Apparently normal phenytoin metabolism in a patient with phenytoin-induced rash and lymphadenopathy

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A 10-year old female on phenytoin therapy developed a rash and lymphadenopathy. H.p.l.c. assays of urinary metabolites indicated no differences in stereoselective metabolism of phenytoin to phenolic and dihydrodiol metabolites as compared with volunteers given the drug or with pediatric patients without adverse reactions. This suggests that no obvious difference in stereoselective metabolism of phenytoin to potentially toxic arene oxides exists between this patient and other patients on phenytoin. Our results are consistent with the hypothesis that differences in peripheral detoxication of phenytoin arene oxides and not differences in hepatic metabolism of phenytoin may be responsible for such adverse reactions.

Keywords adverse reaction phenytoin stereoselective metabolism arene oxides

Introduction

Some adverse reactions to many drugs are presumed to be as a result of metabolism to toxic intermediates with subsequent covalent binding of such intermediates to key cellular nucleophiles, a process that subsequently results in cell death or toxicity (Jerina & Daly, 1974). The development of many adverse reactions to phenytoin, a widely-used antiepileptic, has been assumed to be a result of tissue binding of phenytoin arene oxide[s]. A similar process is considered to be the cause of teratogenesis in an animal model (Martz *et al.*, 1977), and of *in vitro* responses of human lymphocytes from patients with other toxic reactions to the drug (Spielberg *et al.*, 1981a, 1981b; Gerson *et al.*, 1983).

Phenytoin [5,5-diphenylhydantoin] metabolism via arene oxide[s] is well documented, although the isolation of such reactive arene oxides has not yet proved possible. The prochiral phenytoin molecule is stereoselectively metabolized to enantiomeric phenol [5-[4-hydroxyphenyl]-5-phenylhydantoin, *p*-HPPH] and dia-

stereomeric dihydrodiol [5-[3,4-dihydroxy-1, 5-cyclohexadien-1-yl]-5-phenylhydantoin, DHD] metabolites, both of which are derived from the corresponding isomeric arene oxides, [S]- and [R]-AO (Figure 1). It could be argued that development of some adverse reactions to phenytoin might be a result of stereoselective production of different amounts of the isomeric arene oxides (Figure 1), a situation that could expose an individual to greater levels of a potentially more toxic arene oxide isomer. With the development of methods to study isomeric composition of *p*-HPPH and DHD metabolites, estimates of stereoselective arene oxide production can now be made. We here describe the use of such methods in the study of one case of an adverse reaction.

Case report

The patient was a 10-year old girl with type I diabetes that was well controlled with insulin

Figure 1 Stereoselective metabolic pathways of phenytoin to arene oxide (AO), dihydrodiol (DHD), and phenolic (*p*-HPPH) metabolites.

injections twice daily. Seizures with symptoms indicating epilepsy of psychomotor type presented in January 1983. EEG was initially normal as was the neurological examination. She was treated with carbamazepine 100 mg twice daily ($6 \text{ mg kg}^{-1} \text{ body weight day}^{-1}$). After 11 days the patient displayed symptoms suggestive of drug allergy: redness on the cheeks, enlarged lymph nodes on the neck, and ache on opening the mouth. Three days later, 14 days after start of therapy, the girl displayed an urticarial rash on the face and on the body, particularly on the proximal parts of the extremities. She also complained of headache. Her haemoglobin was normal while the thrombocytes were only $95,000/\text{mm}^3$ and the white blood count was $3600/\text{mm}^3$. Carbamazepine treatment was discontinued and 1 week later her clinical status and blood data were normal. After another week, carbamazepine treatment, 50 mg twice daily, was attempted again. This time the patient reacted with rash, redness on the cheeks, and headache within 1 day after restarting the treatment. Carbamazepine was therefore discontinued and the patient continued to have seizures that included amnesia, absent mindedness, flexion of the arms, oral automatism, guttural sounds, and a tendency to fall.

On April 28 phenytoin 100 mg twice daily ($6 \text{ mg kg}^{-1} \text{ day}^{-1}$) was started. Eleven days later the patient displayed enlarged lymph nodes bilaterally on the neck and in the axillae. The liver and spleen were normal. The patient also

had redness on her cheeks with an urticarial rash. Blood chemistry data were normal including complete blood count, electrophoresis, serum creatinine, ANF, and liver enzymes. The drug was discontinued 1 day after presentation of the exanthem. One day after phenytoin discontinuation blood samples were drawn and urine samples collected such that phenytoin and its metabolites could be analyzed.

Repeat EEG after 6 weeks showed sporadic frontotemporal dysrhythmia. Six months after presentation of the symptoms the patient was treated with valproic acid 300 mg twice daily ($18 \text{ mg kg}^{-1} \text{ day}^{-1}$). This drug was effective and the patient has continued to take valproic acid for at least 2 years without seizures. Her diabetes has also been well controlled on diet, regular physical activities and three daily injections of insulin.

Methods

Plasma samples were assayed for phenytoin concentration by the Epilepsy and Anticonvulsant Drug Research Laboratory of the University of North Carolina with the use of an on-column methylation gas chromatographic assay (Dudley *et al.*, 1977). Urine samples were assayed for total DHD and *p*-HPPH content by the method of Maguire *et al.* (1979). Subsequently, urine samples were incubated with β -glucuronidase and DHD and *p*-HPPH fractions were collected according to the method described for assay of DHD diastereomeric content by reverse-phase h.p.l.c. (Maguire & Wilson, 1985). Fractions of urinary *p*-HPPH so collected were further assayed for enantiomeric content on a chiral β -cyclodextrin h.p.l.c. column (McClanahan & Maguire, 1986).

Results

Based upon assays of five plasma samples (9 to $4 \mu\text{g ml}^{-1}$ range), log-linear phenytoin kinetics appeared to be followed, and an apparent plasma terminal half-life ($t_{1/2,z}$) was calculated (Least squares analysis, $r^2 = 0.94$) to be 16.4 h. Assays of the three sequential 12 h urine samples for DHD and *p*-HPPH content gave DHD/*p*-HPPH molar ratios of 0.13, 0.11, and 0.12. Urinary DHD diastereomeric content varied from 71 to 75% [S]-DHD, with a mean value of 72% [S]-. Enantiomeric content of urinary *p*-HPPH in the three samples varied from 95 to 97% [S]-, with a mean value of 96% [S]-. No definitive evidence of temporal changes in metabolite molar ratio or stereoselectivity for either DHD or *p*-HPPH was observed in the sequential urine samples.

Discussion

The molar ratios of DHD/*p*-HPPH urinary metabolites observed following the last dose of the drug were consistent with values previously observed in other phenytoin patients (Maguire *et al.*, 1979), and offered no indication of any abnormal metabolism. The average stereochemical compositions of 72% [S]- and 96% [S]- for DHD and *p*-HPPH metabolites were consistent with values (77% [S]-DHD and 94% [S]-*p*-HPPH, see Figure 1) previously observed in urines from nine volunteers given phenytoin (Steiner *et al.*, 1987), and also with average values (74% [S]-DHD and 89% [S]-*p*-HPPH) in a group of nine pediatric patients treated with phenytoin, yet not experiencing adverse reactions (Maguire & McClanahan, 1986). Similarly, this patient's apparent log-linear elimination of phenytoin allowed calculation of a plasma $t_{1/2}$ of 16.4 h. While this parameter may not be valid at higher or lower phenytoin concentrations, it does suggest that this patient's metabolism is similar to apparent plasma half-lives reported in the literature (Woodbury, 1982). All of this evidence argues against changes in stereoselective metabolism in this adverse reaction patient.

The *in vitro* studies of Spielberg *et al.* (1981a, 1981b) and Gerson *et al.* (1983) involved incubation of phenytoin, a microsomal system, and lymphocytes from control individuals and patients experiencing various toxic reactions to phenytoin. Patients' cells showed higher mortality than controls, although both types of cells were exposed to the same variety and isomeric con-

tent of phenytoin metabolites generated by the microsomes. Such evidence is consistent with the hypothesis that lymphocytes of susceptible individuals are deficient in enzyme systems that detoxify arene oxides. These systems include membrane-bound and soluble epoxide hydrolases which may vary 2.5 to 5-fold (Seidegård *et al.*, 1984a). The soluble glutathione S-transferase system is also responsible for epoxide detoxication and has been found to vary 15-fold between individuals (Seidegård *et al.*, 1984b). This variation has been ascribed to the presence of genetically determined variation in isozymes[s] (Seidegård *et al.*, 1985).

Our results in this one adverse reaction case suggest that the majority of hepatic phenytoin stereoselective metabolism, as judged by urinary metabolites, is very similar to that observed in volunteers and patients. We therefore hypothesize that the detoxification of reactive intermediates of phenytoin was deficient in specific target cells/organs of this individual. Whether this explanation will remain plausible following further such studies of other adverse reaction cases remains to be seen.

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