

Background for Health Care Provider:

Phenytoin is slowly but almost completely absorbed, and it is approximately 90% protein bound in plasma. Phenytoin undergoes extensive metabolism with less than 5% of the dose excreted unchanged in urine. It is also extensively metabolized by the cytochrome P450 isoforms CYP2C9 and CYP2C19.

Many drugs have been reported to interact with phenytoin, resulting in lack of effectiveness or side effects from phenytoin or the other drug it is reacting with. Most of these drug interactions involve the inhibition of its biotransformation or alterations of its protein binding. Phenytoin is also a very potent broad spectrum inducer of the metabolism of various compounds.

Other drugs that are also protein bound can displace phenytoin from its binding site. This interaction is not expected to modify the pharmacologic effect of phenytoin, but these interactions should be considered when interpreting total serum phenytoin concentrations. It has been shown that in the presence of a displacing agent, therapeutic and toxic effects are expected to occur at total serum phenytoin concentrations lower than usual.

Since phenytoin is extensively metabolized, most of its drug interactions have been shown to occur due to changes in metabolism. Phenytoin induces many CYP450 enzymes, which could cause decreased blood levels for drugs metabolized by enzymes in the liver. Drugs that inhibit CYP2C9 and CYP2C19 have been shown to increase blood levels of phenytoin while those that induce these CYP enzymes have been shown to decrease phenytoin blood levels. Both of the CYP450s that are responsible for metabolizing phenytoin are expressed polymorphically in humans and genetic defects in expression of these could cause toxicity in these patients with normal phenytoin doses.

Effect of Other Drugs on Phenytoin Serum Levels:

Decrease Phenytoin Serum Levels:

- Antacids
- Charcoal
- Diazoxide
- Primidone
- Pyridoxine
- Rifampin
- Sucralfate

Increase Phenytoin Serum Levels:

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| • Allopurinol | • Ibuprofen |
| • Amiodorone | • Isoniazid |
| • Carmustine | • Methotrexate |
| • Chloramphenicol | • Nifedipine |
| • Chlordiazepoxide | • Omeprazole |
| • Chlorpheniramine | • Phenylbutazone |
| • Cimetidine | • Salicylates |
| • Clarithromycin | • Sulfamethizole |
| • Dexamethasone | • Ticlopidine |
| • Dicumarol | • Trimethoprim |
| • Disulfiram | • Tolbutamide |
| • Felbamate | • Valproic acid |
| • Fluconazole | (unbound phenytoin levels) |
| • Fluoxetine | |

Effect of Phenytoin on Other Drugs' Serum Levels:

Increase Other Drug Serum Levels:

- No known clinically significant interactions

Decrease Other Drug Serum Levels:

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| • Acetaminophen | • Methadone |
| • Chloramphenicol | • Mexiletine |
| • Cyclophosphamide | • Misonidazole |
| • Cyclosporine | • Oral Contraceptives |
| • Dicumarol | • Praziquantel |
| • Digitoxin | • Prednisone/Prednisolone |
| • Digoxin | • Quetiapine |
| • Doxycycline | • Quinidine |
| • Furosemide | • Theophylline |
| • Intraconazole | • Vecuronium |
| • Meperidine | |

Variable effects on Serum Levels:

- Carbamazepine
- Diazepam
- Warfarin (induction and inhibition possible)

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