulate liver enzymes), liver disease, uraemia (stimulates liver metabolism) and age.

Statistically an 80 year old will have a serum concentration twice that of a 20 year old[5]; and children, except infants up to one month,[4] will metabolise it faster.[4,5]

Another aspect of the hepatic metabolism of DPH, is that at a certain serum concentration the metabolism of DPH no longer increases proportionally to the load, but slows down causing a much steeper rise in the curve **(see fig 1**[4,5]) in which the serum concentration is plotted against the oral dosage.

The reason for this is saturation of the hepatic hydroxylation enzymes, preventing them from handling any further increases in drug load effectively. The serum concentration at

which this happens, differs from person to person,[1,5] so that one cannot apply this curve universally to everybody, (although the shape will remain constant, the values will differ), because of the variation in metabolic rates between people mentioned earlier.

It follows from the above that once

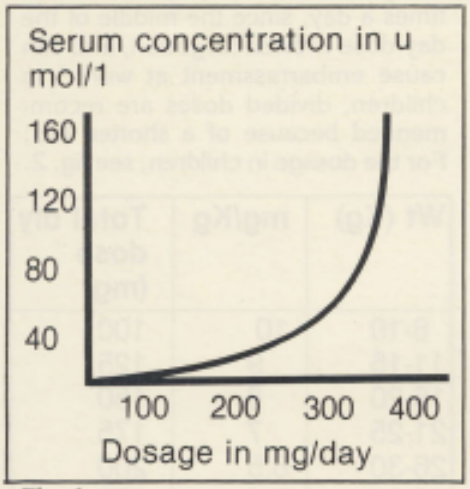

Fig. 1

saturation has taken place at a specific dosage, a slight further increase will lead to a bigger than expected rise in serum concentration (see curve).

Unfortunately this happens when the serum concentration nears the "therapeutic range" at 40 u mol/1[5] - (see graph) - and a further slight increase in dosage may cause toxicity (see the steepness of the last part of the curve!). Richen's case mentioned earlier, demonstrates this very well.

At 300 mg/day, the patient's serum concentration was 116 u mol/1, which is a toxic level. At 200 mg/day, he had a "sub-therapeutic" serum concentration of 36 u mol/1 and his epilepsy got worse.

Finally, optimum control was established at a dosage of 250 mg/day. As Sandyk [7] pointed out, "the control of many patients is on a knife edge; intoxication can be precipitated by a number of environmental changes, which cause only a slight reduction in hydroxylating enzyme activity." These 'environmental changes' are the factors already mentioned influencing the liver's metabolising capacity.

As far as the serum halflife (T-½) of DPH is concerned, it is obviously dependant on the liver's metabolising capacity, since inactivation is by the liver hydroxylating enzymes. Look at the curve again (fig 1): in the initial flat part (below 10 u g/ml or 40 u mol/1), the serum T-½ is about 24 hours[1,2,5,11] (varying at least fourfold[1]).

After that, when the liver enzymes become saturated and the curve becomes steeper, the T-½ becomes much longer — up to two to three days.[1,4,5] In children (not infants) it is generally shorter.

Absorption

Liver metabolism is not the only variable in the pharmacokinetics of DPH however. Another important variability lies in its absorption or bioavailability. DPH itself is poorly absorbed, but its acid or sodium salt, better.[5] (The sodium salt better than the acid.[12]) Particle size,[1,2,12] and the presence of other substances[5] in the tablet/capsule, also play a role.

When changing from one brand name of Phenytoin to another, all these factors can come into play, and can cause a variation in bioavailability of between 80 - 95%[1,2] (others[11,12] put it at 57,7 - 85,6%), which, if one is dealing with the "steeper part" of the curve, can precipitate toxicity.[5,11]

It is therefore advisable to keep to one specific brand name to prevent changes in serum concentration[1].

Peak plasma concentrations are reached two to six hours after ingestion[1,1,12], but may take up to 12 or even 24 hours!

Transport and distribution

90% of DPH is bound to plasma protein (mainly the albumin fraction).[1,5,12] The remaining 10% in solution is the active part, responsible for the anticonvulsant effect on the CNS (central nervous system).

This 10% remains fairly constant, in that removal of the unbound drug from the serum by eg the liver, leads to reversal of the protein binding, re-establishing a 10% unbound fraction.[5]. (This is at therapeutic concentrations).

It is said[1,2,4,5] that at a serum concentration of 80 u mol/l nystagmus develops, at 120 u mol/1 ataxia, and at 160 u mol/1 mental changes.

Even here there is a variation, though - the so-called pharmacodynamic variation: ie the difference in tissue sensitivity by concentrations of 160 u mol/1, while others may be already affected at levels of 60 u mol/1[4,5].

One of the factors playing a role here, is a change in the unbound fraction. In hypoalbuminaemic patients (eg with liver cirrhosis) the unbound fraction is raised, causing an increased risk of toxicity.[1,2,10,12]

The same applies in uraemia,[1,2,9,12] when up to 25% can be free!

Other drugs can also displace DPH from plasma proteins (see later). One must remember that an increase of the unbound fraction from 10% to 15% is already a 50% increase, and can lead to toxicity.[12] The presence of brain damage[7] (especially brain damaged children), genetic factors, and the presence of other drugs, can also render the CNS more susceptible to toxicity.[6].

The first three causes (raising the unbound fraction of DPH) are reasons why people advocate determining both fractions separately when determining the DPH serum concentration,[1,5] or doing CSF or saliva concentrations,[12] in which the unbound fraction is reflected.

Phenytoin is highly lipid soluble and is distributed extensively to the brain.[12] Especially high concentrations are found in the basal ganglia (two to three times the serum concentration), but even higher concentations are present in the cerebellum.

This may explain the picture found in toxicity.[7] (See later) High concentrations are also present in saliva.[12]

Treatment and Dosage

Generally speaking a dosage of 300 mg/day will attain serum levels of 20 - 60 u mol/1 - average 40 u mol/1. **(See graph in fig 1.)**[2,5] As mentioned earlier, this is subject to marked individual variation. One should therefore start at a dosage of 200 mg/day (3 - 4 mg/Kg),[1,4,5] and gradually increase it until a satisfactory response occurs, or until toxicity appears.

Few will tolerate dosages above 500 mg/day. The intervals between increasing dosages, must be 5 x T½ ; for that is the time for serum levels to reach a plateau state.[4] At low serum concentrations intervals of five days (or a week),[1,3] will therefore be in order, but when one nears saturation of liver enzymes (above 300 mg/day or 40 u mol/1) and the serum T½ becomes longer (see earlier), longer intervals (two-weekly) are recommended.[1,4]

It is also necessary to use only small increments, once saturation of hydroxylation enzymes has been reached (see the steepness of the second part of the curve). Some recom-

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mend that the increments should be one-sixth of the total daily dosage,[4] and others, increments of 25 - 50 mg.[5,6]

The long T½ in adults means that once a day dose will be in order[1,4,5] (provided gastric irritation doesn't occur). Conversely one probably shouldn't prescribe it three times a day, since the middle of the day dose is often forgotten, and can cause embarrassment at work.[6] In children, divided doses are recommended because of a shorter T½; For the dosage in children, see fig. 2.

Wt (Kg)	mg/Kg	Total dly dose (mg)
6-10	10	100
11-15	9	125
16-20	8	150
21-25	7	175
26-30	6,5	200
31-35	5,5	200
36-40	5,5	225
41-45	5,5	250
46-50	5,0	250
51-60	5,0	300

Fig. 2

Due to their faster metabolism, higher dosages are needed.[4,5] One should not use it for neonates since their hepatic enzymes are not yet matured.

The time it takes to halve the serum concentration is only that of a single T½[4]. That means that forgetting one's treatment one day, can lead to 'subtherapeutic' serum concentrations that can cause an epileptic attack to occur. It also means that once saturation of liver enzymes have taken place (and the T½ is prolonged), it can take a few days of treatment before there is a significant drop in serum concentration[5] (as will happen with toxicity). In our patient the serum concentration was still at a toxic level the day following his admission!

Phenytoin can also be administered intravenously, eg for status epilepticus (but intravenous Diazepam 10 mg, is the drug of choice here) or for Digoxin toxicity.

If Phenytoin has to be given, it should be given slowly intravenously (not more than 50 mg/min[1,2,4]) as a five percent solution, with ECG monitoring, since it can cause cardiac dysrhythmias or cardiac arrest.

It can be repeated every five minutes up to a total of 700 - 1 000 mg, or until toxicity occurs.[2] It should never be mixed with other drugs or put in another drugs' containers, since precipitation occurs easily.[4]

Intramuscular administration leads to slow absorption over five days,[12] and is not advocated![1,5]

Once the status has been corrected, early administration of a longer acting anti-epileptic drug (eg Phenytoin) is esssential, since an effective serum concentration of Diazepam is maintained for only two hours (one can repeat it after that time[5]).

In cases where the patient cannot swallow (as will often be the case), one can pass a nasogastric tube, and give a loading dose of Phenytoin of 600 - 1 000 mg in divided portions over 8 - 12 hours. This will give an effective serum concentration in 24 hours.[1,2,4]. This is only done, however, if the urgency for control exceeds the risk of adverse effects during the initial therapy.

Monitoring serum concentrations

All that has been said up to now about serum concentrations of DPH and the variability thereof, indicate that monitoring of serum concentations might be of value. Many people[4,6,7] maintain therefore that it will lead to better control of epilepsy, te prevention of side-effects, and the prevention of polypharmacy.

Reynolds[6] quotes figures by Lund, in which he improved the attack rate of 32 patients over a study period of three years from five attacks pa to 1,6 pa by means of monitoring serum concentrations. Some people[1,5,12] go as far as saying that the two fractions (bound and unbound) should be measured separately.

This, however, is a much more difficult and expensive procedure.

Effective control of seizures is usually obtained from 40 u mol/1 upwards, and toxicity (nystagmus) starts from 80 u mol/1.

Due to its pharmacodynamic variation, this is not always the case. Richens[5] states that control is often obtained at so-called 'subtherapeutic' concentrations, in less severe cases, and that sometimes, after years of treatment, one could come down to these concentrations without causing a relapse. Since 'subtherapeutic' concentrations are obviously safer, it is a bad thing, according to him, to treat serum concentrations, rather than the patient.

He uses a working range of 24 - 100 u mol/1, as opposed to the usual 40 - 80 u mol/1 [1, 12] He also cautions against laboratory errors (especially small hospitals doing only the occasional determination and using outdated techniques).

Indications for monitoring serum concentrations would be, for example: the simultaneous use of other drugs that could have an effect on its serum concentration; the presence of diseases that could influence serum concentrations; failure to respond to therapy; the presence of toxicity (typical/atypical); childhood.

He also says that a serum concentration recorded once in the patient's notes, at a specific dosage, can give a fair idea of what is going on, should a patient develop problems later on.

Drug Interactions

Interactions with other drugs are rather important, since epileptics can also become ill with other diseases, and indeed, might happen to be treated by more than one drug for his epilepsy.

In this regard many authors caution that the use of polypharmacy for the control of epilepsy might be inadvisable.[4,5,6] Not only are their anti-epileptic effects supposedly additive (that's the reason why they are given together), but so too are their sedative and toxic effects. It can therefore happen that while none of the drugs' serum concentrations are in their toxic ranges, the patient can present with clinical toxicity.[4,5,7]

The addition of drugs can affect the serum concentrations of the drugs the patient is on already. Other disadvantages of polypharmacy are: poor patient compliance and the fact that one wouldn't know which one of the drugs is the offender, should toxicity (especially hyper-sensitivity) occur.

Monitoring serum concentrations can greatly help you to achieve effective serum concentrations of a drug (in this case D P H), obviating the need for more than one drug.[4,5,6]

The two most commonly involved mechanisms in drug interactions with D P H are: effects on its hepatic metabolism, and displacement from its carrier proteins. Phenytoin can also affect the effectivity of other drugs (especially by means of its own effect on hepatic metabolism).

Due to the easy saturation of its hepatic metabolism, it is particularly vulnerable to drugs which have an effect on liver metabolism.

Most anti-epileptic drugs are strong inducers of liver enzymes, enhancing the metabolism of other drugs, and mostly their own too.[1,4,5] (D P H doesn't induce its own metabolism.[12]) Sultiaam leads to a 75 % increase of D P H.[1,2,5]

Phenobarbitone and Primidone have a variable effect on its metabolism (increasing/decreasing it),[1,4] and the benzodiasepines have the same effect. Valproic acid and Carbamazepine lowers its concentration.[1,5] Phenytoin on the other hand, can lower the concentrations of Primidone,[5,12] the benzodiasepines,[5,12] and Carbamazepine.[12]

Other drugs that can inhibit its metabolism (raising its serum concentration) are:[1,2,5] Disulfiram (Antabuse), I N H (the 10 % slow acetylators only — monitor serum concentration of D P H when given with I N H), Chloramphenicol (avoid this combination), Alcohol (same variable effect as Phenobarb), Chlorpromazine (e g Largactil), Prochlorperazine (e g Stemetil), Dicoumarol (substitute Warfarin), Halothane and certain Sulphas.

Drugs than can raise its concentration by displacing it from plasma proteins, are: Phenylbutazone (substitute Indomethacin), the Salicilates[1,12] and some of the Sulphas.

Drugs[1,2] that can lower its concentration by means of enzyme induction, are Diazoxide (avoid this combination) and Tolbutamide. Folic acid can lower its effectivity.[5]

The effect by Phenytoin on other drugs[5] is mainly by inducing their hepatic metabolism. They are, for example, the contraceptive pill, Cortisol[12] and Dexamethasone, Vitamin D, Phenylbutazone, Chlorpromazine, Doxycycline, Digitoxin, the Coumarins (e g Warfarin), and Tolbutamide.

Combination with Phenytoin might therefore lead to an unwanted pregnancy, failure of anti-bacterial

treatment or failure of a psychosis to respond. The effect of Furosamide on the kidneys is also inhibited to an extent by D P H.

The concomitant use of Phenytoin and the above mentioned drugs is not necessarily contra-indicated, but monitoring of serum concentrations and readjustment of dosage when indicated, is necessary.[2,12]

Uses of Phenytoin

- Epilepsy: Most types of epilepsy with the notable exception of absence seizures.[1,4,5,6] It is particularly useful in grand mal seizures[12] (tonic-clonic convulsions)
- Trigeminal and related Neuralgias (Carbamazepine the drug of choice).[1]
- Digoxin toxicity induced ventricular arrhythmias.

Toxic effects

A whole list exists, which can be found in any textbook of pharmacology. The most important here is the 'acute cerebellar syndrome', which our patient demonstrated well. It consists of nystagmus, gait ataxia, hand tremor, inco-ordination and vertigo.

Dysarthria, raised tendon reflexes, mydriasis, blurred vision, diplopia, and behavioural changes such as sedation/lethargy, hyper-activity, silliness, confusion and hallucinations[1,5] can also occur, as well as an increase of seizures.[1,4,5] An atypical picture, seen especially in brain damaged children,[5,6,7] consists mainly of choreo-athetosis, and can occur at serum concentrations as low as 1 u g/ml (4 u mol/1).

Phenytoin intoxication should therefore be thought of in all cases presenting with neurological or behavioural deterioration receiving this drug, including an increase in seizure rate.[4,5,7] Other side-effects[1,2,5,12] include gingival hyperplasia (in 20 - 50 % - responds to oral hygiene), peripheral neuropathy (especially old people), gastric irritation (give in divided doses), osteomalacia (treat with vitamin D), hyperglycaemia, hirsutism (especially young females), hypersensitivity reactions (including skin rashes in one-to-five percent, erythema multiforme, S L E, reversible lymphadenopathy and liver necrosis), altered thyroid function tests, megaloblastic anaemia due to folate deficiency, and haemorrhagic disease of the new-born (prevent with vitamin K), only to mention a few. It is also slightly teratogenic,[1,2,5,12] though taking a woman off the drug while pregnant, is probably not warranted, due to the danger of an increase in seizures to the mother and foetus.

Hepatic enzyme induction, leads to an increased metabolism of e g vitamin D, folate, steroids and thyroxine.[5,12]

Side-effects are not common, and many epileptic patients benefit from its use. It remains the major drug for generalised tonic-clonic seizures.[12]

Conclusion

Why this patient developed Phenytoin toxicity, I don't know. His ethanol intake (if particularly heavy) might have had something to do with it; or he might have changed to another brand name of Phenytoin at the hospital from which he had come.

He might even have been a slow metabolizer of D P H, or he might have used a liver toxin which affected its serum concentration, or indeed, it might have been a combination of these and other factors.

Be that as it may, what the patient brought to my attention, and what I tried to outline in this article, was the interesting 'metabolism' of Phenytoin and the factors (drugs, heritage and disease) that can have an effect on that, leading to toxicity in a patient on a 'normal' dosage.

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Pharmaceutical companies merge

A new pharmaceutical company came into existence on July 1st when Miles Laboratories (Pty) Ltd. merged with Bayer Pharmaceuticals SA (Pty) Ltd. The new company will be known as Bayer-Miles (Pty) Ltd.

The merger lifts the new company well into the middle sector of the pharmaceutical industry where it is expected to make a most valuable contribution. The pharmaceutical section of the new company will operate at Isando while the diagnostic and industrial divisions and the manufacturing plant will operate from Cape Town.

As before a substantial quantity of the biochemicals produced by this plant will be exported to Europe and North America.

Bayer recently hit the headlines in South Africa with a breakthrough in the treatment of bilharzia.

For further information please contact Bayer-Miles (Pty) Ltd, P.O. Box 198, Isando 1600.

New pack allows direct drop administration

Wellcome has introduced a new 7,5 ml Otosporin pack. The new pack contains 50% more Otosporin at only a marginal increase in price, which is, in effect, a saving for the patient.

The container, which allows direct administration of the drops, is also a vast improvement on the previous pack which consisted of a bottle and separate dropper.

"Sleep and the arthritic patient" — film for GPs

A film, "Sleep and the Arthritic patient", a report of the British studies, is sponsored by Pfizer Laboratories, in the interest of promoting continuing medical education.

The film is available on loan to medical practitioners from representatives of Pfizer, or the Professional Services Department, Pfizer Laboratories (Pty) Ltd, P O Box 783720, Sandton 2146, or telephone (011) 783-5270.