PAPERS AND SHORT REPORTS

Phenytoin-valproate interaction: importance of saliva monitoring in epilepsy

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Abstract

Sodium valproate is often used with phenytoin when epilepsy cannot be controlled by a single drug. Sodium valproate depresses phenytoin protein binding and so invalidates plasma phenytoin monitoring as a means of determining precise phenytoin dosage requirements. Plasma and saliva phenytoin and plasma valproate concentrations were measured in 42 patients with epilepsy receiving both drugs. Phenytoin protein binding was also measured by ultrafiltration in 19 of these patients and 19 patients taking phenytoin alone. Saliva phenytoin concentration bore the same close correlation to unbound (therapeutically active) phenytoin in patients receiving both drugs as it did in patients receiving phenytoin alone, whereas plasma total phenytoin did not. The same therapeutic range for saliva phenytoin (4-9 μmol/l; 1-2 μg/ml) was therefore valid in both groups. The depression of phenytoin binding was directly related to the plasma concentration of valproate both in random samples taken from the 42 patients and in samples taken throughout the day in two of these patients. This was confirmed in vitro.

Even when the concentration of valproate is known the degree of binding cannot be predicted. Saliva rather than plasma monitoring of phenytoin treatment is therefore valuable in the presence of valproate and with reduced phenytoin binding from any cause.

Introduction

Sodium valproate is a broad-spectrum anticonvulsant, which has been used increasingly since its introduction in the early 1970s.[1-4] It is prescribed both alone and in combination with other anticonvulsants, usually phenytoin, when a single drug has failed. Valproate lowers the total plasma phenytoin concentration while increasing the free, therapeutically active fraction.[5-9] The clinical importance of this is not always fully appreciated.[10-13] Though this interaction may not alter the dose requirement of phenytoin,[7 14] monitoring phenytoin in plasma—that is, measuring total plasma concentration—may be misleading. We noticed that some patients treated with valproate and phenytoin showed clinical signs of phenytoin toxicity when plasma phenytoin concentrations were within or even below the accepted optimum range.

Measuring total plasma phenytoin will not predict the free (unbound) phenytoin concentration if phenytoin binding is disturbed. In patients with renal failure saliva phenytoin concentration bears the same close correlation with the unbound concentration as it does in otherwise healthy epileptics.[15] In patients with normal protein binding a close correlation between saliva and plasma phenytoin concentrations has been found in our laboratory[15] and by other workers,[16-22] the saliva phenytoin concentration usually being 10-11% of the total plasma concentration. Hence the therapeutic range that we use for saliva is 4-9 μmol/l (1-2 μg/ml), which is one-tenth of the generally accepted therapeutic range for plasma.[23]

In the presence of valproate, the saliva phenytoin concentration seemed to correlate better than plasma concentration with the clinical state. We have therefore studied the relation between saliva and plasma free and total phenytoin concentrations in the presence and absence of valproate medication and the effect of valproate concentration on phenytoin protein binding in vitro and in vivo.

Patients and methods

We studied 75 epileptic patients aged 5 to 78 years. Forty-two of them (18 female, 24 male) were taking phenytoin (100-450 mg) and sodium valproate (400-2600 mg) daily. Thirty-three epileptics (18 female, 15 male) not in renal failure and taking phenytoin as the only anticonvulsant served as controls.

Sampling procedure—Outpatients attended the laboratory for sampling as part of their routine care, at random times after dosing. A specimen of saliva (about 1 ml) was collected from each patient after stimulation with citric acid,[15] and on the same occasion a venous blood

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sample (3 ml) was taken, heparinised, and the plasma separated for total drug analysis. In 19 of the patients taking valproate and 19 controls saliva and 26 ml of blood were taken for protein-binding estimation by ultrafiltration as described.[15] In two patients plasma and saliva samples were taken at predetermined intervals throughout the day after the morning medication for measurement of phenytoin and valproate. To ensure that saliva samples were free from direct drug contamination, all patients had either brushed their teeth, eaten a meal, or rinsed the mouth thoroughly in the interval between drug ingestion and sampling.[24 25]

In-vitro protein binding—Phenytoin (20-160 μmol/l; 5-40 μg/ml) and valproate (0-692 μmol/l; 0-100 μg/ml) were added to freshly collected plasma from volunteers who had not taken medication, and total and unbound drug concentrations were estimated by ultrafiltration.

Analysis was by gas chromatography. Each sample (0·5 ml) was acidified and extracted into chloroform (8 ml) containing methyl primidone (1 mg/l) to which hexanoic acid (0·03 μl) had been added. The chloroform extract was evaporated to dryness at 60°C under a stream of air and the residue redissolved in 10 μl of trimethyl anilinium hydroxide (0·1 mol/l; 15·3 g/l). Phenytoin concentration was determined by injecting 2·5 μl into a Perkin-Elmer F33 gas chromatograph fitted with a nitrogen detector (oven temperature 275°C; carrier gas: nitrogen at 1·76 kg/cm² (25 psi)) and comparing the peak height with that of methyl primidone. To measure valproate concentration, 2·5 μl was injected into an F11 chromatograph with a flame ionisation detector (oven temperature 105°C; carrier gas: nitrogen at 1·41 kg/cm² (20 psi)) using hexanoate as marker. In each case OV17 3% on chromasorb WHP was the stationary phase. Reproducibility of the assay system, as assessed by the coefficient of variation, was 2·7% for saliva samples and 4·3% for plasma samples.

Results

Figure 1 shows the relations between saliva and plasma phenytoin concentrations. The coefficient of correlation between saliva and plasma concentrations in the 33 epileptics who were not taking valproate was 0·94, and the slope (equivalent to the ratio of saliva to plasma) was 0·11; this corresponded closely with other studies.[7 9 15–17 19 20] All but 10 of the data measured on 144 successive occasions in the patients taking valproate lay above the regression line of the controls, with a relatively wide scatter.

Figure 2 shows the unbound phenytoin concentration, measured in 19 patients in each group and plotted against the plasma total phenytoin; the regression line for both groups is combined (r=0·89). For the control group alone the coefficient of correlation was 0·94 and the slope (equal to the mean unbound fraction) 0·072. In the group taking valproate the coefficient of correlation was 0·91 and the slope and mean unbound fraction 0·10. When saliva and plasma unbound phenytoin concentrations were compared in these 38 patients (fig 3) the two groups clearly formed a single population and the correlation was higher (r=0·96). The slope (equivalent to the unbound to saliva ratio) was similar in the two groups (valproate group 0·62; control group 0·63).

As saliva was clearly an accurate predictor of unbound phenytoin we studied the effect of valproate concentrations on saliva to plasma ratios in the remainder of the study.

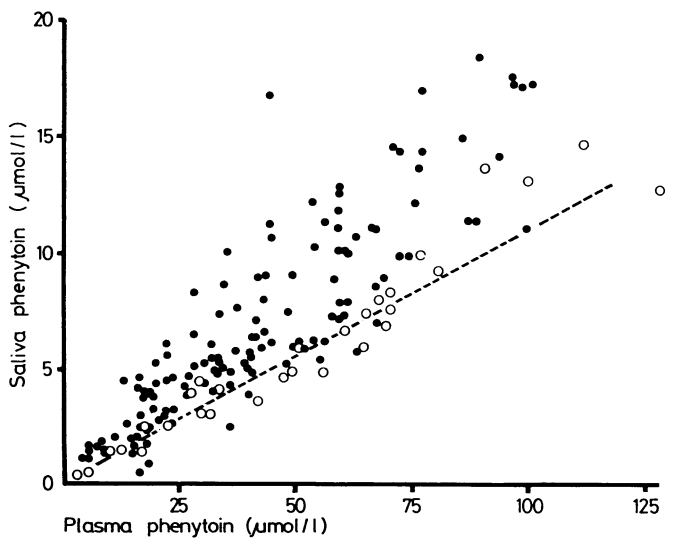

FIG 1—Relation between saliva and plasma phenytoin concentrations on 144 successive occasions in patients taking phenytoin and valproate (●) and in 31 controls (○) (r=0·94 in control group, and slope=0·11).
Conversion: SI to traditional units—Phenytoin: 1 μmol/l≈0·25 μg/ml.

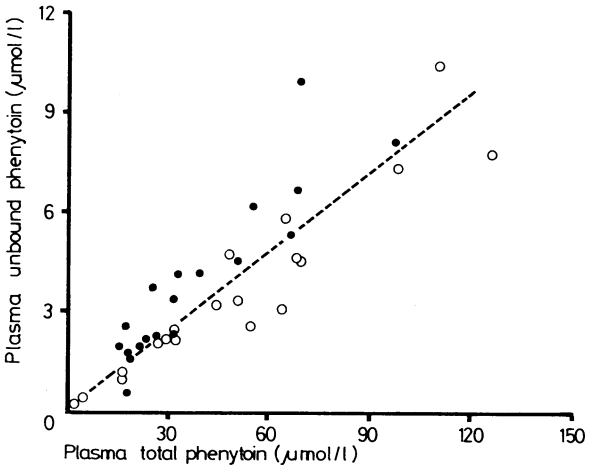

FIG 2—Relation between concentrations of plasma unbound phenytoin and plasma total phenytoin in patients taking valproate (●) and in controls (○). Single regression line shows poor fit to data, indicating that total plasma concentration of phenytoin cannot be used to predict unbound concentration.
Conversion: SI to traditional units—Phenytoin: 1 μmol/l≈0·25 μg/ml.

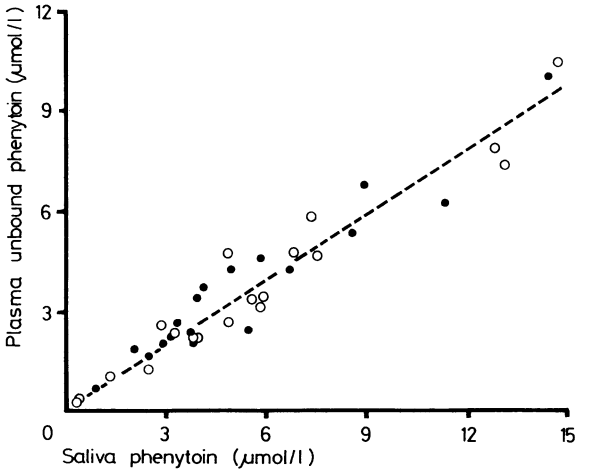

FIG 3—Relation between saliva and plasma unbound phenytoin concentrations in 19 patients taking valproate (●) and in 19 controls (○). Fit is better than in fig 2.
Conversion: SI to traditional units—Phenytoin: 1 μmol/l≈0·25 μg/ml.

Figure 4 plots the saliva to plasma ratio against the plasma valproate concentration. Though the correlation (r=0·54) was significant (p<0·001), it was too weak to predict phenytoin binding from the valproate concentration. The slope was 0·02/100 μmol/l of valproate concentration, and the intercept of 0·09—that is, the saliva to plasma ratio at zero valproate concentration—was consistent with the control data.

The in-vitro protein binding of phenytoin was 93·5±0·16% (n=13) in the absence of valproate, 83·5±2·6% (n=8) at a valproate concentration of 46 μmol/l (50 μg/ml), and 78·7±1·81% (n=13) at 692 μmol/l (100 μg/ml). This substantiated the in-vivo data.

Figure 5 presents data relating to two patients who were studied throughout the day. The increase in unbound phenytoin fraction with

increased plasma valproate concentration is shown clearly in each case. There was also a variation in unbound phenytoin concentration that did not follow an identical pattern since there was a small change in total plasma phenytoin concentration with gastrointestinal absorption of the drug. In patients taking phenytoin alone, binding varies by only about 2% daily (unpublished observation).

Phenytoin concentrations in 15 paired saliva specimens taken before and after venepuncture correlated closely ($r = 0.99$) with a slope of 1·03.

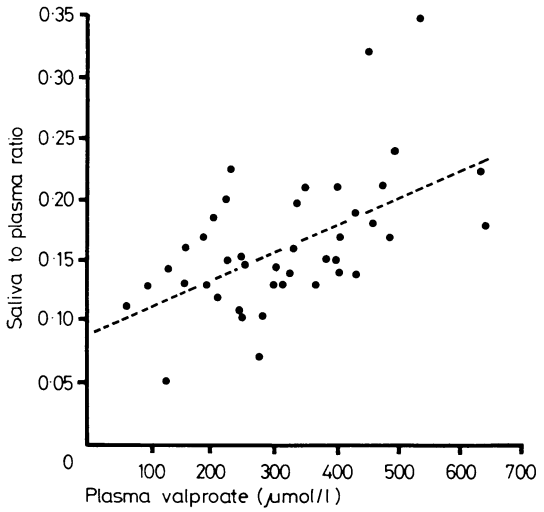

FIG 4—Relation between plasma valproate concentration and saliva to plasma phenytoin ratio in 42 patients taking valproate ($r = 0.54$ ($p < 0.001$); slope = 0·002).

Conversion: SI to traditional units—Valproate: 1 μmol/l ≈ 0·14 μg/ml.

Discussion

Monitoring plasma concentrations of phenytoin is widely advocated and practised, and the results are generally accompanied by a recommended therapeutic range. The curvilinear relation between steady-state plasma concentrations of phenytoin and daily dose, resulting from the Michaelis-Menten-like behaviour of the mixed-function oxidase system, is well established,[26-28] and the disproportionately large and highly variable increases in serum concentrations observed with small dose increments have stimulated numerous investigations aimed at defining the most accurate method of predicting dose requirements.[29 30] These methods commonly rely on measuring the total concentration of phenytoin in plasma and are therefore dependent on a constant degree of protein binding. When protein binding is depressed—for example, in uraemia,[15 31-33] hypoalbuminaemia,[34] pregnancy,[35] and infancy or in polypharmacy with other highly bound drugs—such methods of estimating phenytoin dose requirements are fallacious.

We have shown a depression of phenytoin binding in the presence of valproate which, though dependent on valproate concentration, cannot accurately be predicted from it. Saliva phenytoin concentration—unlike total plasma phenytoin—correlates closely with the plasma unbound concentration and bears the same close relation to it in the presence or absence of valproate (fig 3), so that the therapeutic range of 4-9 μmol/l (1-2 μg/ml) for saliva phenytoin is still valid. Out of a total of 144 estimations of phenytoin concentration in patients taking both drugs (fig 1) there were 27 in which saliva concentrations were above the optimum range while plasma concentrations were apparently optimum or even low, and 37 in which saliva concentrations were within our therapeutic range, whereas plasma concentration suggested the need for a dose increase. Dose adjustments according to the saliva concentrations were more clinically appropriate.

Saliva is quicker and cheaper to sample than plasma and, in our hands, more acceptable to most patients. Some workers find that assays of saliva yield inconsistent results using various sampling methods[36 37] and in one case three different assay techniques for saliva, plasma, and unbound phenytoin.[38] Our method of sampling after stimulation with citric acid, using the precautions described to avoid contamination, and analysing by gas chromatography with a nitrogen detector, yields results that are both reproducible and consistent. The absence of assay techniques sensitive enough to monitor saliva does not validate measurement of plasma concentrations in the presence of decreased phenytoin binding. More sensitive techniques, such as enzyme-linked immunoassay or gas chromatography with nitrogen detector, are readily available. Having carried out over 5000 saliva analyses, we are convinced of the clinical value of saliva sampling.

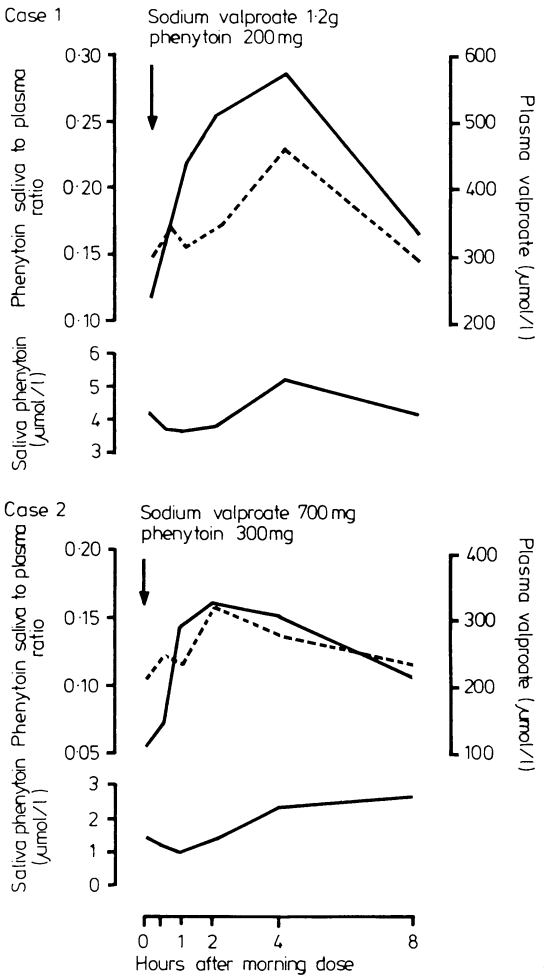

FIG 5—Phenytoin saliva to plasma ratio (dotted line), valproate concentration (continuous line), and saliva phenytoin concentration in two patients studied for eight hours after morning dose.

Conversion: SI to traditional units—Phenytoin: 1 μmol/l ≈ 0·25 μg/ml. Valproate: 1 μmol/l ≈ 0·14 μg/ml.

A further implication of this study is that hourly variations in plasma valproate concentration may result in fluctuation of free phenytoin in and out of the therapeutic range (fig 5). To minimise hourly variation in free phenytoin concentration, it appears that the daily valproate requirement should be taken in two or three divided doses despite a possible loss of compliance.[39]

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SHORT REPORTS

Intravenous amiodarone in atrial fibrillation complicating myocardial infarction

Oral amiodarone has been used as an effective treatment for atrial fibrillation. Intravenous amiodarone has recently become available in the United Kingdom on a named-patient basis, but its use in rapid control of atrial fibrillation has not been established. We report three cases of rapid, resistant atrial fibrillation associated with acute myocardial infarction in which intravenous amiodarone successfully controlled the heart rate.

Case reports

Case 1—A 63-year-old man with maturity-onset diabetes mellitus was admitted with an anterior myocardial infarction, complicated by left ventricular failure. Initially he responded to diuretic treatment but the next day developed atrial fibrillation with an apical rate of 160/min. Digoxin 0·75 mg was given intravenously but an hour later the pulse rate had not changed and he had become anuric. Amiodarone 350 mg was given intravenously over 10 minutes, and over the next 12 minutes the atrial fibrillation came under control, the apex rate being reduced to 75/min. Amiodarone was infused at a rate of 600 mg per 24 hours over the next 48 hours, and digoxin was continued by mouth. Subsequently the atrial fibrillation remained controlled with oral digoxin alone. Eleven days after admission he had a further infarction and died as a result of cardiogenic shock.

Case 2—A 57-year-old man was admitted with an anterior myocardial infarction. He had atrial fibrillation with a rate of 110/min and was hypertensive (blood pressure 190/120 mm Hg). After a nitroprusside infusion to control his blood pressure his pulse reverted to sinus rhythm and after 24 hours his blood pressure was controlled with oral prazosin. The next day he again developed atrial fibrillation with an apex rate of 170/min and his blood pressure dropped to 70/50 mm Hg. Cardioversion (200 joules) restored sinus rhythm, but reversion to rapid atrial fibrillation occurred within 10 minutes. Intravenous amiodarone was given (300 mg over 10 minutes), followed by infusion (600 mg over 24 hours) and then oral treatment (600 mg a day for the first week). He reverted to sinus rhythm within 10 minutes of the bolus dose. Over the next week he had further short runs of controlled atrial fibrillation but remained well and was discharged two weeks after admission.

Case 3—A 67-year-old hypertensive diabetic man was admitted with a right-sided hemiplegia. The next day he had a myocardial infarction and developed atrial fibrillation with an apex rate of 170/min. DC cardioversion (100 joules) resulted in temporary resumption of sinus rhythm, but within