Osmolalities of Propylene Glycol-Containing Drug Formulations for Parenteral Use. Should Propylene Glycol Be Used as a Solvent?

Alfred Doenicke, MD, Alexander E. Nebauer, Rainer Hoernecke, PhD, Michael Mayer, MD, and Michael F. Roizen, MD

Institute of Anaesthesiology, Ludwig-Maximilians-Universität, Munich, Germany, and the Department of Anesthesia and Critical Care, University of Chicago, Chicago, Illinois

Propylene glycol (PG) is a widely used vehicle for water-insoluble drugs. Injection of drugs formulated with this solvent often results in pain, thrombosis, or thrombophlebitis that can be reduced by premedication with local anesthetics or opioids. Because osmolality and pH that are unphysiologic may cause these adverse effects, we assessed the contribution of PG to the osmolality of parenteral drug formulations. Osmolality of PG measured in distilled water showed that PG content and osmolality were directly related: 2% wt/vol PG, 264 mOsm/L; 100% PG, 15,200 mOsm/L. The osmolalities of commercially available preparations of drugs dissolved in PG ranged from 365 mOsm/L (2% PG content) to 12,800 mOsm/L (83.46% PG), with most above 1000 mOsm/L. Replacement of PG by a solvent with lower osmolality in Germany has effectively reduced the incidence of side effects for one drug. Until PG can be replaced in drugs, we recommend diluting drugs in a large volume of saline solution; this may help to minimize the undesirable effects of this solvent.

(Anesth Analg 1992;75:431–5)

Pain on injection and thrombosis or thrombophlebitis after intravenous administration of various drugs are frequent, undesired side effects (1–3). Besides causing direct chemotoxic effects, the unphysiologic osmolality and pH of these drugs are mechanisms of inflammation and histologic changes in vessels (4–6) and may cause hemolysis (7). Etomidate, for example, known to be painful on injection and to frequently cause thrombophlebitis (2), has an osmolality of 4965 mOsm/L (8).

Muscle damage and increased creatinine phosphokinase activity in plasma are directly associated with both the volume and the osmolality of substances injected intramuscularly (9). Most of the irritant properties on intramuscular injection of a chlordiazepoxide preparation have been attributed to the osmolality and pH conveyed by propylene glycol (PG), the solvent in which it is prepared and administered (3). Propylene glycol is also the solvent vehicle for many other drugs that anesthesiologists administer, for example, etomidate, nitroglycerin, diazepam, lorazepam, and dexamethasone.

Although the osmolalities of many parenteral drugs often used in anesthesia have been measured, their solvents have not been listed (8). The purpose of this study was to assess the proportion contributed by the solvent PG to the overall osmolality of drug preparations. We measured the osmolality of standard solutions of PG in distilled water and the osmolality and pH of drug formulations containing PG. These values were also determined for two new preparations of etomidate, apparently devoid of venous side effects (2,10), and for propofol, known to be painful on intravenous injection (11).

Methods

Eighteen commercially available drugs for parenteral administration with PG contents ranging from 2% to 83.64% (wt/vol) were investigated. Included were an induction hypnotic, benzodiazepines, corticoids, an antibiotic, five drugs often used by anesthesiologists in emergency or intensive care settings, and diclofenac formulations for intramuscular injection. In addition to PG, 10 of these drugs contained other

Accepted for publication April 13, 1992.

Address correspondence to Dr. Doenicke, Institut für Anaesthesiologie der LMU-München, Innenstadtkliniken, Pettenkoferstr. 8a, D-8000 München 2, Germany.

0003-2999/92/$5.00

solvents or preservatives, such as benzyl alcohol, benzoic acid, ethanol, and sodium disulfite.

Etomidate in lipid emulsion (10% medium-chain triglyceride and 10% soybean emulsion, B. Braun, Melsungen, Germany) and etomidate in hydroxypropyl-β-cyclodextrin (Janssen, Neuss, Germany), two new preparations currently under clinical investigation, were supplied by the manufacturers. Stock solution of PG (Caelo, Hilden, Germany) was used. For dilution we used double-distilled water and commercially available 0.9% saline solution or glucose 5%. Three series of measurements were performed:

1. Osmolality of solutions containing 0%–100% PG dissolved in distilled water.
2. Osmolality and pH of all selected drugs after dilution, as indicated by product information. Etomidate in PG was diluted 1:2 in 0.9% saline solution.
3. Osmolality and pH of seven drugs kept in syringes over a 24-h period. Measurements were performed immediately after drawing the drug into a syringe and after 2, 4, 6, and 24 h. During the first 6 h, syringes were stored at room temperature (23°C) and thereafter in a refrigerator.

Osmolality was measured on an osmometer (Knauer Semi-micro Osmometer, Berlin, Germany) with an analogic, triple-range scale (0–400, 0–800, and 0–1600 mOsm/L). Drugs with osmolality >1600 mOsm/L were diluted 1:10 with double-distilled water using a 1000-μL Eppendorf pipette and a 10 (±0.04)-mL volumetric flask. The result was multiplied by 10. Mean osmolalities were calculated from five different measurements. The coefficient of variation in measurement with this osmometer was ±1%. Values >800 mOsm/L were rounded to the nearest 10. Values of osmolality were also calculated according to the formula of theoretical osmolality:

$$Osm_{theor} = \phi nC,$$

where ϕ is the osmotic coefficient ($\phi = 1$); n the number of particles into which each molecule in solution dissociates ($n = 1$); and C the concentration in moles per kilogram (12). The pH value of the drug undiluted in solution was measured using a pH meter and an electrode (WTW pH meter 521 and electrode E50, Weilheim, Germany).

Results

The values of osmolality for standard solutions of PG dissolved in water (Table 1) correspond well with those calculated. Tables 2 and 3 contain osmolality and pH measurements of drugs of interest to anesthesiologists. The graphic presentation of these data show the linear relationship between PG content and the osmolality of the drug preparation (Figure 1).

Table 1. Measured and Theoretical Osmolalities of Standard Solutions of Propylene Glycol Diluted in Distilled Water

Propylene glycol		Propylene glycol dissolved in distilled water (mOsm/L)	Calculated theoretical osmolality (mOsm/L)
%	mg/mL		
0	0	0	—
2	20	264	263
10	100	1,440	1,314
20	200	2,570[a]	2,629
40	400	5,350[a]	5,257
60	600	8,300[a]	7,885
80	800	11,200[a]	10,514
100	—	15,200[a]	13,142

[a]Measurements were performed after a 1:10 dilution with distilled water.

Table 2. Osmolality and pH of Etomidate and of Propofol

	mOsm/L	pH
Etomidate in PG (35% vol, 362.6 mg/mL)[a]	4900	5.1
Etomidate in PG (diluted to 17.5 vol %, 181.3 mg/mL, 1:2 dilution with 0.9% NaCl)[a]	2450	5.5
Etomidate in 2-hydroxypropyl-β-cyclodextrin	307	6.4
Etomidate in lipid emulsion[a]	400	7.6
Propofol[a]	295	8.2
Propofol (1:4 dilution with glucose 5%)[a]	285	8.1

PG, propylene glycol.
[a]Commercial preparation.

The osmolalities of diclofenac preparations containing at least one additional substance (benzyl alcohol, sodium disulfite, or both, or lidocaine) were between 3150 and 6210 mOsm/L, depending on PG content (194–400 mg/mL). Osmolalities of these preparations were higher than calculated from their PG content. Glucocorticoids for intravenous administration measured were dexamethasone, 2% PG, 365 mOsm/L, and prednisolone, 15% and 20% PG, 1850 and 2970 mOsm/L, respectively.

Osmolality and pH did not change for the following drugs stored in a syringe for 24 h: etomidate, diluted etomidate, etomidate in hydroxypropyl-β-cyclodextrin, etomidate in lipid emulsion, propofol, lormetazepam, diluted lormetazepam, diazepam, and diluted diazepam.

Discussion

Osmolality is a measure of the number of solute particles dissolved in 1 L of solvent. For a given concentration, solutes with a low molecular weight,

Table 3. Osmolality and pH of Drugs Administered Parenterally

Drug	Dilution ratio and solution	Propylene glycol		
		mg/mL	mOsm/L	pH
Lormetazepam (2 mg)[a]		500	6,750	5.7
Lormetazepam (2 mg)[a]	1:2 with 5% glucose	250	3,510	5.3
Diazepam (10 mg)[a,b]		450	9,900	6.5
Diazepam (10 mg)[a,b]	1:60 with 5% glucose	7.5	485	5.1
Lorazepam (2 mg)[a,c]		834.6	12,800	8.0
Lorazepam (2 mg)[a,c]	1:2 with distilled water	417	5,700	6.5
Urapidil (50 mg)[a]		100	1,530	5.8
Urapidil (2 mg/mL)[a]	1:2.5 with saline solution	40	750	5.7
Theophyllin (150 mg)/ proxyphyllin (400 mg)		200	3,020	5.1
Nitroglycerin (50 μg)[a]		331.5	4,550	3.7
Nitroglycerin (200 μg/mL)[a]	1:5 with distilled water	66.3	1,240	4.3
Digitoxin (0.25 mg)[a,d]		415	7,600	7.2
Digitoxin[a,d]	1:3 with saline solution	138.3	1,810	—
Cotrimoxazol (80/400 mg)[a,e]		414.4	8,900	10.4
Cotrimoxazol (80/400 mg)[a,e]	1:26 with saline solution	3.08	608	9.6
Phenobarbital (200 mg)[a,f]		Not declared	13,200	10.3

[a]Commercial preparation.
[b]With benzyl alcohol, 30 mg; benzoic acid, 16 mg; sodium benzoate, 196 mg; ethanol 12.6 vol %.
[c]With benzyl alcohol, 20.9 mg; Macrogol 400, 202.5 mg.
[d]With ethanol 11 vol %.
[e]With ethanol 500 mg; benzyl alcohol, 50 mg; sodium disulfite, 5 mg.
[f]With alcohol 10 vol %.

such as PG (76.1) or ethanol (46.1), contribute considerably more to the osmolality of a drug formulation than to its weight or volume (13). Figure 1 shows that the drug itself and especially additional solvents and preservatives add to the total osmolality. The measurement of osmolality with the osmometer used had a coefficient of variation of ±1%, a negligible error rate by comparison to that for measurement after dilution and supercooling.

Propylene glycol (1,2-propanediol), a polyhydric alcohol, is a viscous, colorless liquid widely used as a solvent for water-insoluble drugs and as a preservative in parenteral, oral, and topical formulations. It is regarded as less toxic than other glycols and is harmless when taken orally, with acceptable daily oral intake estimated at 25 mg/kg (13). Propylene glycol is metabolized by hepatic alcohol and aldehyde dehydrogenases to pyruvate and lactate, which can enter gluconeogenic pathways. It does not accumulate in organ tissues, but plasma levels of PG may increase rapidly with impaired renal function (14,15).

In recent years there have been many reports about side effects with PG. Hyperosmolality, increased osmolal gap, and lactic acidosis are considered responsible for neurologic symptoms, including stupor, coma, and seizures (14–16). Cardiovascular disturbances including sinus arrhythmia (17), cardiorespiratory arrest (18), myocardial infarction, and asystole (19) have been associated with drugs containing PG. Pentobarbital anesthesia in sheep resulted in pulmonary hypertension attributed to PG (20). In rats, both PG and etomidate diluted with PG inhibited the hepatic metabolism of enflurane (21).

The most frequent adverse effects are pain on intravenous injection and thrombophlebitis (1,2). Histology after injection of a diazepam formulation containing PG and of PG alone revealed vessel dilation, interstitial edema, and polymorphonuclear leukocyte infiltration with subsequent thrombotic organization. Addition of lidocaine did not alter the inflammatory reaction (4).

In vitro studies reported hemolysis when PG had been added in various concentrations to blood samples (22); however, hemolysis has also been observed in animals (7,23) and in humans (16). Radiologists have long been aware of the detrimental effects of high osmolality contrast media on cells. Erythrocyte damage is caused by loss of intracellular fluid, leading to formation of desiccocytes, which, because of rigidity, can decrease capillary blood flow and increase pulmonary arterial pressure (23). Endothelial damage led to increased permeability in rat aortic endothelium at threshold levels of approximately 1400–1600 mOsm/L (5). Hyperosmotic solutions have triggered histamine release from human basophils in vitro (24). Finally, heparin resistance has been attributed to a protaminelike effect of PG (25).

To reduce the uncomfortable sensations for patients receiving etomidate, premedication with local anesthetics or opioids is common. Premedication,

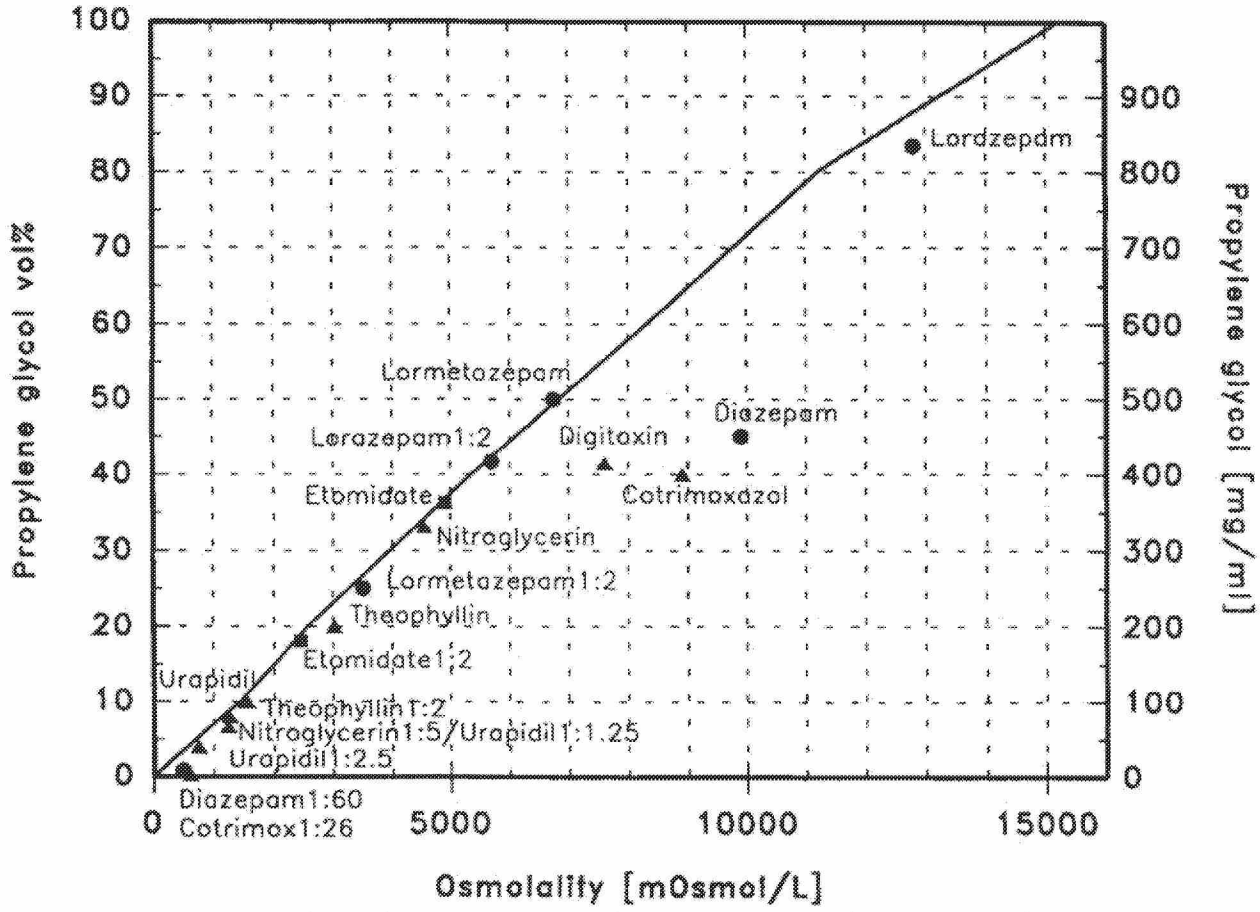

Figure 1. Propylene glycol content and osmolality of various drugs administered parenterally. *Solid line*, standard solutions of PG in distilled water; *squares*, formulations of etomidate; *circles*, the benzodiazepines; *triangles*, various drugs used in anesthesia (see Table 3).

however, does not abolish the underlying mechanism of tissue damage. Limited hemolysis and the release of mediators such as histamine are difficult to detect, and the venous sequelae that may arise during the first or second week after an operation are not always seen by an anesthesiologist.

Osmolalities of diclofenac preparations of >3000 mOsm/L cause pain on intramuscular injection and an increase in mean creatinine phosphokinase plasma activity by 120 mU/mL (3,9). Drug preparations tested that use PG as a solvent vehicle have osmolalities >1000 mOsm/L, with most >3000 mOsm/L. These values exceed those of hyperosmolar solutions that produced pain sensation in veins on the back of the hand after infusion (1.5 mL/min) or injection (1 mL/s) (6).

Diluting a drug reduces its osmolality. Osmolality is reduced by half, for example, in dilution of a drug with an equal volume of distilled water (designated 1:2); however, large volumes would have to be infused to reduce osmolality of some drugs to near plasma osmolality, 285–295 mOsm/L. Thus, necessary dilution is seldom practicable for intramuscular administration when large volumes are unacceptable. All drugs except nitroglycerin (3.7) have pH values between 4 and 11, below and above which levels pain is evoked (6).

Pharmaceutical manufacturers in the United States are not required to report the osmolalities of their drug preparations. Most package inserts of the drugs we tested listed pain and venous sequelae as possible adverse effects without giving their cause. Package inserts warned against intraarterial injection of etomidate (35% PG), lormetazepam (50% PG), and lorazepam (84% PG) because of subsequent necrosis, and mandated dilution for lorazepam and cotrimoxazol (41.4% PG).

We believe that it might be beneficial to reduce the osmolality of drug formulations to more physiologic levels and to reevaluate the use of PG in parenteral drug formulations such as nitroglycerin solutions (16). Replacement of PG in formulations of diazepam (1) and of etomidate (2,10) has successfully reduced adverse effects. Possibly, new solvents such as 2-

hydroxypropyl-β-cyclodextrin or a lipid emulsion may prove to be better alternatives.

We thank Dr. Viktoria Mönch and Dr. Wolfgang Breugst of the University Pharmacy, Munich, for their assistance in performing the measurements and providing the drugs.

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