

Involuntary movements caused by phenytoin intoxication in epileptic patients

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SYNOPSIS The case histories of four patients who developed choreoathetoid movements during intoxication with phenytoin are presented. Drug intoxication was confirmed in each case by measuring the serum phenytoin concentration. Drug interactions were, in part, responsible for the occurrence of intoxication in three of them. Phenytoin intoxication is not always easy to recognize, particularly when nystagmus is minimal or absent, as in these four patients. The estimation of the serum phenytoin concentration is invaluable in this situation.

The classical signs of phenytoin intoxication are coarse nystagmus, ataxia, and dysarthria, which are signs of cerebellar dysfunction. Less commonly, other neurological disturbances may be caused by phenytoin intoxication (Glaser, 1972). Although choreoathetosis has been described (Peters, 1962; Logan and Freeman, 1969; Kooiker and Sumi, 1974; McLellan and Swash, 1974), only a few cases have been documented adequately. During the last two years we have seen involuntary movements in four patients, two of whom presented with severe choreoathetosis. These patients are described in the following case reports.

CASE 1

Patient R.C. was a 19 year old man who developed epilepsy at 7 years of age. Investigations at this time revealed no focal lesion, although the generalized abnormalities seen on the electroencephalogram (EEG) were more marked in the right frontoparietal region. Four days after he was started on phenytoin 150 mg and phenobarbitone 120 mg daily, he became drowsy and developed coarse nystagmus and an extensor plantar response. Withdrawal of drug therapy was followed by a disappearance of the neurological signs.

When 10 years old, he was admitted to hospital with frequent major fits, occurring once or twice hourly on the day of admission. He was semi-conscious and irritable, but there were no localizing

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signs. A left carotid arteriogram showed a shift to the right of the anterior cerebral artery, and a pneumoencephalogram (AEG) showed displacement of the ventricles to the right without significant alteration of ventricular size or shape. A gross unilateral abnormality over the left hemisphere posteriorly was seen on EEG. The pathological significance of these findings was uncertain. His fits were bizarre in pattern and were asymmetrical, being more marked on the right, and being accompanied by transient aphasia. A three day course of corticotrophin (ACTH) was without effect, but when pheneturide 400 mg daily was started the fits appeared to decrease in frequency and severity. However, four days after starting this drug, he developed marked choreoathetoid movements involving head, neck, and upper limbs. Although it was felt at the time that this was due to the same process as that causing the fits, the movements disappeared when pheneturide was withdrawn.

The following year four admissions were required to attempt to achieve better control of his fits. On two occasions he was noticed to have minimal signs of a transient left hemiplegia.

In May 1973, he was admitted to a mental hospital and during his stay there his anticonvulsant therapy was altered in order to control his frequent fits. Sulthiame 300 mg and diazepam 30 mg daily were added, and the primidone which he had been receiving for several years was discontinued. Phenytoin 300 mg daily was continued unchanged. His fits appeared to come under better control on this new drug regime, but when interviewed in June 1973 for

possible admission to the National Hospitals-Chalfont Centre for Epilepsy, he was noted to be fidgety, almost to the extent of making choreiform movements. Admission was arranged for the following month but he failed to arrive. Almost two months later an urgent request for his transfer to the Chalfont Centre was made by another hospital to which he had been admitted three weeks earlier with an episode of vomiting and repeated major fits. During his stay in this hospital, his drug therapy had been increased to 600 mg phenytoin, 300 mg sulthiame, 180 mg phenobarbitone, and 1 500 mg of beclamide daily.

When admitted to the Chalfont Centre on 10 September 1973, he was unable to stand and showed bizarre dystonic posturing. The upper limbs were abducted and internally rotated at the shoulder, semiflexed at the elbow, markedly flexed at the wrist and metacarpophalangeal joints, and extended at the interphalangeal joints. This posture was continuously disturbed by choreoathetoid movements involving the face, trunk, and all four limbs. Slow extension and flexion movements of the wrists and fingers were seen and adduction and abduction, retraction, and internal rotation movements of the shoulders. The feet were plantar-flexed and the big toe dorsiflexed. There were continuous slow flexion and extension movements of the hips and knee joints. He was unable to hold his tongue protruded, and grimacing movements of the face were occurring frequently. Slight nystagmus was seen on lateral gaze. The limb and trunk movements so disturbed his posture that he twice fell out of bed, and had eventually to be managed for the first 24 hours in a side ward with no furniture and with mattresses lining the floor and walls. A serum phenytoin level measured on admission was 203 μM (51 $\mu\text{g/ml}$) which is well into the toxic range (100 μM , 25 $\mu\text{g/ml}$ is regarded as the upper limit of the therapeutic range in our laboratory).

All drug therapy was withheld for seven days and the decay of the serum phenytoin concentration was followed (Figure). The decay was at first very slow, but by the fifth day the concentration was only a little above the limit of detection (see Discussion section for comment on these observations). An EEG recorded 24 hours after admission showed a moderately severe generalized abnormality, with a dominant frequency of 4–6 Hz. A week after admission the dominant had increased to a frequency of 6–7 Hz.

At this time his abnormal movements had largely ceased, although he continued to have odd, unrestrained movements for the rest of his four months stay at the Chalfont Centre. After seven days without anticonvulsant therapy his minor fits were occurring

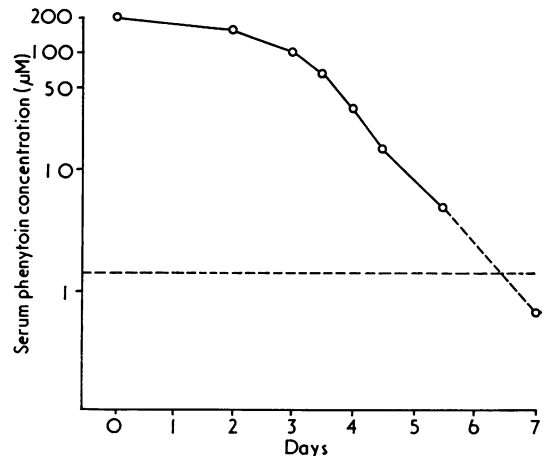


FIG. 1 Case 1. Decay in serum phenytoin concentration after discontinuing all drug therapy. The horizontal dotted line indicates the limit of accurate detection of the method. Note: 4 μM = 1 $\mu\text{g/ml}$.

with increasing frequency and he was therefore started on 150 mg phenytoin and 150 mg phenobarbitone daily. Two weeks later the dose of phenytoin was increased to 250 mg daily, but without an exacerbation of the choreoathetoid movements. At this time, examination of his nervous system revealed only slight fine tremor of his hands and mild impairment of coordination, in addition to the odd movements mentioned above, which occurred mainly when he was talking. No nystagmus was seen. A serum phenytoin level measured when he had been stabilized on 250 mg of the drug was 23 μM (6 $\mu\text{g/ml}$). He was eventually discharged four months after his admission.

CASE 2

Patient M.H., a 34 year old woman, developed epilepsy of unknown aetiology at 8 years of age. Her major and minor fits had proved difficult to control. She had received 500 mg phenytoin and 250 mg phenobarbitone daily (as five Epanutin and phenobarbitone capsules) for 10 years before her admission to the Chalfont Centre, although her parents reduced the dose to three capsules daily whenever she developed diplopia.

On admission on 9 November 1972, no neurological abnormalities were found. An EEG showed a mild diffuse abnormality, with a dominant rhythm of 7–9 Hz. On 16 November her drug dosage was reduced to 300 mg phenytoin and 180 mg phenobarbitone daily because she was becoming ataxic.

Phenytoin intoxication was later confirmed when the result of a serum phenytoin level was available on a specimen taken at the time of drug reduction. The level was 180 μM (45 $\mu\text{g/ml}$).

On 25 November she developed a febrile illness which was treated with ampicillin 250 mg six hourly. Her temperature rose to 39.5°C but settled again within two days. Ten days later, on 5 December, she was noticed again to be ataxic and dysarthric, and showed incoordination on heel-to-shin testing. She did not have nystagmus. An EEG at this time showed rather more slow activity, with runs of rhythmic waves at 4–5 Hz anteriorly. The following day a relief doctor diagnosed status epilepticus and transferred her to a local hospital, where her drug dosage was increased to the original level. Her 'fits', however, did not improve and it became obvious that the diagnosis was incorrect. She was returned to the Chalfont Centre and drug therapy was immediately withdrawn. Twenty-four hours later her serum phenytoin level was 170 μM (42.5 $\mu\text{g/ml}$). She was dysarthric, grossly ataxic, and she showed continuous movements of her limbs. She was transferred to the National Hospital, Queen Square, for investigation.

On arrival she was found to be fully conscious and followed events around her, but cooperation was extremely limited. She was perpetually grimacing, frowning, raising her eyebrows, pursing her lips, smiling, and showing bizarre movements of mouth and tongue. She was unable to stand, even with help, and exhibited restless movements of trunk and limbs which were considered to resemble athetosis more than chorea. The only reflexes which could be elicited were the biceps and triceps bilaterally and these were diminished. The plantar responses were flexor. Muscle power, coordination, and sensation were untestable. After withdrawal of her phenytoin therapy, the involuntary movements slowly improved, but she remained generally incoordinated and ataxic. Her fits were adequately controlled on 750 mg primidone and 180 mg phenobarbitone daily. Investigation at this time showed an erythrocyte sedimentation rate (ESR) of 51 mm in the first hour, but this gradually fell to normal. Cerebrospinal fluid, chest and skull radiographs, and an AEG were normal. EEGs on this and previous occasions showed only a diffusely abnormal record.

On her return to the Chalfont Centre on 3 January 1973, she remained ataxic and her fits became inadequately controlled. It was noted that after fits she showed involuntary movements resembling those which occurred during phenytoin intoxication. In order to achieve better control of her fits she was started on 150 mg phenytoin daily on 9 February.

Three days later she was beginning to show signs of a return of her previous ataxia, dysarthria, involuntary movements, and sleepiness. On 15 February she was unable to stand unaided, and therefore phenytoin was again withdrawn. A serum sample taken just before stopping the drug showed a phenytoin level of less than 5 μM (1 $\mu\text{g/ml}$).

Her fits were again difficult to control, requiring an intravenous drip of diazepam on one occasion. Eventually satisfactory control was achieved with 180 mg phenobarbitone, 750 mg primidone, and 600 mg carbamazepine daily. The involuntary movements gradually disappeared during the next month and, although her ataxia has improved, her gait remains a little unsteady at the time of writing a year later.

CASE 3

Patient W.C., a 28 year old woman, had her first epileptic fit when 18 years of age. Investigations at the National Hospital, Queen Square, when she was 20 years old revealed no cause for her epilepsy, but her father had been epileptic since early childhood. On admission to the Chalfont Centre in 1969 she was receiving 250 mg phenytoin, 750 mg primidone, 300 mg sulthiame, and 10 mg dexamphetamine daily. Larger doses of sulthiame had caused ataxia. Soon after admission she was noted to be ataxic, and had slight nystagmus on lateral gaze. Withdrawal of sulthiame led to a disappearance of these signs. In May 1970, 200 mg pheneturide daily was started because of frequent major fits. She remained on this treatment for the following three years. Several EEG recordings during her first four years at the Chalfont Centre had shown runs of bilateral, high amplitude slow waves, spikes, and polyspikes.

In February 1972 she developed athetoid movements of her right arm, and uncontrollable twitching of her mouth, but these symptoms appeared to respond to 10 mg diazepam given intravenously.

On 13 June 1973 she was started on chlorpheniramine 12–16 mg daily for hay fever, which she had had annually since childhood, and this drug was continued until the end of the month. On 25 June she was noticed to be fidgeting her hands and toes. She had slight grimacing movements of her face, and, although she could protrude her tongue and hold it steady, involuntary movements of her lower jaw caused her to bite the protruded tongue. Her speech was slightly explosive, but not slurred. She was not ataxic and she did not have nystagmus. A serum phenytoin level estimated on 28 June was 120 μM (30 $\mu\text{g/ml}$). By the time this result was available four weeks later, the abnormal movements

had settled spontaneously, and a repeat serum phenytoin estimation without a change of anti-convulsant therapy was $63 \pm 4.4 \mu\text{M}$ (mean \pm SD of seven specimens estimated over four days). Subsequently the single tablet of pheneturide which she had been receiving was withdrawn without change in the frequency of her fits, and the serum phenytoin level fell further, to $39 \pm 4.1 \mu\text{M}$.

CASE 4

Patient L.A., a 61 year old woman, had been admitted to the Chalfont Centre in 1967. She had had fits since the age of 45 years, and these were considered to be temporal lobe in origin. Several EEG recordings had demonstrated frequent sharp wave and spike discharges of greatest amplitude and showing phase reversal over the right temporal lobe, accentuated by overbreathing. Intellectual deterioration had caused her admission to a mental hospital in 1966. On admission to the Chalfont Centre, she was receiving 300 mg phenytoin, 600 mg sulthiame, 1000 mg phensuximide, and 150 mg promazine daily. Soon after admission, diazepam was substituted for promazine. In 1968 it was noticed that she had a tremor of her right hand with possibly a slight increase in the tone of the right arm, accompanied by occasional twitching movements. These were thought to be signs of Parkinsonism and she was started on 150 mg orphenadrine daily.

In November 1972, an attempt was made to withdraw sulthiame therapy, but frequent minor fits occurring a few days later made it necessary to start the drug again. A serum phenytoin level measured earlier in the year was $80 \mu\text{M}$ ($20 \mu\text{g/ml}$), but just before withdrawal of sulthiame a lower value was recorded, $60 \mu\text{M}$ ($15 \mu\text{g/ml}$).

A year later, in November 1973, she became ataxic and had marked tremor of both hands. Shortly afterwards, she became confused and developed involuntary jerkings of the upper limbs, shrugging of the shoulders, bizarre movements of the mouth and facial muscles, and fidgeting of her fingers. She had coarse finger tremor, mild nystagmus on lateral gaze, and incoordination of upper and lower limbs. A serum phenytoin level at this time was $105 \mu\text{M}$ ($26.5 \mu\text{g/ml}$). Sulthiame, phensuximide, and diazepam were withdrawn and she was started on 750 mg primidone. The dose of phenytoin remained unchanged at 300 mg/day. Within seven days the involuntary movements had disappeared, although she remains unsteady on her feet at the time of writing four months later. Two weeks after the change of drug her serum phenytoin level had fallen to $30 \mu\text{M}$ ($7.5 \mu\text{g/ml}$).

DISCUSSION

Although phenytoin is one of the most valuable drugs in current use for the management of major epilepsy, it produces a wide range of adverse effects (Glaser, 1972). The commonest adverse effect on the central nervous system is the well-recognized syndrome of phenytoin intoxication. This syndrome is an expression of a functional disturbance of the cerebellum, producing coarse nystagmus on lateral gaze, ataxia, and slurred speech. The syndrome is reversible in its early stages, although prolonged intoxication can lead to permanent ataxia. Whether phenytoin toxicity is responsible for the Purkinje cell loss in the cerebellum is disputed (Dam, 1972).

Less commonly, a syndrome which has been called 'phenytoin encephalopathy' occurs. Roseman (1961) coined the term 'Dilantin inebriety' to describe the association of cerebellar signs and behavioural abnormalities, changes in mood, and a slowing of the dominant rhythm in the EEG, with the appearance of high voltage delta waves, sometimes occurring in paroxysms. Subsequently, Levy and Fenichel (1965) described an increase of fit frequency and a change in pattern occurring with phenytoin intoxication. The fits changed from typical tonic-clonic convulsions to ones in which opisthotonic posturing was evident, resembling those described in animals by Gruber *et al.* (1940). Two of their patients had unilateral motor and sensory signs, including hemianaesthesia, hemiparesis, and homonymous hemianopia, and these signs receded on withdrawal of phenytoin. Transient hemiplegia had also been described by Morris *et al.* (1956), although the two patients presented by these authors were receiving only 200 mg phenytoin daily. Confusion with a post-ictal Todd's paralysis must, of course, be borne in mind.

One of the patients studied by Levy and Fenichel (1965) developed lip smacking which occurred during fits provoked by phenytoin intoxication. More obvious involuntary movements associated with intoxication had been mentioned by Peters (1962). Several adult patients manifested bizarre extrapyramidal symptoms, including head nod, fish mouthing, and athetoid movements. Logan and Freeman (1969) also describe a patient (case 4) in whom choreic

and athetoid movements of face and all extremities, with dystonic posturing of the arms, occurred. In this and three other patients, a diagnosis of a childhood degenerative disease was entertained, and the authors stress that phenytoin intoxication should always be considered when mental and neurological deterioration occurs in a patient receiving the drug.

Kooiker and Sumi (1974) have reported two patients with severe involuntary movement disorders characterized by facial grimacing and mouthing movements, flailing movements of the arms, dystonic posturing of the trunk, and ataxia. Both patients were dysarthric but nystagmus was seen only transiently in one. Serum phenytoin levels were well into the toxic range. McLellan and Swash (1974) have also described two patients with prominent choreoathetoid movements and dystonia associated with toxic serum phenytoin levels. It was noted that voluntary movement accentuated the choreoathetosis. Although cerebellar signs were seen, in neither case were these a prominent feature. One patient was noted to have asterixis, a sign described also by Engel *et al.* (1971). Both patients lost their involuntary movements when the dose of phenytoin was lowered.

Although the movement disorders shown by our patients were, in general, similar to those of previously reported cases, a few points of neurological interest arise. The occurrence at an earlier age of choreoathetoid movements and other neurological signs in case 1, and, albeit less clear cut, in cases 3 and 4, supports the suggestion by Logan and Freeman (1969) that drug toxicity seems to interact with underlying cerebral disease. Our patients' rate of recovery from intoxication was variable, but was slowest in the two (cases 1 and 2) who were most severely intoxicated. In our experience, the neurological manifestations of phenytoin intoxication may long outlast the presence of the drug in the serum, sometimes by many months. The subsequent sensitivity of case 2 to small amounts of phenytoin was notable. A dose of 150 mg daily, leading to a serum concentration of only 5 μM (1 $\mu\text{g/ml}$), provoked marked signs of intoxication within a few days. Levy and Fenichel (1965) had the same experience with one of their patients.

Perlo and Schwab (1969) pointed out that

phenytoin intoxication can occur in the absence of nystagmus. In our patients nystagmus was either minimal or absent, despite the presence of gross ataxia and involuntary movements. We would agree with Perlo and Schwab (1969) and Logan and Freeman (1969) that the diagnosis of phenytoin intoxication is not always an easy one to make, and emphasize that it should be considered when any unusual neurological or behavioural disturbance occurs in a patient receiving the drug. The estimation of serum phenytoin concentration is invaluable in this situation.

PRACTICAL IMPLICATION IN MANAGEMENT A few important points in the management of epilepsy are illustrated by these cases. Case 1 highlights the danger of introducing sulthiame in a patient who is already receiving phenytoin. Judging by the serum phenytoin level subsequently obtained when he was taking 250 mg daily, the level on 300 mg daily in this patient would probably be within the therapeutic range of 40–100 μM (10–25 $\mu\text{g/ml}$). Sulthiame is a potent inhibitor of phenytoin metabolism, and has been shown to produce an average increase in the serum level of approximately 75% (Houghton and Richens, 1974a, b). Of the 194 patients newly admitted to The National Hospitals-Chalfont Centre for Epilepsy during the last two years 33 (17%) had toxic serum phenytoin concentrations, and of these 10 (30%) were receiving sulthiame in addition to phenytoin. Phenytoin intoxication would explain his odd, athetoid movements when he was interviewed before admission. The presence of these movements, or perhaps an actual increase in fit frequency, provoked by intoxication, accounts for the increase in the dose of his drugs before admission to the Chalfont Centre, although doubling the dose of phenytoin to 600 mg daily was inappropriate, particularly with the simultaneous administration of sulthiame.

Withdrawal of all therapy led to a slow fall in serum phenytoin concentration (Figure). If the rate of metabolism were proportional to the serum concentration of the drug, as occurs with first order kinetics, a log-linear fall in serum concentration against time would have been predicted (Arnold and Gerber, 1970). This was obviously not so, and the deviation from first

order kinetics in this patient has two explanations. At high serum concentrations phenytoin metabolism becomes saturated, resulting in kinetics more closely resembling zero order than first order—that is, a linear, rather than log-linear, fall in serum concentration (Arnold and Gerber, 1970; Gerber and Wagner, 1972; Atkinson and Shaw, 1973; Houghton and Richens, 1974c; Richens, 1974). Furthermore, the simultaneous withdrawal of sulthiame in this patient would have resulted in a progressive restoration of the activity of the hydroxylase enzyme metabolizing phenytoin, and this exaggerated the change in rate of metabolism during the first few days after drug withdrawal.

Case 2 illustrates one of the problems which arises with the management of epilepsy in a neurological outpatients clinic. Unreliable drug taking occurs frequently, and admission to hospital results in a substantial increase of serum drug concentrations (Gibberd *et al.*, 1970). In our experience, titration of drug dosage by the patient or his parents is also frequently encountered. While this may lead to effective control, it presents a hazard when the patient is admitted to hospital and given the prescribed dose regularly. Although this patient had been prescribed 500 mg phenytoin daily, her average intake was probably substantially below this. It is known that quite small increments in drug dosage can lead to a considerable increase in the serum level once the therapeutic range of serum concentration has been reached, for the relationship between the two is non-linear, becoming progressively steeper as the dose increases (Bochner *et al.*, 1972; Atkinson and Shaw, 1973; Mawer *et al.*, 1974; Richens, 1974). The control of many patients with therapeutic serum phenytoin levels is on a knife edge, so that intoxication can be precipitated by a number of environmental changes which cause only a relatively slight reduction in hydroxylating enzyme activity. It is possible that a febrile illness in case 2 was an additional precipitating factor. The timing of the antihistamine therapy in case 3 suggests that chlorpheniramine might inhibit phenytoin metabolism, although we know of no reports indicating such an interaction. It is recognized, however, that a number of drugs may inhibit phenytoin metabolism—for example, sulthiame (Hansen *et al.*, 1968; Houghton and

Richens, 1974a, b), pheneturide (Huisman *et al.*, 1970), isoniazid (Kutt *et al.*, 1966), and various others (Kutt, 1972). It is notable that two of our patients (cases 1 and 4) were receiving sulthiame, and one (case 3) was receiving pheneturide in addition to phenytoin. It is also worthy of comment that a factor responsible for inhibition of phenytoin metabolism was mentioned in three of the published case reports of choreoathetosis in epileptic patients. Administration of anaesthetic agents preceded the onset of involuntary movements in two of the patients studied by Logan and Freeman (1969); the case reported by Engel *et al.* (1971) was receiving isoniazid for tuberculin conversion; and one of the patients described by McLellan and Swash (1974) had been receiving sulthiame.

Although multiple drug therapy is sometimes necessary in severe epilepsy, it is unfortunately true that toxic combinations of drugs are most often encountered in the patient whose epilepsy is essentially drug resistant. He sometimes suffers not only his fits, but iatrogenic disease in addition. In our experience often the most valuable contribution to the welfare of such a patient is to withdraw all or most of his drug therapy. Sometimes, dramatic improvement in both mental and physical state results.

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