Capecitabine–phenytoin interaction is dose dependent with an unexpected time course

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The main objective of this study was to further analyze the drug interaction between capecitabine and phenytoin with special emphasis on magnitude, timing, and the dose effect. A single patient had multiple phenytoin levels at various doses of capecitabine. Phenytoin levels were subjected to analysis of variance and the dose effect was approached using a multiple comparison test. All phenytoin levels meeting the criteria for steady state were subjected to box plot analysis. Analysis of 35 phenytoin levels over a 25-month period demonstrated a statistically significant interaction between the medications. The interaction onset was delayed by 4 weeks and persisted up to 9 weeks after capecitabine dose increases or decreases. The magnitude of interaction was directly proportional to the capecitabine dosage. We concluded that capecitabine caused a marked increase in phenytoin levels that was capecitine dose dependent, with a delayed time course not predicted by phenytoin kinetics, suggesting a novel interaction mechanism. The magnitude and complexity of this interaction suggest that alternate antiepileptic medications should be used in combination with capecitabine. *Anti-Cancer Drugs* 22:1027–1029 © 2011 Wolters Kluwer Health | Lippincott Williams & Wilkins.

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Introduction

Phenytoin has been used as an antiepileptic drug (AED) since 1938. Despite its complex pharmacokinetics with many drug–drug interactions, saturable metabolism, and high-protein binding, it remains one of the most commonly used AEDs in the USA [1]. Capecitabine is a carbamate derivative of 5′-doxifluridine that is metabolized to flurouracil, and has multiple indications for the treatment of primary and metastatic cancer. Several case reports have demonstrated increased levels of phenytoin when used in combination with capecitabine, but the interaction was not well described in terms of magnitude and timing and whether a dose effect was present [2–5].

We report a case in which phenytoin levels that had been stable for decades increased markedly in the presence of capecitabine. As the patient had well-controlled seizures for many years and was reluctant to change AED, we performed regular monitoring of phenytoin levels as part of routine clinical care and had an opportunity to observe the interaction over 18 months allowing more extensive characterization of the interaction, including timing and dose effects. Despite the extensive experience of one of the authors in phenytoin metabolism, the complex characteristics of this interaction caused multiple episodes of clinical toxicity [6,7].

Case history and methods

The patient is a 76-year-old, right-handed, white woman who is being followed up in our epilepsy clinic since 1989 for diagnosis of complex partial seizures related to stroke during pregnancy in 1969. She had been on a stable dose of phenytoin (range, 400–460 mg/day) since 1992, with a mean phenytoin level of 11 (range, 7.9–14.9 μg/ml) over a 19-year period. Seizures occurred in 2003 in the setting of sleep deprivation and phenytoin levels of 10–11 μg/ml. In 2006, she was diagnosed with breast cancer and underwent modified radical mastectomy and adjuvant radiotherapy. She received adjuvant chemotherapy consisting of four cycles of cyclophosphamide, doxorubicin, and taxotere. During this time, her phenytoin levels ranged from 8.1 to 14.3 μg/ml. In late 2007, she was found to have metastatic bone disease, and on 18 June 2008 capecitabine was initiated at a dose of 2000 mg/day, 2 weeks on and 2 weeks off. On 19 August 2008, the patient complained of increasing ataxia, falling, sedation, and fatigue. Her phenytoin level was 29.8 μg/ml, and a week later it was 37.8 μg/ml despite a reduction in phenytoin dose. At that time, her medications included multivitamin, glucosamine, capecitabine, hydrochlorothiazide, enalapril, naproxen sodium, levothyroxine, fulvestrant, and zolendronic acid. Of these, capecitabine, fulvestrant, and zolendronic acid were new prescriptions.

Phenytoin levels were frequently monitored, and phenytoin doses were adjusted, sometimes stopping phenytoin for days at a time, taking into account the saturable metabolism and variable time to steady state of PHT, attempting to target phenytoin levels in the 15–20 μg/ml range. This phenytoin range had produced an excellent seizure control and minimal adverse effects over the previous decade. During the time of observation, the patient also

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experienced adverse effects of capecitabine including skin changes of her hands and feet with cracking and bleeding, requiring several changes in capecitabine dose.

Phenytoin levels were included in the analysis if they were drawn at least 2 weeks after phenytoin dose change to assure attainment of phenytoin steady state. The timing and magnitude of all phenytoin and capecitabine dose changes were analyzed along with all qualifying phenytoin levels.

Analysis was performed to determine whether there was a clear interaction, whether the interaction was dependent on the dose of capecitabine, how rapidly the interaction appeared after dose changes of capecitabine, and whether the interaction involved protein-binding changes for phenytoin.

Results

A total of 167 levels were drawn over the 25-month period at various doses of phenytoin and capecitabine. Thirty-five phenytoin levels met the inclusion criteria. Table 1 shows the distribution of the steady-state levels of phenytoin according to the dose of capecitabine. Box plot analysis of the 35 steady-state levels did not indicate any dramatic outliers in the data set and suggests that the data are adequately distributed given the number of observations. As the doses of phenytoin were varied, a ratio of dose to phenytoin level was used as the comparison with capecitabine dose.

An analysis of variance to phenytoin dose/level ratio at the six different doses of capecitabine demonstrated that a statistically significant interaction was present and that the magnitude of this interaction was dependent on capecitabine dose ($P < 0.0001$). As such, 5000 mg of capecitabine resulted in higher phenytoin levels compared with lower doses (2000 mg). Interestingly, there was no significant difference in the magnitude of this interaction within the two highest dosages of capecitabine (5000 and 3500 mg).

An insufficient number of steady state phenytoin levels was available to perform a statistical analysis of the time delay of the interaction. However, there were several instances in which, after the initiation of capecitabine the phenytoin levels did not increase for almost a month. After the first administration of capecitabine, without a change in the phenytoin dose, the phenytoin level increased from 14.4 to 21 μg/ml in 8 weeks. By week 9, the PHT level had reached 29.8 μg/ml and caused substantial ataxia. When the capecitabine dose was reduced, a similar delay in the decrease of phenytoin levels occurred. Figure 1 shows how the phenytoin level decreased from 20.1 to 16.8 μg/ml, 1 month after capecitabine was discontinued, but then decreased more precipitously to 11.3 μg/ml over the next 6 weeks, all without a change in phenytoin dose. The timing of these changes in level is far beyond what would be predicted by phenytoin kinetics. Once capecitabine was discontinued completely, the patient's phenytoin levels decreased to her usual 15–20 μg/ml range and have remained at that level subsequently.

The patient's albumin levels and her total-to-free phenytoin ratio remained stable throughout the observation period, indicating that a variation in protein binding of phenytoin was not a factor in the interaction or adverse effects. Genotyping of the patient's CYP2C9 isoenzyme revealed that she carried an extensive metabolizer phenotype, suggesting that a genetic anomaly in the phenytoin-metabolizing enzymes would not explain the interaction seen.

Table 1 Distribution of phenytoin steady state levels according to capecitabine dose

Capecitabine dose	Number of phenytoin steady state levels	Mean phenytoin steady state level/ phenytoin dose[a]	Means with the same letter are not statistically different
5000	1	0.085500	A
3500	3	0.080000	A
2500	9	0.060111	B
2000	4	0.054250	B
200	7	0.035786	C
0	11	0.033859	C

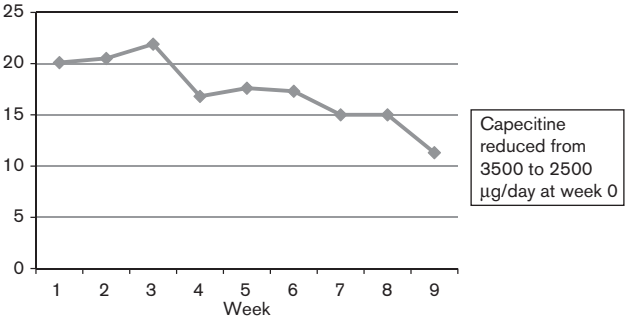
[a]Phenytoin level in micrograms/ml; phenytoin dose in milligrams/day.

Discussion

Our patient had an important drug–drug interaction in which the addition of capecitabine to a stable phenytoin dose caused inhibition of phenytoin metabolism in a manner that was dependent on capecitabine doses and had an unusual delayed time of onset for a typical hepatic enzyme inhibition interaction. This interaction caused substantial clinical toxicity, and was difficult to manage despite close monitoring of phenytoin levels and dose adjustments by a neurologist with extensive experience in phenytoin pharmacokinetics.

Statistical analysis of our extensive dose-level data allows us to confidently state that there is a drug–drug interaction present in our patient, and that it is dose dependent. This

Fig. 1



Timeline of phenytoin levels after a single capecitabine dose reduction.

is the first report of the dose dependence of the capecitabine–phenytoin interaction. Furthermore, the data suggest a substantial delay until this inhibition is at its maximum, also a new observation.

The source of the phenytoin–capecitabine interaction is believed to be inhibition of the CYP2C9 isoenzyme of the cytochrome p450 group of enzymes (the primary metabolic route of phenytoin) by capecitabine [8,9]. Although this may be true, the time delay evidenced in our patient points to an additional mechanism of interaction, because hepatic enzyme inhibition typically occurs over days [10]. One possibility is that low folic acid levels may inhibit the metabolism of phenytoin [11,12] and capecitabine has known antifolate activity [13,14]. It is possible that capecitabine interacts with phenytoin initially by inhibiting the CYP2C9 isoenzyme and a delayed interaction could be seen in susceptible patients by inhibition of folic acid activity. If this were true, folic acid supplementation would have reversed the observed inhibition to some extent. Unfortunately, this was not attempted in this case.

Plasma protein binding of capecitabine and its metabolites is reported to be lower than 60%, independent of dosage. Protein binding interactions did not appear to contribute to the problems in this patient because the ratio of total and free serum phenytoin levels remained relatively stable irrespective of capecitabine dosage changes.

Our study had important limitations. Although we report the most extensive analysis of the phenytoin and capecitabine interaction, our findings remain limited to one patient and may not be generalizable. The mechanism of this drug–drug interaction remains speculative in this case. Our patient had two other new medications started along with capecitabine: fulvestrant and zolendronic acid. Both have no reported interaction with phenytoin, and remained unchanged during the time frame presented. Finally, adherence to medication was not rigorously assessed, but the patient has steady drug levels over the last 21 years of clinical follow-up and analysis of these data did not reveal any outlying levels making significant nonadherence unlikely.

The magnitude and complexity of this interaction led to clinical toxicity on several occasions over the treatment period, despite frequent phenytoin levels and rigorous attempts to adjust phenytoin doses according to known phenytoin kinetic parameters. From a clinical perspective, these findings suggest that, if at all possible, alternative AEDs should be considered in a patient in whom capecitabline is indicated. If the two drugs must be used together, frequent monitoring of phenytoin levels is necessary, because changes in phenytoin levels beyond the usual time course predicted by phenytoin kinetics occur.

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Conflicts of interest

There are no conflicts of interest.

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