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TECHNICAL NOTE

Solubilization of Various Benzodiazepines for Intranasal Administration, a Pilot Study

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INTRODUCTION

The benzodiazepines indicated for the acute treatment of seizures (primarily diazepam and clonazepam) are all practically insoluble in water (1,2). Formulations of benzodiazepines are therefore difficult to prepare as solutions. For the management of seizures, an intravenous or rectal dose may be contained in a volume up to 3 ml. Considerable effort has been put into the development of intravenous administrations, since dilution with intravenous fluids or plasma may cause precipitation, resulting in irritation of the vein endothelium, and possibly in thrombophlebitis, e.g., in the lungs and in the kindneys (3,4). In general, the solubility decreases exponentially with the dilution of the cosolvent comprised in the vehicle (5).

Investigations have demonstrated that the nasal mucosae may represent a potential site for absorption of various drugs, as reviewed by Chien (6) and Chien and Chang (7). The epithelial barrier is very permeable and the mucosal tissue is well provided with blood vessels. Various drugs have been shown to cross the nasal mucosa relatively fast after administration and with reasonable bioavailability. For intranasal application, however, the solubility problem is very critical, since one clinical dose needs to be dissolved in a volume not exceeding about 300 μl for administration into two nostrils (8). Various studies have been conducted in which benzodiazepines have been administered intranasally to animals and humans. For humans, the most common benzodiazepine has been midazolam, used to induce sedation in children. The drug was administered as an undiluted parenteral formulation (9,10). Flurazepam, midazolam, and triazolam have been administered to dogs in an aqueous solution with methocel J5MS (11,12). The antiepileptic benzodiazepines, however, have been administered to humans with an unsatisfactory absorption as diazepam in the very lipophillic Cremophor EL (13) and clonazepam in dimethyl-β-cyclodextrin (14).

Focusing on the nasal route as a potential route for acute treatment of epileptic seizures, minor adverse reactions or irritation may be acceptable, since the benefit due to treatment exceeds the risk of local irritation. The objective of this study was to investigate the solubility of diazepam as well as other benzodiazepines in various glycols. Water was avoided in all formulations, due to

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decreased solubility and stability, although lack of a major content of water may increase local irritation. The criterion was primarily to solubilize a clinically relevant amount of the high-dosed benzodiazepine in about a 200-μl vehicle.

MATERIALS AND METHODS

Materials

Diazepam and nitrazepam were kindly provided by Dumex A/S (Copenhagen, Denmark); lorazepam from Ferrosan (Novo Nordisk A/S, Bagsvaerd, Denmark); flunitrazepam, midazolam, clonazepam, and glycofurolum 75 (GF) from Hoffman-la Roche (Basel, Switzerland); triazolam from the Upjohn Co. (Kalamazoo,MI); and lormetazepam from Wyeth Europe Ltd. (Berks., UK). Mono-, di-, tri-, tetra-, penta-, hexa-, heptaethyleneglycol, and polyethyleneglycol 200 (PEG200) were obtained from Merck-Schuchardt (Darmstadt, Germany), and propyleneglycol was obtained from Mecobenzon (Copenhagen, Denmark). Distilled water was used throughout and other chemicals were of analytical grade.

Procedures

The solubility of benzodiazepines depends greatly on the lipophillic characteristics of the vehicle. Excess drug was capped with about 600 μl of vehicle in a 5-ml glass test tube for 45 min, in an ultrasound bath (Branson 3200, Branson Ultrasonic Corp., Danbury, CT) at 25°C. After about 1 hr, the samples were centrifuged (Labofuge Ae, Hereaus, Germany) at 3000 $\times g$ for 30 min. Previous experiments were performed to confirm that several hours were required for equilibrium. The samples were therefore analyzed after storage for 16 hr at 25°C, protected from light. They were withdrawn in duplicate from the top of the solution for quantitative analysis by HPLC. To confirm the solubility, the samples were reanalyzed in duplicate after 40 hr.

The solubility of lormetazepam, however, was determined by visual inspection, after terminal addition of small solvent volumes (accuracy about ±5%).

Apparatus

The HPLC system was a Merck-Hitachi model L6000 pump, model L4000 variable-wavelength UV-detector (Hitachi Ltd., Tokyo, Japan), and a Rheodyne model 7125 injection valve (Rheodyne, Cartati, CA). The column was a Spherisorb S5 ODS, 5 μm, from Phase-Sep (Clwyd, UK). The column was heated in a Microlab column oven (Microlab, Aarhus, Denmark).

Analytical Procedures

Each sample was diluted 25,000-fold with methanol. The dilution was carried out by diluting 100 μl to 25.0 ml; thereafter, 250 μl of that solution was diluted to 25.0 ml. Samples for HPLC analysis were withdrawn from this solution. The mobile phase consisted of 30% acetonitrile (HPLC grade, Rathburn Chemicals Ltd., Wilkerburn, Scotland) in 7 mM phosphate buffer (pH 3.7). The analytical parameters were as follows: detection at 242 nm; flow rate at 1.5 ml/min, column temperature at 55°C, and injection volume of 20 μl.

The retention times for clonazepam, diazepam, flunitrazepam, lorazepam, midazolam, nitrazepam, and triazolam were 6.7; 10.3; 20.1; 9.3; 6.2; 19.7; 5.9, and 15.5 min, respectively. The reproducibility of the method was less than about 5%, and the method was linear in the relevant range covering the concentrations in the diluted samples. The concentration in each sample was calculated on the basis of peak height, relative to an external diazepam standard (1.0 μg/ml in methanol).

RESULTS AND DISCUSSION

The solubility of diazepam in various glycols is shown in Table 1. Although diazepam is practically insoluble in water, it dissolves readily in hydrophillic glycols. The solubility of diazepam in polyethyleneglycol 200 is 61 mg/ml, which is equivalent to one clinical dose in a volume of 250 μl. The solubility in

Table 1

Solubility of Diazepam in Various Glycols

Solvent	Solubility (mg/ml)
Monoethyleneglycol	8
Diethyleneglycol	34
Triethyleneglycol	49
Tetraethyleneglycol	63
Pentaethyleneglycol	67
Hexaethyleneglycol	79
Heptaethyleneglycol	66
Polyethyleneglycol 200	61
Propyleneglycol	17
Glycofurolum 75	101

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Table 2

Solubility of Various Benzodiazepines at 25°C in Polyetheneglycol 200 (PEG200) and Glycofurolum 75 (GF). The Indexes Show How Many Maximal Clinical Doses That May be Dissolved in 200 μl Solvent. The Clinical Dose Used is iv (unless otherwise expressed).

Drug	Clinical Dose (mg)	Solubility (mg/ml)		Index	
		PEG200	GF	PEG200	GF
Clonazepam	1	21	51	4.2	10.2
Desmethyldiazepam	15[a]	17	29	0.2	0.4
Diazepam	10	61	101	1.2	2.0
Flunitrazepam	2	14	42	1.4	4.3
Lorazepam	4	168	391	8.4	19.6
Lormethazepam	1	17	48	3.4	9.6
Midazolam	5	140	202	5.6	8.1
Nitrazepam	5[a]	37	84	1.5	3.4
Triazolam	0.125[a]	6.7	14	10.7	22.4

[a]Expresses the peroral dose.

ethyleneglycols, ranging from tri- to hexaethyleneglycol, was found to increase from 49 to 79 mg/ml. One solvent, glycofurol (15), was found to solubilize considerably more than most other solvents in the literature. Both polyethyleneglycol and glycofurol are hydrophilic excipients, but they have pronounced lipophillic characteristics as well, which explains their ability to dissolve benzodiazepines.

The solubilities of various benzodiazepines in polyethyleneglycol 200 and glycofurol are shown in Table 2. The solubility index is introduced because it directly shows how many intravenous doses can be dissolved in an application volume of 200 μl (100 μl into each nostril). The volume, 200 μl, has been chosen because 300 μl is considered to be the upper limit with respect to keeping the formulation in the nasal cavity. How large the index should be is not known. Ideally it should be more than 2–3, depending on the bioavailability of the benzodiazepine and the exponential solubility lowering effect of water from mucus in the nasal cavity. In clinical situations it may not be favorable to use concentrations close to saturation. The risk of precipitation of drug in the humid nasal cavity may be very much increased.

The results indicate that the formulations may be administered successfully intranasally for the treatment of seizures. Both excipients (polyethyleneglycol and glycofurol) are well known and acceptable. Toxicological studies have shown that they are safe and may be used intranasally without damaging the mucosa (16), and are used in preparations already on the market, both for parenteral and mucosal delivery. (1,17,18). Glycofurol is also known to have a short biological half-life of about 1.1 hr (19). Polyethyleneglycol 200 has recently been added to the USP (NF XVIII) monograph for polyethyleneglycols.

This study demonstrates that it may be possible to produce formulations, using only acceptable excipients, to dissolve clinically relevant amounts of benzodiazepines in a volume not exceeding 300 μl.

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