Influence of TPGS and PEG 400 on the permeability of etoposide across everted sacs of rat small intestine

A. Parsa\textsuperscript{1,*}, S. Dadashzadeh\textsuperscript{1}, R. Saadati\textsuperscript{1}, Z. Abbasian\textsuperscript{1}, S. Azad\textsuperscript{2},

\textsuperscript{1}School of Pharmacy, Shahid Beheshti University of Medical Sciences, Tehran, Iran  
\textsuperscript{2}Khatam Hospital, Tehran, Iran

**Background and Aims:** Etoposide, a widely used anticancer drug, exhibits low and variable oral bioavailability and the efflux transporter, P-glycoprotein (P-gp) has been considered as an important barrier against the intestinal absorption of this drug. Therefore, the present study was aimed to investigate the effect of D-\(\alpha\)-tocopheryl polyethylene glycol 1000 succinate (TPGS) and PEG 400 as P-gp inhibitors on the intestinal absorption of etoposide.

**Methods:** Intestinal transport studies were examined by everted gut sac method. Everted sacs of rat small intestine were incubated in 25 ml of Krebs buffer solution which contained etoposide in the absence or presence of various concentrations of TPGS or PEG 400. The effect of verapamil as a known P-gp inhibitor on the absorption of drug was also studied. The solution was maintained at 37 \(\degree\)C with 95% O2/5% CO2. Samples from the solution inside the sacs were taken at predetermined times for 90 min. For exsorption studies etoposide was added into the sacs and samples were taken outside the sacs. The intestinal membrane damage was evaluated by measuring the release of LDH. Epithelial transport of a paracellular and a passive transcellular marker, lucifer yellow and imipramine respectively, in the absence and presence of excipients were also determined.

**Results:** The absorptive transport of etoposide was significantly enhanced \((p<0.001)\) in the presence of verapamil (100 \(\mu\)g/ml) and TPGS (over the concentration range of 0.002 – 0.1 mg/ml), however no significant change was observed by adding various concentration of PEG400 (0.05, 0.1 and 0.5% w/v). No significant difference was found between permeability values in the absence and presence of maximum concentration of TPGS for transport markers, lucifer yellow and imipramine, indicating that enhancement in etoposide permeability in the presence of TPGS were not due to compromise in tight junctions or membrane integrity of epithelial cells.

**Conclusions:** The current data suggests that the use of TPGS as a safe excipient in etoposide formulations may enhanced oral bioavailability of etoposide and result in predictable oral absorption.

**Keywords:** TPGS; PEG400; Etoposide; Everted gut sac