Review

Pharmaceutical and pharmacological approaches for bioavailability enhancement of etoposide

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Etoposide, a semi-synthetic derivative of podophyllotoxin, is one of the most active and useful antineoplastic agent used routinely in firstline combination chemotherapy of testicular cancer, small-cell lung cancer and non-Hodgkin's lymphoma. Etoposide displays narrow therapeutic index, erratic pharmacokinetics and dose individualization that needs to be achieved for overcoming inter- and intra-patient variability (25–80%), so as to maintain proper drug exposure within a therapeutic range. Etoposide posses high plasma protein binding (97%) and is degraded via complex metabolic pathways. The main pharmacokinetic determinants of etoposide are still not completely defined in order to optimize the pharmaco-therapeutic parameters including dose, therapeutic schedule and route of administration. Much research has been done to determine drug–drug and herb–drug interactions for improving the bioavailability of etoposide. The present article gives insight on pharmaceutical and pharmacological attempts made from time to time to overcome the erratic inter- and intra-patient variability for improving the bioavailability of etoposide.

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1. Introduction

Synthesized in 1963, etoposide (figure 1) is a semi-synthetic derivative of podophyllotoxin isolated from the dried roots and rhizomes of species of the genus *Podophyllin.* The first clinical trial of etoposide was reported in 1971 and approved for use in the Unites States of America in 1983. Etoposide inhibits DNA topoisomerase II, thereby inhibiting DNA synthesis at the pre-mitotic stage. Etoposide is also used in combination with other chemotherapeutic agents for the treatment of refractory testicular tumours, small-cell lung cancer, lymphoma, non-lymphocytic leukemia and glioblastoma multiforme *(http://www.drugbank.ca/drugs/DB00773).* Being a chiral drug, its trans-isomer is pharmacologically active. An ataxia telangiectasia mutated (ATM)-dependent activation of AMPK (AMP-activated protein kinase), activated p53 pathway and caspase have been suggested to play a role in etoposide-induced DNA damage (Fu *et al.* 2008; Rudolf *et al.* 2009).

Numerous studies and several reviews have reported the pharmacokinetics of etoposide (supplementary table 1). However, the main pharmacokinetic determinants of this drug are still not completely defined in order to optimize the pharmaco-therapeutic parameters of etoposide including dose, therapeutic schedule and route of administration. Etoposide displays erratic pharmacokinetics with large inter- and intra-individual variations of area under curve (AUC) values and steady state concentrations, along with variability in clearance and systemic exposure. Dose individualization has to be achieved in order to maintain proper drug exposure with in therapeutic range. There is evidence that bioavailability decreases with doses probably due to a

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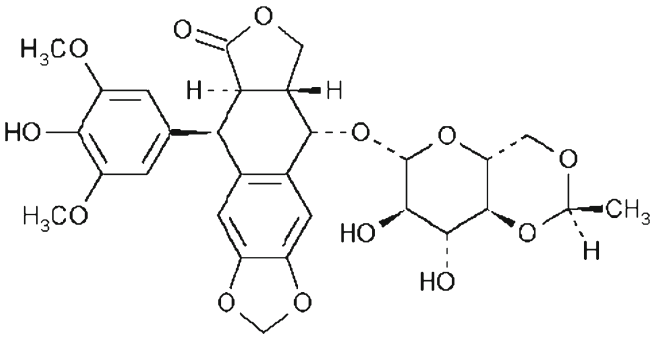

Figure 1. 4′-Demethylepipodophyllotoxin 9-(4,6-*O*-(R)-ethylidene-β-D-glucopyranoside.

concentration-dependent reduction in the solubility of etoposide in the stomach and small intestine (Lavit *et al.* 1995; Ciccolini *et al.* 2002; Lacayo *et al.* 2002; Hartmann and Lipp 2006; Lagas *et al.* 2010).

The present review deals with various pharmaceutical and pharmacological strategies that have been attempted in recent times to overcome the poor/variable bioavailability of etoposide.

2. Pharmaceutical approaches

An etoposide phosphate has been developed as a water-soluble pro-drug for clinical use. In patients with established solid tumours, the bioequivalence of etoposide phosphate to etoposide has been demonstrated. However, variable conversions of etoposide phosphate to etoposide within the intestinal lumen after oral administration remained a major cause for high inter-patient pharmacokinetic variability. Variability in absorption of etoposide is considered to play an important role in its instability in gastric or intestinal solutions (Shah *et al.* 1989; Hande *et al.* 1999); however, some earlier approaches using drugs that influenced the rate of gastric emptying while modulating the time of drug absorption did not significantly alter the etoposide AUC or bioavailability (Joel *et al.* 1995). Attempts to enhance the aqueous solubility and dissolution rate of etoposide were made by preparing various polymorphs of etoposide by crystallizing it from organic solvents (Shah *et al.* 1999).

2.1 *Microemulsions*

Several drug-targeting vehicles such as phospholipid-based microemulsions and cholesterol-rich microemulsions of etoposide have been found to be robust, safe and suitable for patient use (Pinheiro *et al.* 2006; Jain *et al.* 2010).

2.2 *Micelles*

Amphiphilic poly(2-oxazoline)s micelles have been developed as a promising high-capacity delivery platform; etoposide solubilized in defined polymeric micelles were found to achieve high total loading capacities (Han *et al.* 2012). Fatty acid chain length grafted to etoposide delivery has been another approach; etoposide showed high solubility in methoxy polyethylene glycol (MPEG) micelles (Varshosaz *et al.* 2012). Diblock copolymers of MPEG-b-poly(ε-caprolactone) of six different molecular weights were used for fabrication of etoposide-loaded micelles by nano-precipitation technique. Compared with plain etoposide, these micellar formulations have shown enhanced permeability and retention effect in Ehrlich ascites tumour-bearing Balb/C mice. Similarly, Tyr-Ile-Gly-Ser-Arg-conjugated etoposide-loaded micelles were shown to enhance cytotoxicity and cellular uptake with significant reduction in colony formation and cell migration activities compared with non-conjugated micelles in overexpressed tumour cells (Ukawala *et al.* 2012). Other miceller formulations included MPEG polepsilon caprolactone and were found efficient as drug delivery vehicles for pancreatic cancer therapy (Mohanty *et al.* 2010). An etoposide-loaded linear PEGylated as well as PEG-b-poly(D,L lactic acid) offered a promising alternative for combination drug therapy without formulation related side-effects (Shin *et al.* 2009). Etoposide encapsulated in the micelles formed from poly(epsilon-caprolactone)-poly(ethylene glycol) and poly(L-lactide), poly(ethylene glycol) exhibited high etoposide loading capacity and were found suitable as a potential drug delivery carrier (Wang *et al.* 2008).

Enhancement of etoposide uptake by tumour via subcutaneous injection through etoposide-loaded polysorbate 20 micelles resulted in significantly higher tumour uptake and prolonged tumour retention due to relatively high brain concentrations compared with etoposide (Reddy *et al.* 2006b). Micelles containing poly(*N*-vinylpyrrolidone)-block-poly(D,L-lactide) were also found to be efficient solubilizers of teniposide and etoposide (Le *et al.* 2004).

2.3 *Nanoparticles*

High residence of nanoparticles, compared with etoposide, was suggested to be advantageous as drug carriers for etoposide in enhancing the bioavailability and reducing the etoposide associated toxicity (Snehalatha *et al.* 2008). Etoposide loaded into strontium carbonate nanoparticles, a novel biodegradable nanosystem, possessed both high loading capacity and efficient encapsulation, and were more potent in antitumour activity as compared with free etoposide (Qian *et al.* 2012). Use of poly(lactide-co-glycolide)(PLGA) and PLGA/P188-blended nano-encapsulations over pre-existing

etoposide formulation induced improved cytotoxic activity, showing a promising perspective for parenteral delivery of etoposide (Callewaert *et al.* 2012). Recently, PLGA-PEG nanocarriers have been considered to be a better administration schedule in multiple drug delivery in cancer chemotherapy (Saadati *et al.* 2013).

In a recent study colloidal formulations based on poly(butyl cyanoacrylate) nanoparticles of etoposide using two different non-ionic colloidal stabilizers (pluronic F68 and polysorbate 80) exhibited the highest cytotoxicity towards adenocarcinoma human epithelial (A549) cells (Yordanov *et al.* 2012). Etoposide and rubusoside (RUB) nanoparticles completely reconstituable in water and remained stable for at least 24 h. RUB has been shown to effectively solubilize and stabilize etoposide (Zhang *et al.* 2012). Etoposide-loaded nanoparticles were also prepared using PLGA, PLGA-MPEG block copolymer and PLGA-Pluronic copolymer. PLGA-based nanoparticles showed higher cell uptake and cytotoxicity compared with that of the free drug (Yadav *et al.* 2011). Etoposide-loaded and folic-acid-attached polymer poly(3-hydroxybutyrate-co-3-hydroxyhexanoate (PHBHHX) nanoparticles were more effective on HeLa cells than etoposide-loaded PHBHHX nanoparticles without folic acid (Kılıçay *et al.* 2011). Etoposide nanostructured lipid carrier formulation remarkably improved the oral bioavailability of etoposide phosphate (Zhang *et al.* 2011). Intravenous administration of etoposide-loaded poly(lactic-co-glycolic acid) (PLGA) nanoparticles of sizes 105 nm and 160 nm in mice and rats were present in the blood up to 24 h at higher levels than that of pure drug (Yadav and Sawant 2010).

A sustained release formulation of etoposide-loaded biodegradable nanoparticles, has been developed to replace the conventional therapy of continuous intravenous administration. Studies showed that the etoposide-loaded PLGA nanoparticles sustained the release up to 72 h (Yadav and Sawant 2010). Functional nanomaterials that included gold, silver nanoparticles and single wall carbon nanotubes were delivered to the two cell lines, MLO-Y4 osteocytic cells and HeLa cervical cancer cells, in combination with etoposide, showed higher efficacy. Etoposide loaded with tripalmitin, glycerol monostearate and glycerol distearate nanoparticles showed greater and prolonged apoptotic induction properties, resulting in the higher increase in survival time of tumour-bearing mice compared with free etoposide (Reddy *et al.* 2006a). Pharmacokinetic data of etoposide incorporated tripalmitin nanoparticles radiolabelled with Technetium-99m revealed high blood concentrations and prolonged blood residence time. In another study, etoposide lipid nanocapsules showed higher efficiency than the drug solution in glioma cell lines (Lamprecht and Benoit 2006). Etoposide loaded nanoparticles with glyceride lipids characterized and evaluated for *in vitro* steric stability and drug release characteristics (Reddy and Murthy 2005). Recently an HPLC method with fluorescence detection was developed and fully validated for determination and pharmacokinetic study of etoposide-loaded nanoparticles in dog plasma after intravenous administration (Yang *et al.* 2012).

2.4 *Liposomes*

Encapsulation of etoposide in lipid nanospheres (LN) improved the anticancer activity, and further inclusion of polyethylene glycol-distearoylphosphatidyl ethanolamine (DSPE-PEG) increased the circulation time and stability of LN. Folate-targeted etoposide-encapsulated lipid nanospheres showed higher tissue distribution of the drug in the kidney of normal mice compared with that of non-targeted etoposide or a commercial formulation. Etoposide lipid nanocapsules showed 4- to 40-fold higher efficiency than the drug solution (Patlolla and Vobalaboina 2008). Pulmonary liposomal delivery of etoposide showed better particle fraction and drug content over the period of 6 months (Parmar *et al.* 2011).

Liposomal etoposide were found to enhance the cytotoxicity when used alone or in combination with p53 tumour suppressor gene in non-small-cell lung cancer cell lines. These formulations when developed as dry powder inhalers showed significant *in vitro* lung deposition pattern and demonstrated new strategy to treat resistant lung cancer (Jinturkar *et al.* 2012). Liposomal etoposide have shown an improved pharmacokinetic profile: 60% increase in AUC with a 35% decrease in clearance, resulting in 70% increase in the mean residence time of the drug (Sistla *et al.* 2009). Liposomized etoposide and tuftsin-bearing liposomized etoposide formulations were found to reduce tumour volume and tumour growth, and was considered a promising treatment strategy for various forms of cancers, including fibro sarcoma (Khan *et al.* 2007). Similar anti-metastatic activity of etoposide liposomes was also observed against pulmonary tumour nodule formation in murine experimental B16F10 melanoma model (Sant *et al.* 2003). Encapsulated etoposide in cationic liposomes significantly delayed tumour growth and were found to increase the area under the concentration vs time curve and half-life (Sengupta *et al.* 2000).

3. Pharmacological approach

Equally noteworthy developments are documented for natural compounds from medicinal plants which have been evaluated in order to explore bioavailability enhancement of etoposide. Application of P-glycoprotein (P-gp)/CYP3A4 dual role inhibitors in improving per oral drug delivery have gained special interest. P-gp expressed in the apical membranes of the epithelial cells of the intestine is known to reduce the oral bioavailability of a wide range of drugs, including etoposide.

Etoposide is degraded via complex metabolic pathways. CYP3A4 is a principal isoform involved in the 3′-demethylation of etoposide, with the suggestion that CYP1A2 and 2E1 are the minor isoforms involved in the etoposide metabolism (Takashi *et al.* 1998). Therefore, the possibility of improving the bioavailability of etoposide by combining this anti-cancer agent with several pharmacologically active substances, especially P-gp/CYP3A inhibitors, has been explored in recent times. Several known P-gp inhibitors have been shown to increase the bioavailability of etoposide by reducing its efflux from target sites. Eudesmin a (bicyclic lignin) and diphyllin (arylnaphthalene lignin) isolated from H. perforatum Kar et Kir, (Rutaceae) reversed P-gp mediated multidrug resistance (MDR) in MDR1 transfected Madin-Darby canine kidney (MDCK-MDR1) and doxorubicin-resistant human breast carcinoma cells (MCF7/Dox) (Lim *et al.* 2007). Quercetin, a flavonoid with P-gp modulating activity, has been reported to increase etoposide absorption in everted sacs of rat jejunum or ileum (Lo and Huang 1999). A similar effect was also noticed with quinidine, an anti-arrhythmic agent in the rat everted gut sacs; its intravenous perfusion increased the serum level of etoposide in a dose-dependent manner (Leu and Huang 1995).

Ketoconazole increased the area under the plasma concentration–time curve (AUC) of oral etoposide by a median of 20%. Ketoconazole reduced the apparent clearance of oral etoposide, did not alter its toxicity profile and did not reduce inter-patient pharmacokinetic variability (Wei *et al.* 2007). Ketoconazole increased systemic exposure of etoposide due to inhibition of hepatic CYP3A4 (Zee *et al.* 2012). Curcumin was found to increase the oral bioavailability (AUC and C_{max}) of etoposide, possible due to inhibition of the P-gp efflux pump in the small intestine and possibly by reduced first-pass metabolism in the small intestine by inhibition of CYP3A activity in rats. *N*-octyl-*O*-sulfate chitosan (NOSC) and verapamil enhanced the transport of etoposide from apical side to basolateral side in Caco-2 cell monolayers. Moreover, both these agents decreased the transport of etoposide from basolateral side to apical side, by inhibiting P-gp (Mo *et al.* 2011). Orally administered morin (an inhibitor of CYP isozyme and P-gp) significantly increased the AUC, C_{max} and the absolute bioavailability of orally administered etoposide (Li *et al.* 2007). Kaempferol also enhanced the AUC of intravenously administered etoposide due to inhibition of cytochrome P450 CYP3A and P-gp (Li *et al.* 2009). Quercetin, a P-gp and CYP3A inhibitor, altered the pharmacokinetic parameters of etoposide in the orally treated group, but not in the intravenous treated group. Quercetin significantly increased the AUC and absolute bioavailability of orally administered etoposide and decreased the total body clearance (CL) of oral etoposide mainly due to inhibition of P-gp-mediated efflux and CYP3A catalysed metabolism in the intestine (Li and Choi 2009). Potentiation effect of wogonin, a flavone in the roots of *Scutellaria baicalensis*, was observed to potentiate the anticancer action of etoposide due to P-gp inhibition and accumulation of this agent in etoposide-induced apoptosis in tumour cells (Lee *et al.* 2009; Enomoto *et al.* 2011). A piperine analogue, namely, 4-ethyl 5-(3,4-methylenedioxyphenyl)-2E, 4E-pentadienoic acid piperidide (PA-1), was shown to cause 2.32-fold enhancement of the absolute bioavailability of co-dosed etoposide in mice (Sachin *et al.* 2010). Enhancement in the oral bioavailability of etoposide by PA-1 could possibly be due to its ability to modify P-gp/CYP 3A4-mediated drug disposition mechanisms (Najar *et al.* 2011).

4. Conclusion

Several pharmacokinetic and biopharmaceutical aspects have been suggested to play a major role in the poor/variable oral bioavailability of etoposide, such as its poor dissolution characteristics, rapid elimination via P-glycoprotein. In the last two decades many novel approaches have been explored in order to overcome these limitations, which have been discussed.

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