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A novel use of Intralipid for the parenteral delivery of perilla ketone (NSC-348407), an investigational cytotoxic drug with a high affinity for plastic

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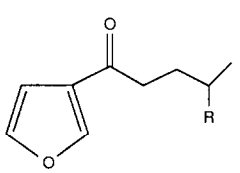
Summary

Simulated i.v. infusions of perilla ketone, a highly lipophilic investigational cytotoxic agent, in 5% dextrose injection (D5W) through various types of i.v. administration sets resulted in considerable loss of the drug due to uptake by the plastic. Ipomeanol, a structurally similar cytotoxic agent with reduced lipophilicity, where a methyl group was replaced by a hydroxyl group, was not subject to uptake as predicted by the differences in the partitioning behavior of the two compounds. Uptake of perilla ketone by polyvinylchloride -based sets was much greater than by polyethylene- or polyolefine-based sets. This phenomenon was completely prevented by incorporating perilla ketone into a commercially available fat emulsion, Intralipid.

Introduction

Perilla ketone and ipomeanol (Fig. 1), two investigational cytotoxic agents, are potent lung toxins (Linnabary et al., 1977). It is generally accepted that both compounds undergo a metabolic activation in vivo to produce highly reactive, electrophilic, metabolites which are probably responsible for their cytotoxic activity (Boyd, 1980; Garst et al., 1985). During the initial attempts to formulate perilla ketone in a pharmaceutically acceptable solvent for i.v. administration, it was found that perilla ketone exhibited a high degree of affinity for plastics. Such a phenomenon has been observed in the past for a number of drugs including nitroglycerin (Baaske et al., 1980; Roberts et al., 1980), warfarin sodium (Moorhatch and Chiou, 1974), diazepam (Cloyd et al., 1980;



R = -CH_3, PERILLA KETONE
R = -OH, IPOMEANOL

Fig. 1. The structures of perilla ketone and Ipomeanol.

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Illum and Bundgaard, 1982; Hancock and Black, 1985; Kowaluk et al., 1983; Mason et al., 1981), amiodarone (Weir et al., 1985) and insulin (Weisenfeld et al., 1968). Generally, drugs exhibiting absorptive behavior enjoy a high degree of lipophilicity and poor aqueous solubility while adsorptive behavior is often exhibited by peptides. Perilla ketone is a viscous oil with an aqueous solubility of 0.3 mg/ml and is miscible with dimethyl acetamide (DMA), dimethyl sulfoxide (DMSO), and soybean oil. Perilla ketone is reasonably soluble ($\approx$ 7 mg/ml) and has an adequate chemical stability ($t_{90} > 2.5$ years) at room temperature in a cosolvent system of 10% ethanol, 40% propylene glycol, 50% water. The preliminary results of simulated i.v. infusion of solutions of perilla ketone diluted from the primary cosolvent with D5W through a PVC-based i.v. administration set resulted in significant loss of perilla ketone. Therefore, the purpose of this study was to assess the extent of perilla ketone uptake by various types of i.v. administration sets and to develop an alternative formulation.

Fat emulsions have been used as a vehicle for the formulation of a number of drugs administered by the i.v. route (Jeppsson, 1972; Jeppsson and Ljungberg, 1975; El-Sayed and Repta, 1983; Repta, 1981; Fortner et al., 1975; Singh and Ravin, 1986). Thus, perilla ketone was formulated extemporaneously in Intralipid and infusion of this vehicle through commercially available i.v. administration sets was tested. The basic premise behind this approach was that the drug would reside mainly in the internal oil phase of the emulsion, thereby significantly reducing its affinity for plastics during infusion.

Materials and Methods

Chemicals and reagents

Intralipid (a 10% i.v. fat emulsion) was obtained from Cutter Medical (500 ml; code no. 490-16; lot NR 11805-A; Miles Laboratories, Inc., Berkeley, CA 94710, U.S.A.). 5% Dextrose injection USP (1000 ml; code 2B0064 Viaflex 8C97059) was obtained from Travenol Laboratories Inc., Deerfield, IL 60015, U.S.A. The following i.v. administration sets were used: nitroglycerin i.v. set 3076 (length, 188 cm; Abbott Laboratories, North Chicago, IL 60064, U.S.A.); solution administration set 2C0006s (length, 240 cm; Travenol Laboratories Inc., Deerfield, IL 60015, U.S.A.); Tridilset, i.v. administration set ACC604-1 (length, 231 cm; McGaw Laboratories, Inc., Sabana Grande, Puerto Rico 00747); Cutter Saftiset i.v. fat emulsion administration set 808-40 (length, 229 cm; Cutter Medical, Miles Laboratories, Inc., Berkeley, CA 94710, U.S.A.). Perilla ketone (NSC-348407) and ipomeanol (NSC-349438) were supplied by the National Cancer Institute (NCI) and were used without further purification.

Assay method for perilla ketone and ipomeanol

Perilla ketone and ipomeanol concentrations were determined by stability-indicating HPLC assays. The liquid chromatograph was constructed from a Kratos Spectroflow 400 pump, a Kratos Spectroflow 783 detector (set at 254 nm), and a Rheodyne 7125 injector fitted with a 20-μl loop. For perilla ketone an ODS Hypersil column (5 μm, 15 cm $\times$ 5 mm, i.d.) was eluted with a mobile phase of 70% methanol in water, while for ipomeanol, 30% methanol in water was used. With these mobile phases and a flow rate of 1 ml/min, perilla ketone eluted with a retention volume of 4.2 ml while ipomeanol eluted with a retention volume of 7.3 ml. Quantification was by peak area using an electronic integrator (Nelson Analytical).

Perilla ketone analysis in intralipid

An aliquot of Intralipid (100 μl) containing perilla ketone was added to a centrifuge tube along with 4 ml of 12.5% (w/v) aqueous sodium perchlorate and 5 ml of *n*-heptane. After agitation for 5 min using a Vortex-Genie mixer, the solution was centrifuged for 10 min with a Dynac centrifuge to separate the aqueous and *n*-heptane layers. The *n*-heptane layer containing perilla ketone was analyzed by direct injection onto the HPLC column. Recovery of perilla ketone was 100% for all the samples.

Simulated i.v. infusion of a D5W solution of perilla ketone and ipomeanol

A stock solution of perilla ketone (4–5 mg/ml) in 10% ethanol, 40% propylene glycol, 50% water

was prepared. This solution was then diluted 1 : 40 or 1 : 50 with D5W to give a solution of 0.1 mg/ml. To assess the extent of perilla ketone loss during passage through various types of i.v. administration sets at room temperature (22–24° C), the infusion sets were attached to glass infusion bottles containing 400–420 ml of 0.1 mg/ml perilla ketone in D5W. The bottles were then inverted and the solution was allowed to pass through the i.v. sets at a flow rate of approximately 1–1.3 ml/min. The concentration of perilla ketone in the effluent was monitored by collecting 1 ml aliquots in glass vials at various time intervals and analyzing for perilla ketone content by HPLC. In addition, the concentration of perilla ketone in the delivery bottle and in the glass collecting bottle, after completion of the infusion, were determined. For ipomeanol, a stock solution of ipomeanol (0.1 mg/ml) in D5W was prepared and its uptake assessed after passage through the Travenol set in a manner identical to the perilla ketone experiments.

Simulated i.v. infusion of perilla ketone in Intralipid

A 5 mg/ml solution of perilla ketone in 10% ethanol, 40% propylene glycol and 50% water was prepared as before. This solution was then diluted 1 : 50 with 10% Intralipid. The simulated i.v. infusion of this emulsion through various types of i.v. administration sets was carried out under identical conditions to those described for the D5W solutions.

Partition coefficient determination

The apparent partition coefficients of perilla ketone and ipomeanol between several organic solvents and water were determined at 25° C. For perilla ketone, the organic solvents used were *n*-heptane, iso-octane, 1-octanol, soybean oil and DEHP (plasticizer; di(2-ethylhexyl)phthalate). For ipomeanol, only *n*-heptane and 1-octanol were studied. Standard solutions of perilla ketone or ipomeanol were prepared in the organic solvents. In the case of 1-octanol, both the 1-octanol and water were presaturated with the other phase. An appropriate volume of the standard solution of perilla ketone was transferred to an Erlenmeyer flask containing the appropriate volume of water (organic phase: water, 5 : 50 v/v), sealed and placed in a shaking water bath and equilibrated at 25° C for 24 h. Equilibration time, less than 24 h, was established by analyzing each phase after centrifugation as a function of time. After centrifugation and separation, each phase was analyzed for perilla ketone concentration by the HPLC method reported earlier. Similar experiments were conducted with ipomeanol.

The apparent partition coefficient of perilla ketone between the inner oil phase and the aqueous phase of Intralipid was determined at 25° C. A standard solution of perilla ketone (5 mg/ml) was prepared in 10% ethanol, 40% propylene glycol, and 50% water. This solution was then diluted 1 : 40 with Intralipid, placed in a flask, sealed and placed in a shaking water bath and equilibrated at 25° C for 24 h. The overall concentration of perilla ketone in the final emulsion was assessed by the extraction procedure described earlier. After equilibration, the emulsion was transferred to two glass centrifuge tubes (JA-20) and ultracentrifuged at 20K rpm for 60 min using a Beckman Ultracentrifuge (Model J-21C). Although two distinct phases resulted upon centrifugation, neither phase was clear. The semi-solid oil-like phase was assayed for perilla ketone as follows. Some of the oil phase was removed, weighed, and dissolved in 5% tetrahydrofuran/methanol and assayed directly. The aqueous phase was also analyzed for perilla ketone by diluting an aliquot with 5% tetrahydrofuran/methanol, extracted with *n*-heptane, and analyzed as for the oil phase.

Results and Discussion

Perilla ketone and ipomeanol uptake during simulated infusion

Simulated i.v. infusion of a 0.1 mg/ml D5W solution of perilla ketone through 4 types of i.v. administration sets (Travenol, Tridilset, Abbott Nitroglycerin, Cutter Saftiset) was carried out under identical conditions at room temperature. A significant loss of perilla ketone, as high as 57% of the original overall concentration, was observed when the Travenol and a Cutter Saftiset sets were employed for infusion. However, substitution of

TABLE 1

Summary of the uptake of perilla ketone by various plastic i.v. sets after simulated i.v. infusion at room temperature (22–24 °C) of 400–420 ml of a 0.1 mg/ml solution of perilla ketone in D5W

I.v. set	% Loss [a]	% Remaining in delivery bottle [b]	Type of plastic	Plasticizer
Travenol Cutter Saftiset	57.0	94.5	PVC	Yes
Abbott Nitroglycerin	25.8	98.1	PE	No
Tridilset	21.8	96.4	PO	No

[a] %Loss of perilla ketone was calculated by determining the overall concentration of the perilla ketone in the collecting bottle after completion of the 400–420 ml infusion.

[b] %Remaining of perilla ketone was calculated by determining the concentration of perilla ketone in delivery bottle after completion of the 400–420 ml infusion.

these sets with either Tridilset or Abbott Nitroglycerin set decreased the loss considerably and lowered the extent of uptake to about 22–26% overall. The results of these studies are presented in Table 1. Also presented in Table 1 is the concentration of perilla ketone remaining in the delivery bottle at the end of the infusion. The data suggest that some of the apparent perilla ketone loss was due to sorption of the perilla ketone by the glass bottle or the rubber stopper.

A plot of the percentage of the initial concentration of perilla ketone in the effluent during simulated i.v. infusions through a Travenol i.v. administration set and a Saftiset are shown in Fig. 2. Similar plots for simulated infusion through Tridilset, and Abbott Nitroglycerin sets are shown in Fig. 3. The data presented in Figs. 2 and 3 show that when solutions of perilla ketone in D5W were infused through various types of i.v. administration sets from glass bottles, the concentration of perilla ketone in the effluent generally decreases dramatically immediately after the beginning of the infusion and then gradually increases with time. This observation seems to be generally true for all the sets examined. The rapid decrease in concentration of perilla ketone in the effluent in the early time points is consistent with sorption of perilla ketone by the layer of tubing in immediate

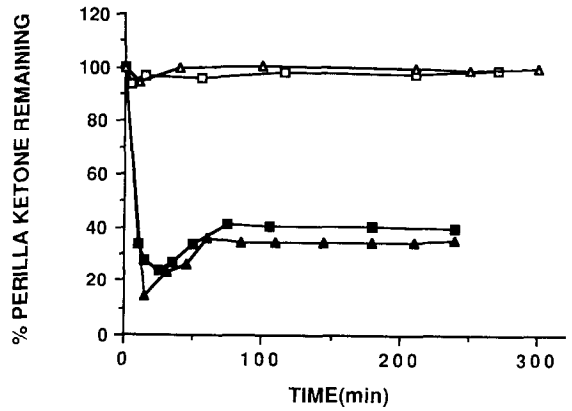

Fig. 2. Percentage of the initial concentration of perilla ketone remaining in the effluent following infusion at room temperature (22–24 °C), of 400–420 ml of 0.1 mg/ml perilla ketone through Travenol (■, D5W; □, Intralipid) and Saftiset (▲, D5W; △, Intralipid) i.v. administration sets.

contact with the infusate. The rate and the extent of subsequent perilla ketone uptake decreases due to the slower diffusion of perilla ketone into the core of the tubing. A model that adequately describes these observations along with the effects of other variables such as flow rate and tubing length is currently under investigation and will be reported elsewhere.

The results shown in Table 1 and Figs. 2 and 3 indicate that the extent of perilla ketone loss is

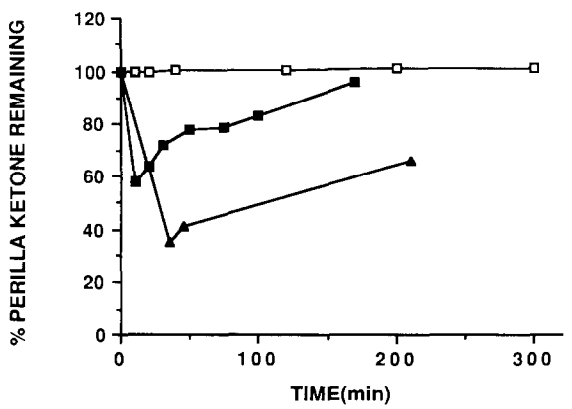

Fig. 3. Percentage of the initial concentration of perilla ketone remaining in the effluent following infusion at room temperature (22–24 °C), of 400–420 ml of 0.1 mg/ml perilla ketone through Tridilset (■, D5W; □, Intralipid) and Abbott Nitroglycerin (▲, D5W) i.v. administration sets.

TABLE 2

Apparent partition coefficient of perilla ketone and ipomeanol between various organic solvents and water

Solvent	Perilla ketone		Ipomeanol	
	K	log K	K	log K
Intralipid *	95.6	1.98		
iso-Octane	235	2.37		
n-Heptane	290	2.46	0.021	−1.68
Soybean Oil	413	2.62		
1-Octanol	569	2.76	6.98	0.84
DEHP	1172	3.07		

The partition coefficients reported here were determined after 24 h equilibration at 25 ° C.

* The reported partition coefficient is between the oil and aqueous phases of Intralipid.

TABLE 3

Assessment of ipomeanol (NSC-349438) uptake by a Travenol i.v. administration set during a simulated infusion at room temperature of a 0.1 mg/ml D5W solution of ipomeanol [a]

Time, min	% Remaining
0	100.0
5	99.74
15	99.23
45	98.77
165	98.81
235	99.06
235	99.37 [b]
235	99.36 [c]

[a] [Ipomeanol] = 0.1 mg/ml in D5W; i.v. administration set (2C00065; 2.4 m long; lot 9JOP2A9R; Travenol Laboratories Inc., Deerfield, IL 60015, U.S.A.); flow rate, 1.75 ml/min.

[b] This value corresponds to the concentration of ipomeanol in the glass delivery bottle after completion of infusion.

[c] This value corresponds to the concentration of ipomeanol in the glass collecting bottle after completion of infusion.

higher for the Travenol and the Saftiset sets which are both polyvinyl chloride (PVC)-based materials, whereas the extent of uptake is much lower for the polyolefin (PO)-based Tridilset and the polyethylene (PE)-based Abbott Nitroglycerin set. These observations are consistent with the findings of other investigators that the uptake of lipophilic drugs by PO- or PE-based i.v. sets is much less than by sets based on PVC (Illum and Bundgaard, 1982; Kowaluk et al., 1983; Hancock and Black, 1985; Lee, 1986). Illum and Bundgaard (1982) have attributed the higher uptake of lipophilic drugs by PVC to the presence of plasticizers which are not present in polyethylene or polyolefin. The partition coefficients, K, and the log partition coefficients, log K, of perilla ketone between various organic solvents, including the principal plasticizer in most PVC tubing, DEHP, and water are given in Table 2 along with some data for ipomeanol. The very large log K values for perilla ketone, especially between DEHP and water are consistent with the high degree of PVC tubing uptake of perilla ketone.

Based on the partition data in Table 2 ipomeanol, which differs structurally from perilla by a methyl group being replaced by a hydroxyl group, would not be expected to be taken up as avidly by PVC-based tubing. Table 3 shows the effluent percent ipomeanol remaining after passage through a Travenol i.v. set during a simulated infusion of a 0.1 mg/ml D5W solution. No significant loss of ipomeanol was observed.

Simulated infusion of perilla ketone diluted with Intralipid

Based on the apparent partitioning of perilla ketone between the oil (soybean oil) and aqueous phases of Intralipid and the soybean oil/water partition coefficient data in Table 2, it was reasoned that dilution of the perilla ketone solution with Intralipid should minimize the contact between perilla ketone and the plastic tubing.

Simulated i.v. infusions of perilla ketone in Intralipid through 3 types of i.v. administration sets (Travenol, Tridilset, and Cutter Saftiset) were conducted at room temperature (22–24 ° C). The conditions employed were identical to those for perilla ketone in D5W. The concentration of perilla ketone in the effluent was monitored as a function of time. The results for the Travenol, Cutter Saftiset, and Tridilset sets are shown in Figs. 2 and 3. The data show that in the emulsion form no significant uptake of perilla ketone by the sets occurred, regardless of the type of plastic tubing. Diluting a 5 mg/ml solution of perilla ketone in its cosolvent mixture 1 : 50 with Intralipid did not appear to damage the emulsion. The

concern of emulsion damage following extemporaneous addition of drugs to Intralipid has been expressed by Singh and Ravin (1986). However, microscopic examination of the formulation of perilla ketone in Intralipid revealed no apparent changes in physical appearance over 2–3 days.

Intralipid has been demonstrated to be a suitable vehicle for the administration of several drugs (Fortner et al., 1975; El-Sayed and Repta, 1983). Commercially available Intralipid (10%) has also been used in development of an extemporaneous formulation of another cytotoxic agent, Valinomycin, with poor aqueous solubility (Repta, 1981). In most cases the purpose for using Intralipid was to enhance either the solubility or the chemical stability of the drugs where other formulations had failed. In the present case, perilla ketone is chemically stable and has adequate solubility in a solvent consisting of 10% ethanol, 40% propylene glycol, 50% water (≈ 7 mg/ml) as well as on adequate dilution with D5W (solubility ≈ 0.3 mg/ml), but presents formulatory problems, due its high affinity for plastics. This can be prevented by diluting perilla ketone with Intralipid.

Conclusions

The investigational cytotoxic agent, perilla ketone, is highly lipophilic. The results described here demonstrate that simulated infusions of a solution of 0.1 mg/ml perilla ketone in D5W through various PVC- as well as PE- and PO-based i.v. administration sets led to significant loss of the drug. This was attributed to the sorption of perilla ketone by the plastics and probable partitioning of the perilla ketone into the matrix of the plastic. The data indicate that the extent of uptake is highly dependent on the type of i.v. set used. PVC-based i.v. administration sets exhibited significantly more uptake than PE and PO tubing. The uptake of perilla ketone by plastics could be completely prevented by incorporation into Intralipid, a commercially available parenteral o/w emulsion. Simulated i.v. infusion of perilla ketone in this vehicle through various i.v. administration sets revealed no appreciable uptake by plastic tubing.

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