Absorption and safety of rectally administered phenytoin

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SUMMARY

Parenteral phenytoin solution (Dilantin®) was given rectally three times a day for three days to two beagle dogs. This was well tolerated, with no evidence of mucosal irritation noted either on endoscopic nor on rectal mucosal biopsy. When given in this manner, phenytoin is absorbed to a limited degree in canines. Parenteral phenytoin solution can be safely administered rectally, despite a pH of 12. Further study in normal volunteers is needed to assess the usefulness of this route of administration in situations in which the oral and/or parenteral route of administration is unavailable.

INTRODUCTION

Phenytoin, a hydantoin derivative, is used intravenously for the treatment of status epilepticus and orally for the maintenance treatment of epilepsy. Circumstances may arise in which rectal administration would be useful, such as: the presence of nausea and vomiting; home use in patients with frequently occurring status epilepticus; the small infant or uncooperative patient in whom intravenous access is difficult to secure; and unavailability of medical staff to administer and monitor intravenous therapy.

Most antiepileptic drugs are significantly absorbed from the rectum when the appropriate pharmaceutical preparation is used rectally (1–6). Since the absorbing surface of the rectum is much smaller than that of the duodenum, the dosage form design is a critical factor (7). Rectal absorption from alcoholic and aqueous solutions may occur very rapidly, which has proven to be of considerable therapeutic value in the rapid suppression of status epilepticus. Parenteral diazepam and valproic acid syrup are examples of such pharmaceutical preparations (1, 3, 8, 9). Suspensions and suppositories tend to produce slow, continuous absorption, making these preparations useful in maintenance therapy (2, 10–12).

The literature on rectal administration of phenytoin is sparse. Kvan and Johannessen (13) reported absorption of phenytoin does not occur at all when administered as suppositories. However, the pharmaceutical preparation, a fatty suppository base, may have been inappropriate. Only one crossover study of the rectal absorption of phenytoin exists (14). Plasma concentrations were compared after administration of extemporaneously prepared rectal suppositories and rectal and oral aqueous suspensions, each containing 200 mg of phenytoin. Rectal administration produced undetectable serum concentrations (<0.2 µg/ml). Oral administration of the aqueous suspension produced a maximum serum
Table I: Serum concentrations in \( \mu g/ml \)

<table>
<thead>
<tr>
<th>Dose</th>
<th>0.5 h</th>
<th>1.0 h</th>
<th>3.0 h</th>
<th>5.0 h</th>
<th>7.0 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>20 mg/kg</td>
<td>0.435</td>
<td>0.467</td>
<td>0.479</td>
<td>0.4</td>
<td>0.325</td>
</tr>
<tr>
<td>100 mg/kg</td>
<td>1.33</td>
<td>1.77</td>
<td>1.96</td>
<td>1.76</td>
<td>1.46</td>
</tr>
</tbody>
</table>

concentration of 2.8 \( \mu g/ml \) at 2.5 hours. The addition of alkali and glycofural increased the rectal absorption of an aqueous solution, although this absorption occurred at an appreciable rate only during the first 30 minutes after administration. In contrast, a rectal solution using polyethylene glycol 600 as a solvent produced a slow but continuous absorption over the 8 hours that plasma concentrations were measured.

The results of Moolenaar’s study (14) and the general characteristics of rectal mucosa suggest that the parenteral phenytoin solution (Dilantin®) may be significantly and rapidly absorbed when given rectally for several reasons. First, the parenteral solution is alkaline (pH = 12.0), a property which resulted in rapid absorption for 30 minutes after rectal phenytoin administration.

Second, the solution has an alcoholic base (10% alcohol). This has been associated with drug absorption (7). Third, the 40% propylene glycol component should allow greater rectal absorption than the polyethylene glycol 600 which produced slow and gradual phenytoin absorption (14). Polyethylene glycol 600 is a viscous liquid that is poorly absorbed from the gastrointestinal tract (15), whereas propylene glycol is lipophilic and rapidly absorbed orally from the GI tract (16). Since it is more lipophilic than phenytoin, it may provide solvent drag, to enhance phenytoin absorption (17). Diazepam is an example of excellent rectal absorption of a drug dissolved in 40% propylene glycol and 10% alcohol.

The rectal absorption of phenytoin suspension deserves examination in spite of the poor absorption seen by Moolenaar (14). In his study a suspension was prepared from phenytoin capsules in a medium consisting of 1% methylcellulose 400 in distilled water. The commercially available suspension (Dilantin®) is quite different; the four major ingredients are glycerin, polysorbate 40, aluminium magnesium silicate and sodium carboxymethyl cellulose. Because the two preparations are different and Dilantin® suspension is readily available to practitioners, it is worthwhile to assess its rectal absorption.

To determine the safety and absorption of commercially available phenytoin parenteral and oral suspension administered rectally, the canine model was used.

**METHODS**

Phenytoin oral suspension and parenteral solution (Dilantin®, Parke–Davis) were administered rectally to the dogs by inserting a small diameter infant feeding tube (argyle 7FR) approximately 20 to 25 cm into the rectal cavity. The suspension was diluted 1 : 1 with tap water to reduce its osmolarity, and therefore the defaecatory urge that may result from rectal administration. To ensure ideal absorptive conditions and maximal exposure of the rectal mucosa to the two preparations, each dog received 5 mg bisacodyl orally 12 hours before rectal administration and a tap water enema immediately before administration. The animals were fasted after administration of the bisacodyl, but allowed water *ad libitum*.

**Dose Finding Study**

A pilot mongrel dog received 20 mg/kg phenytoin parenteral solution rectally. The results in Table I prompted administration of 100 mg/kg phenytoin parenteral solution rectally.

**Absorption and Safety Study**

The 100 mg/kg dose of phenytoin parenteral solution was administered rectally three times a day for three days to two beagles. Serum samples were obtained immediately prior to and 30 minutes after each dose. The rectal and sigmoid colon were examined endoscopically prior to and at the conclusion of three days of administration of rectal phenytoin parenteral solution. In addition, multiple biopsies were obtained.

A single 100 mg/kg dose of phenytoin oral