CASE REPORT / ÉTUDE DE CAS

Probable Phenytoin — Dexamethasone Interaction: A Case Report of Subtherapeutic Phenytoin Concentrations

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INTRODUCTION

Phenytoin and dexamethasone are often given to patients with brain tumours or those who undergo neurosurgical procedures. Serum phenytoin concentrations assist in guiding therapy and avoiding toxicity.[1] Literature on phenytoin-dexamethasone interactions describing changes in phenytoin concentrations is scant. Increased and decreased phenytoin serum concentrations have resulted from concurrent dexamethasone therapy.[2–6] This case illustrates a probable phenytoin–dexamethasone interaction resulting in subtherapeutic phenytoin serum concentrations in a previously stable patient.

CASE

A seven year old boy (14.8 kg) diagnosed with anaplastic astrocytoma four months prior to admission presented with chronic vomiting and intermittent

headaches. Medications on admission were phenytoin suspension (Dilantin®) 75 mg po tid (15 mg/kg/day) and oral nystatin. The recommended initial phenytoin maintenance dose for children is 5–6 mg/kg/day.[7] The patient was prescribed dexamethasone after his initial diagnosis, but was not receiving it on admission. A trough phenytoin serum concentration the day of admission was 90 µmol/L (accepted therapeutic range = 40–80 µmol/L) so phenytoin was held. On day 2, sixteen hours after the initial concentration, the phenytoin serum concentration was 37 µmol/L. As well, on day 2 of admission ranitidine 25 mg po q12h and total parenteral nutrition were added to the patient's regimen. Dexamethasone 2 mg po q6h was prescribed for cerebral edema noted on head CT scan. Phenytoin suspension was reinitiated at 60 mg po q8h (12 mg/kg/day), twenty-five hours after the initial phenytoin serum concentration was obtained. On day 5, the trough phenytoin serum concentration was 15 µmol/L. The phenytoin dose was increased to 70 mg po tid (14.2 mg/kg/day) on day 6. On day 9, the trough phenytoin concentration was 28 µmol/L. The phenytoin dose remained unchanged. The patient was discharged on day 17 with phenytoin 75 mg po q8h, dexamethasone 2 mg po q6h, and newly started enteral feeds by gastro-jejunal (GJ) tube. Figure 1 summarizes the phenytoin doses and concentrations in hospital. Phenytoin suspension continued to be given by mouth to avoid adsorption to the GJ tube. Administration of the dose one hour prior to or two hours after feeds was recommended in the patient's chart. No seizure activity was noted during the admission. Intermittent vomiting related to increased intracranial pressure persisted which was controlled with dexamethasone. Albumin values on days 2, 6, and 16 ranged from 34–35 g/L (normal = 33–58 g/L). Serum creatinine (normal <70 µmol/L) on days 1, 2, and 6 ranged from 24–30 µmol/L.

DISCUSSION

Possible explanations for phenytoin concentration changes in our patient include: incorrect drug administration technique, drug-food interaction, drug-disease interaction, drug-drug interaction, and laboratory error. Phenytoin suspension requires thorough shaking prior to administration to ensure consistent dosing. The bioavailability of the oral suspension may differ from other dosage forms.[1] G-tube administration of phenytoin suspension requires flushing to prevent binding of phenytoin to enteral feeding tubes. Chronic vomiting may interfere with absorption. Further, enteral feeds may alter phenytoin bioavailability, which necessitates spacing of feeds and phenytoin.[1,8]

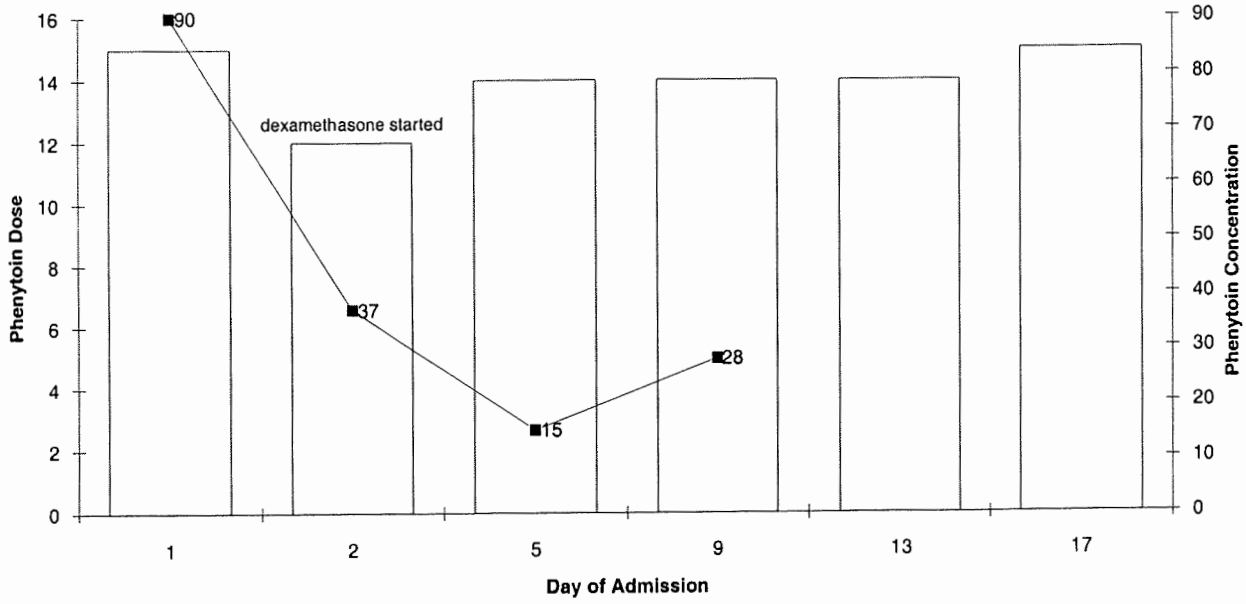
Disease states (i.e. renal or hepatic disease) affecting plasma protein binding alter total phenytoin concentration.[1,9] Decreased protein binding causes higher unbound phenytoin concentrations which necessitate phenytoin dose reductions. Critically ill patients with traumatic head injuries may have increased phenytoin clearance due to changes in protein binding or induced metabolism.[10] Febrile illnesses may also increase phenytoin metabolism.[11]

Drug interactions have been reported between phenytoin and charcoal, antacids, sucralfate, theophylline, and antineoplastic drugs.[9] Drugs which alter plasma protein binding may decrease total phenytoin concentration,[1,9] and increased phenytoin metabolism due to autoinduction is possible.[12] Drugs reported to induce phenytoin metabolism include: carbamazepine, dexamethasone, diazepam, alcohol, folic acid, nitrofurantoin, phenobarbital, and rifampin. Case reports suggest that ranitidine may increase phenytoin concentrations in a small subset of people.[13] Dexamethasone has been reported to increase[2] and decrease[3–6] phenytoin concentrations. While the mechanism of the interaction has not been fully elucidated, there is evidence that dexamethasone can enhance the hepatic clearance[4] of phenytoin.

The patient received the suspension formulation of phenytoin since diagnosis and the patient's care-giver shook the suspension adequately. On admission, the patient was malnourished and had been vomiting, so a GJ tube was placed on day 13. Nutritional supplements started day 14 and continued after discharge. Phenytoin adsorption to GJ tubing was avoided by using the oral route for phenytoin. When the subtherapeutic phenytoin concentration was reported, our patient was clinically stable. No febrile episodes were reported during the admission. Liver enzymes, serum albumin, and creatinine remained within normal ranges. The high phenytoin concentration on admission precludes the likelihood of autoinduction. Ranitidine was started on day 2, but a drug interaction between ranitidine and phenytoin was not apparent. Of the possible interacting drugs, only dexamethasone was administered concurrently and could explain the change in serum concentrations.

There have been few reports of the phenytoin–dexamethasone interaction in the literature. Wong et al[3] reviewed six patients receiving phenytoin in a

Figure 1: Phenytoin Dose vs. Serum Concentration



retrospective study. Serum phenytoin concentrations decreased by 50% when dexamethasone therapy (doses unknown) was added ($p<0.05$). Phenytoin doses remained constant. Lackner[4] described a case report of a 46 year old patient who required a daily phenytoin dose of greater than 10 mg/kg during concurrent treatment with dexamethasone to maintain therapeutic phenytoin concentrations. Discontinuation of dexamethasone resulted in an almost 300% increase in phenytoin concentrations. Recuenco et al.[6] described phenytoin requirements in a metastatic lung cancer patient. Phenytoin doses up to 1 g/day (14 mg/kg/day) were required to achieve therapeutic phenytoin concentrations and adequate seizure control during concurrent dexamethasone therapy. The authors noted that increasing dexamethasone doses were required to maintain adequate intracranial pressure as phenytoin doses were increased and hypothesized that each of the drugs induced the metabolism of the other. In another case report, Gattis and May[5] describe a patient with a seizure disorder secondary to malignant melanoma. The patient received phenytoin with dexamethasone after receiving antineoplastic therapy. Inadequate seizure control and subtherapeutic phenytoin concentrations were noted with phenytoin doses of up to 550 mg/day (7.4 mg/kg/day). Possible mechanisms for subtherapeutic phenytoin concentrations suggested by the authors include decreased absorption due to antineoplastic agent-induced gastrointestinal toxicity, and increased metabolism secondary to dexamethasone or antineoplastic therapy. The patient received chemotherapy (carmustine, cisplatin) one month prior to phenytoin. However, gastrointestinal toxicity was ruled out since it usually occurs two to fourteen days after chemotherapy. Cisplatin–induced metabolism was considered remotely possible due to persistence of cisplatin in the tissues. A more likely explanation was felt to be either the phenytoin–dexamethasone interaction or that the patient fell outside the predicted pharmacokinetic model for phenytoin.

Conversely, higher phenytoin concentrations have been described in patients concurrently receiving dexamethasone and phenytoin. In a retrospective chart review using predetermined criteria (unspecified), Lawson et al.[2] describe 38 patients in whom concurrent dexamethasone therapy resulted in higher phenytoin concentrations measured 24 hours after a loading dose.

As part of a study protocol, patients received a combination phenytoin loading dose of 11 mg/kg given intravenously and 13 mg/kg given intramuscularly. Mean phenytoin concentrations in 23 patients treated with both phenytoin and dexamethasone were 68 ± 14 μmol/L. This concentration was significantly higher than the concentrations (49 ± 14 μmol/L) of 15 patients who did not receive dexamethasone concurrently ($p < 0.001$). The mechanism suggested for the interaction was competition for hydroxylation via liver microsomal enzymes.

Previously, our patient had received concurrent phenytoin and dexamethasone therapy. Unfortunately, serum phenytoin concentrations were not documented. The child presented with a phenytoin level of 90 μmol/L and was not receiving dexamethasone. It is possible the supratherapeutic level resulted from recent discontinuation of dexamethasone. Phenytoin was reinstituted at 12 mg/kg/day after the concentration fell to 37 μmol/L. Commencement of dexamethasone therapy coincided with subtherapeutic phenytoin concentrations despite increasing the phenytoin dosage to 14 mg/kg/day. An accurate Vmax and Km could not be calculated, however the low serum concentration and age of the child would suggest that the value of 28 μmol/L on day 4 of the new dose (70 mg tid) fairly represents a new steady-state concentration. To complicate the situation further, the patient was started on enteral feeds just prior to discharge and was to be followed as an outpatient by the neurology clinic. During subsequent admissions, phenytoin concentrations were subtherapeutic, but could be explained by vomiting prior to admission. Temporal and dose relationships between phenytoin and dexamethasone administration could not be assessed. The patient died two years after the initial diagnosis.

CONCLUSION

The subtherapeutic phenytoin concentrations in this patient cannot be unequivocally attributed to concurrent dexamethasone therapy, however other possible explanations seem unlikely. Therefore, it appears that a meaningful drug–drug interaction does exist between dexamethasone and phenytoin, resulting in subtherapeutic phenytoin concentrations.

Phenytoin concentrations should be monitored carefully, especially upon the addition or discontinuation of dexamethasone therapy. Further studies are essential to document and clarify the nature and mechanism of the interaction between dexamethasone and phenytoin.

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