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Colonic Absorption of Antiepileptic Agents

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Summary: *Purpose:* To evaluate a canine intestinal access-port model to study colonic absorption of drugs. The antiepileptic drugs phenytoin and gabapentin were chosen to study absorption of a lipophilic and hydrophilic compound, respectively.

Methods: Drug plasma level–time plots were generated subsequent to small intestinal and colonic drug administration of both drugs. The poorly water-soluble phenytoin was administered in two doses to evaluate the impact of dissolution rate limits on colonic absorption. Maximal plasma concentration (C_{max}) and area under the plasma level–time curve (AUC) were used to assess the relative contribution of colonic absorption to plasma levels.

Results: Whereas colonic gabapentin AUC and C_{max} were only 0.25 and 0.15 of those seen after small intestinal administration, colonic phenytoin AUC and C_{max} were one half and equivalent to, respectively, those observed for small intestinal administration. Furthermore, colonic administration of a higher phenytoin dose showed secondary maxima and continued increases in drug plasma levels with time.

Conclusions: Colonic gabapentin absorption is poor compared with upper intestinal absorption, consistent with membrane transport rate limits to the absorption of this hydrophilic AED. Peak phenytoin plasma levels from colonic and small intestinal administration are comparable, indicating membrane transport does not limit absorption of this lipophilic agent. Continued plasma-level increases from higher phenytoin doses are consistent with dissolution-rate control of drug absorption in the colon. We suggest that colonic absorption provides a greater potential for toxicity from phenytoin overdose as a function of continued drug dissolution than for gabapentin overdose. **Key Words:** Gabapentin—Phenytoin—Toxicity—Colonic absorption.

Massive overdose cases have been reported (1,2) for the antiepileptic agents (AEDs) carbamazepine and phenytoin. Both of these agents are poorly water soluble (3,4), and their intestinal absorption is dissolution-rate controlled at typical oral doses. The case reports for carbamazepine overdose (1) suggested that the presence of insoluble drug coagulum in the gastrointestinal tract may have been responsible for the maintenance of toxic plasma levels of carbamazepine and its metabolites over a 3-day period. In the case of the phenytoin overdose (2), a zero-order absorption process was observed to maintain toxic plasma levels of the drug for a 12-day period. This zero-order absorption process is consistent with continued dissolution of undissolved phenytoin controlling drug absorption at a constant rate fixed by aqueous solubility.

In each of these cases, patients were reported to be comatose, and adequate time for undissolved drug to reach the lower bowel had been achieved. Thus continued dissolution with subsequent absorption of drug from the large intestine could result in sustaining plasma levels in the toxic range. As permeation of these lipophilic molecules across intestinal membranes is not rate limiting to absorption, continued absorption provided by dissolution in the lower intestine is ensured.

A number of oral-delivery systems have been designed for site-specific release of drug in the large intestine (5). We have used a long-term canine colonic-absorption model to study the potential for oral delivery of peptide drugs subject to degradation by proteolytic enzymes in the upper gastrointestinal tract (6). Upper and lower intestinal access ports permit delivery of drug directly into the small intestine and colon so that site-specific absorption can be studied uncoupled from dosage-form release. Drug plasma level pharmacokinetics are assessed to permit a comparison of drug absorption from small intestinal and colonic administration. In the initial development of this animal model to study peptide absorption, the colonic absorption of lipophilic and hydrophilic AEDs, phenytoin and gabapentin, respectively, were used to test the access-port system in a single dog. Although there was no intent systematically to evaluate

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the absorption of these agents in this model, the results with these test compounds may be of clinical relevance.

Phenytoin and gabapentin are cleared more rapidly in dogs than in humans. Phenytoin's short elimination half-life in dogs results from a high capacity metahydoxylation pathway in the liver (7). Gabapentin is *N*-methylated in dogs, whereas it is not metabolized in other species (8). Elimination half-life for both drugs is 2–4 h in dogs (7,8), which is in the range of intestinal residence time. This dictates that changes in intestinal absorption will influence substantial control of drug plasma levels from oral and small intestinal dosing in dogs. Lengthy dissolution times for high doses of phenytoin in the colon will control absorption rate and in turn affect drug plasma-level kinetics.

METHODS

Vascular access ports (Access Technologies, Skokie, IL, U.S.A.) were surgically implanted to empty into the small intestine (40 cm distal to the pylorus) and colon (10 cm distal to the ileocecal junction) with external access from a syringe port in the animal's back. Phenytoin was administered as Parke Davis Dilantin Suspension, 25 mg/ml, at doses of 300 mg/12 ml in the small intestine and colon and 600 mg/24 ml in the colon. Gabapentin (also provided by Warner Lambert/Parke Davis) was administered as a 200 mg/10 ml dose in solution in normal saline. Access-port tubing was flushed with normal saline to ensure complete administration of the drug dose. Phenytoin administration was carried out initially with a washout period of $\geq$1 week between treatments. The 600-mg colonic dose was the last of these three studies. Gabapentin administration was carried out several months later with a washout period of $\geq$1 week between treatments.

High-performance liquid chromatography (HPLC) plasma assays for gabapentin (8) and phenytoin (9) were used as previously reported. Phenytoin plasma samples were extracted with ethyl ether, dried under nitrogen, and reconstituted with mobile phase after addition of methyl phenylhydantoin as an internal standard. The five standard concentrations used covered experimental plasma-level concentration ranges, and between-day precisions were between 3.2 and 7.8%. The minimal level of detection for phenytoin was 0.025 mg/ml. Gabapentin plasma samples were mixed with equal volumes of 5% trintrobenzene sulfonic acid and 6N hydrochloric acid, half saturated with sodium chloride, extracted with cyclohexane, evaporated to dryness, and reconstituted with a 10% aqueous ethanol mobile phase after addition of cyclopentane acetic acid monohydrochloride as an internal standard. Five standard concentrations covered experimental plasma-level concentration ranges, and between-day precisions were between 0.8 and 6%. The minimum level of gabapentin detection also was 0.025 mg/ml. The HPLC system consisted of a Spectroflow 773 absorbance detector, a Waters 501 HPLC pump, and a Waters 710B WISP autoinjector. Samples were injected onto a LiChrosorb RP-18 column at a flow rate of 1.2 ml/min and analyzed at an absorbance of 228 nm for phenytoin and at a flow rate of 0.9 ml/min and absorbance of 335 nm for gabapentin.

RESULTS

Drug plasma levels and pharmacokinetic parameters (C_{max}, peak plasma levels, and AUC, area under the plasma level–time curve) from oral, upper intestinal, and colonic administration of 200-mg gabapentin are shown in Fig. 1 and Table 1, respectively. Comparison of the blood-level data from oral and jejunal administration of gabapentin indicates that there is substantial absorption from the duodenum and upper jejunum. Most important, gabapentin plasma levels from colonic administration are substantially lower than those obtained from oral and upper intestinal administration (Fig. 1 and Table 1).

Drug-plasma levels and pharmacokinetic parameters from upper intestinal administration of 300 mg and colonic administration of 300 mg and 600 mg of phenytoin are shown in Fig. 2 and Table 1, respectively. Peak plasma levels from colonic administration are in a range similar to those obtained from small intestinal administration of 300 mg phenytoin. Oral administration of phenytoin was not carried out in this study. However, a comparison of plasma levels from oral and intestinal phenytoin administration with a much higher volume load in a previous fasted- versus fed-state study (10) yielded comparable peak drug-plasma levels from the two administration sites in the fasted state.

Phenytoin plasma levels from colonic administration of 600 mg phenytoin mirror 300-mg levels to 4 h. However, drug-plasma levels are observed to increase further from 4 to 8 h, suggesting that continued dissolution of phenytoin in the colon provides continued drug absorption (Fig. 2 and Table 1).

DISCUSSION

Small intestinal absorption of gabapentin is postulated to include a carrier-mediated (neutral amino acid transport) system (11) in parallel with a nonsaturable pathway. The presence of amino acid carriers and a leaky nonsaturable paracellular pathway in the upper small intestine may contribute to the rapid upper intestinal absorption of gabapentin observed when gabapentin was administered orally compared with intestinal and colonic administration. The absence of amino acid carriers in the colon combines with a more restricted paracellular pathway to limit colonic absorption of this hydrophilic drug. Gabapentin absorption from the colon is further re-

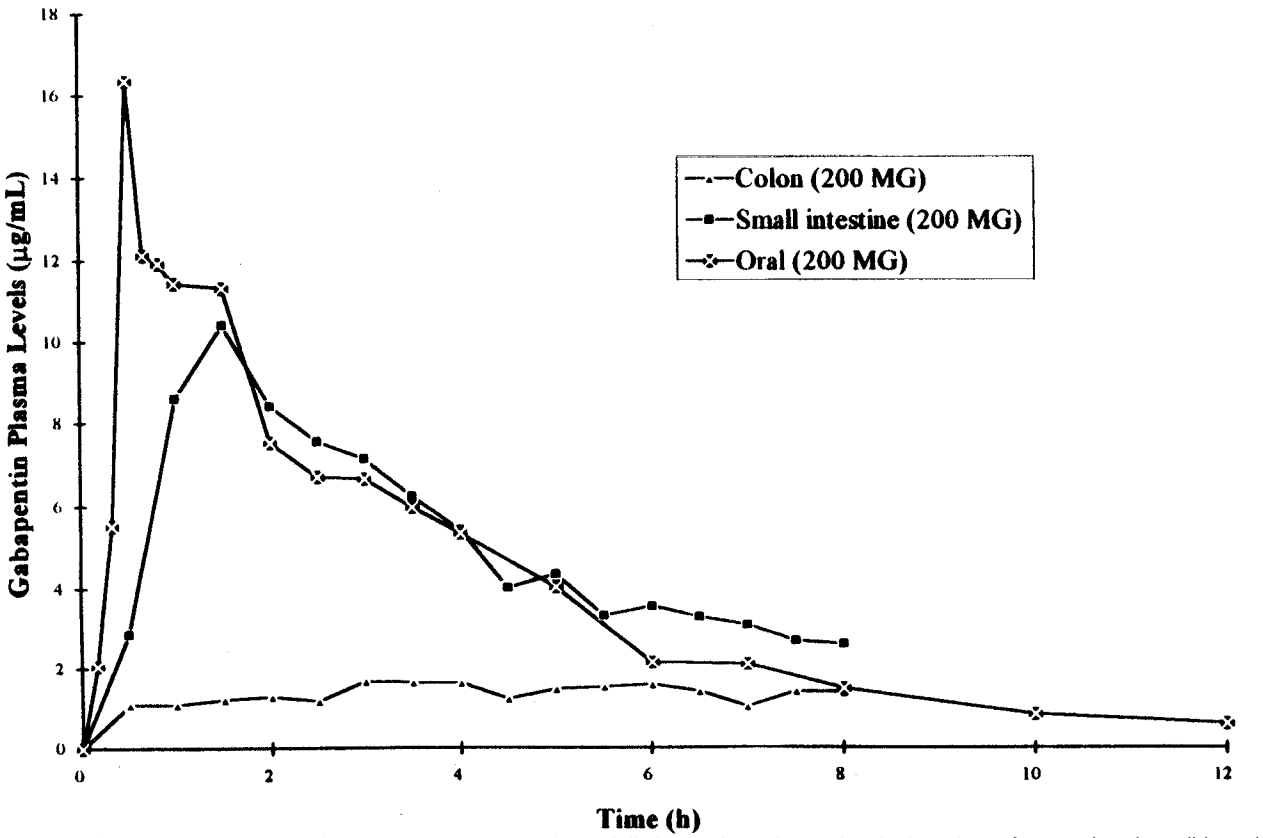

FIG. 1. Colonic administration of gabapentin provides substantially lower drug-plasma levels than those from oral and small intestinal administration of an equivalent dose.

stricted by lipid-membrane permeation. Based on a log octanol–water partition coefficient of −1.1 (8), colonic absorption of this zwitterionic drug should be minimal. Increasing the oral dose of gabapentin has been shown to result in a decreased fraction of absorbed dose, suggesting saturable absorption (11). Unabsorbed gabapentin that might reach the colon from oral overdose should not be a toxicity concern because of poor colonic permeation coupled with a distribution and excretion profile favorable for drug elimination.

Membrane permeation of phenytoin is rapid [log octanol–water partition coefficient of 2.0 was determined in our laboratory; log 2.4 and 2.47 in other laboratories (12)], and dissolution rate is the limiting step for phenytoin absorption from either gastrointestinal region (10). It is noteworthy that very low plasma levels (0.5–3 mg/ml) have been obtained in this canine study compared with those typically observed from equivalent oral dosing in human studies (2,9). This is a result of high first-pass clearance of phenytoin in the dog, a factor that has contributed to low canine plasma levels with subsequent therapeutic failure in veterinary practice (7). Nonetheless, three- to fourfold differences in phenytoin plasma levels 4.5–8 h after administration document continued absorption of drug from the colon at the higher dose, because rapid clearance dictates that absorption will dominate phenytoin plasma-level variability.

In massive overdose cases for lipophilic AEDs like

TABLE 1. *Extent of absorption parameters for gabapentin and phenytoin*

Drug	Administration site	Dose (mg)	AUC (0–6 h) (μg/h/ml)	AUC (0–8 h) (μg/h/ml)	C_{max} (μg/ml)
Gabapentin	Oral	200	39.3	43.9	16.3
	Small intestine	200	34.2	41.1	10.6
	Colon	200	7.4	10.5	1.6
Phenytoin	Small intestine	300	11.2	ND	1.7
	Colon	300	5.4	6.9	1.9
	Colon	600	8.7	13.7	3.0

AUC, area under the drug plasma-versus-time curve; C_{max}, peak drug plasma concentration; ND, not determined.

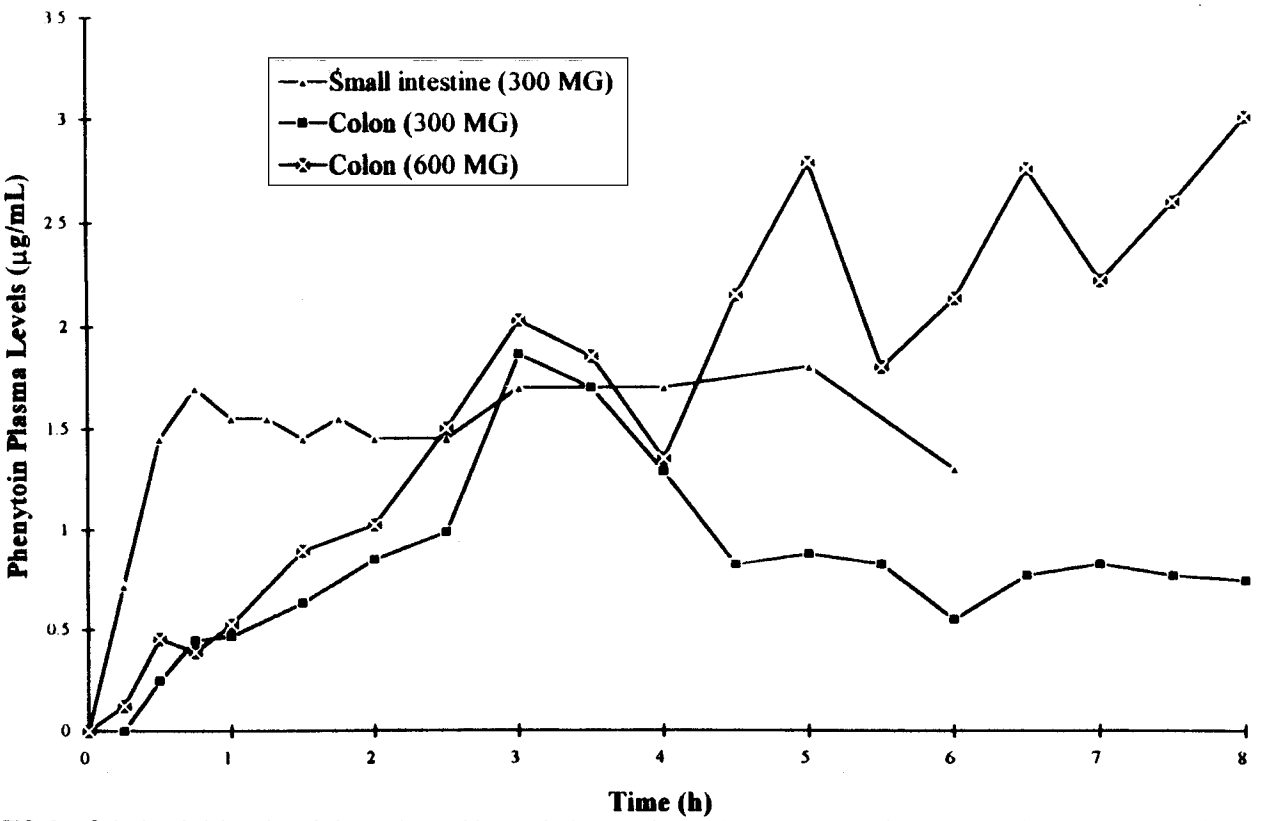

FIG. 2. Colonic administration of phenytoin provides equivalent maximum plasma concentrations compared with jejunal administration. Small intestinal administration results in an earlier time to peak plasma concentrations sustained by continued absorption as drug proceeds down the gastrointestinal tract. Colonic administration of higher doses provides equivalent initial plasma concentration, but continued dissolution and absorption in the colon results in continued plasma-level increases.

phenytoin, continued absorption of undissolved drug in the colon of comatose patients may provide the sustained toxic plasma levels reported in the literature. Based on rotating-basket dissolution studies performed in our laboratory (13), total dissolution time for 250 mg phenytoin powder in aqueous media is 11.5 h. Whereas the amount of phenytoin overdose that resulted in measurable blood levels for 12 days was not known (2), 62 capsules containing 100 mg of phenytoin would require 12 days for total dissolution. Because hepatic clearance of phenytoin is saturable within the normal dose range in humans, considerably less phenytoin powder mass would be required to sustain plasma levels over the time reported for massive overdose (2). Massive overdose of more hydrophilic AEDs like gabapentin would not be anticipated to sustain elevated drug-plasma levels, provided elimination half-life is relatively short [5–6 h in humans (8)]. Although the high concentration from an overdose increases the gradient driving force for absorption, membrane permeation rather than dissolution limits colonic absorption of hydrophilic drugs.

Although phenytoin plasma levels are more sensitive to variable absorption in a canine model, this study confirms that colonic absorption should not be rate limiting to plasma levels, a result that should extend to human subjects. Based on phenytoin's slow elimination in humans, which is typical of marketed lipophilic AEDs, it may be important to purge the bowel in patients who have overdosed on poorly water-soluble AEDs like phenytoin.

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