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CLINICAL INVESTIGATION

Chemical Compatibility of Depacon® with Medications Frequently Administered by Intravenous Y-Site Delivery in Patients with Epilepsy or Head Trauma

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OBJECTIVES Intravenous Y-site administration of more than one medication through the same in-line catheter is a common practice used in the management of acute seizures. The objective of this study was to determine the compatibility of valproate sodium (Depacon®; 2 or 20 mg/mL) with 13 medications that are frequently administered to manage seizures or are given to patients with an acute head injury who are at risk for developing post-traumatic epilepsy.

METHODS The study medications included atracurium, dexamethasone, diazepam, fosphenytoin, lorazepam, magnesium sulfate, mannitol, methyl-prednisolone, midazolam, pentobarbital, phenytoin, ranitidine, and thiopental. Equal volumes of valproate and each of the study drugs were admixed and immediately examined using several physiochemical criteria: Tyndall effect, color and pH change, gas evolution, and particle formation (HIAC/Royco liquid particle counter). Samples were also evaluated using HPLC analysis (C_{18} column; methanol/ tetrahydrofuran/ phosphate buffer; 44/1/55% v/v, at 1.5 mL/min; 50°C) with UV (190-400 nm) photodiode detection. The valproate peak (220 nm) was quantified by both peak area and height. Samples were analyzed within 5 minutes of admixture and were reassessed at 15 and 30 minutes.

RESULTS With the exception of diazepam, midazolam, and phenytoin, all of the remaining drugs were chemically compatible with valproate, both in 5% Dextrose Injection, USP(D5W) and in 0.9% Sodium Chloride Injection, USP (Normal Saline -NS). None of the compatible medications produced a significant pH change, discernible gas, particle formation, reduced valproate titer by HPLC analysis (coefficient of variability $< 1.5\%$), or the temporal formation of unidentified UV absorbing (190-400 nm) peaks.

CONCLUSIONS Intravenous valproate is compatible with most agents employed in seizure management or used in patients at risk for seizures following head injury and is safe for concurrent Y-site drug administration.

KEYWORDS anticonvulsants, Depacon®, drug compatibility, seizure medications, valproate sodium Y-site delivery

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INTRODUCTION

Since its release in 1978, valproic acid has proven to be a broad spectrum anticonvulsant that is clinically effective in the treatment of most generalized seizures[1] and in the management of partial seizures as adjunctive- and monotherapy.[2] Valproate is commonly administered orally, as a tablet, a gel-capsule, a sprinkle product, or as an immediate release syrup. Prior to the release of an intravenous (IV) drug preparation (Depacon®; Abbott Laboratories, North Chicago, IL), patients who were temporarily unable to tolerate or receive an oral dose were either given the anticonvulsant as a rectal solution or were changed to an alter-

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native drug. The IV valproate product Depacon® is currently labeled by the Food and Drug Administration (FDA) as a replacement agent for the individuals who are unable to ingest an oral dosage form for the treatment of partial seizures.[3] In addition, clinical studies have shown that intravenously administered valproate is an effective treatment for acute seizures and refractory status epilepticus, although the drug is not presently approved for these indications.[4-9]

Valproate joins the benzodiazepines, hydantoins and barbiturates as one of several anticonvulsants that can be administered intravenously. Because patients with acute seizures or refractory status epilepticus can require the concurrent administration of numerous other medications, the chemical compatibility of intravenous valproate with other agents becomes a relevant issue. Unfortunately, a review of the literature and references on parenteral admixtures provides no information on the chemical compatibility of IV valproate with other anticonvulsants, non-seizure medications, or IV solutions. Because this lack of information could result in sub-optimal or compromised drug therapy, the objective of this study was to determine the Y-site compatibility of IV valproate with thirteen medications commonly used in the acute care setting.

METHODS

Materials

Valproate Sodium (100 mg/mL),[a] Atracurium Besylate (10 mg/mL),[b] Dexamethasone Sodium Phosphate (4 mg/mL),[c] Diazepam (5 mg/mL),[d] Fosphenytoin (500 PE/mL),[e] Lorazepam (2 mg/mL),[f] Magnesium Sulfate (500 mg/mL),[g] Mannitol (25%),[h] Methylprednisolone Sodium Succinate (40 mg/mL),[i] Midazolam (5 mg/mL),[j] Pentobarbital Sodium (50 mg/mL),[k] Phenytoin Sodium (50 mg/mL),[l] Thiopental Sodium (25 mg/mL),[m] Ranitidine Hydrochloride (25 mg/mL),[n] 5% Dextrose Injection, USP (D5W),[o] and 0.9% Sodium Chloride Injection ,USP (NS)[p] were obtained from the University of Tennessee Hospital pharmacy as sterile IV formulations. Methanol,[q] tetrahydrofuran[r] and water for analysis were of HPLC grade. Dilution and admixture of all drugs was accomplished with sterile 1 mL and 10 mL hypodermic syringes and needles[s], using freshly opened drug vials. Whereas this method is inherently less precise than the use of calibrated pipettes, it does replicate much more closely the clinical situation. Potential dilution errors were assessed by a series of 10 × 1 mL and 10 mL water weighings, dispensed by representative syringes. Percent accuracy/reproducibility (coefficient of variability) were 99.8/0.3 and 98.0/0.4 for the 1 mL and 10 mL syringes, respectively.

Admixture preparations

Drugs were prepared to manufacturer's specifications and diluted to the required concentrations in one of two vehicles, D5W or NS. Two valproate concentrations (2 and 20 mg/mL) were chosen to represent respectively the lower and upper range of therapeutic drug administration in epileptic patients.[10-11] The concentrations employed for the admixed drugs likewise represent the respective recommended dosages and were selected after interviewing pharmacists and physicians who have clinical experience in the use of these agents. The relative dilution of each agent to these concentrations was dependent upon the commercially available drug product.

Following preparation, equal volumes of valproate and the secondary drug, diluted in the same vehicle, were combined in a colorless borosilicate glass vessel at room temperature (23 ± 2°C). The resulting admixtures were monitored immediately and again at 15 and 30 minutes, thus encompassing the maximum catheter residence time for such drug admixtures during clinical administration. All tests were conducted in duplicate and were replicated on a separate date.

Drug compatibility was assessed using commonly accepted methods according to USP guidelines for spectrophotometry and light scattering,[12] pH,[13] and particulate matter in injections.[14]

Physical compatibility

This was determined both qualitatively and quantitatively. Drug combinations were immediately examined against a dark background with horizontal illumination[t] for light scattering (Tyndall effect) and against a light background with vertical illumination for color change, and the outcomes were recorded. In both instances, solutions were also observed for evolution of gas; none was observed for any of the drug combinations. Admixtures were also analyzed for a change in pH using a polycarbonate $Ag/AgCl_2$ electrode[u] calibrated with pH 4, 7 and 9 certified buffer standards.[v] Finally, the extent of component precipitation in the admixtures was de-

Table 1. Solution pH Following Admixture of Valproate Sodium at 2 or 20 mg/mL in D5W or Normal Saline with Select Medications That Are Frequently Used in Patients With Epilepsy or Head Trauma

	pH ADMIXED DRUG		
		PLUS VALPROATE	
ADMIXED DRUG	Drug Diluted in D5W (NS)	2 (20) mg/mL in D5W	2 (20) mg/mL in NS
Atracurium Besylate (0.2 mg/mL)	5.2 (5.2)	7.0 (7.5)	6.9 (6.9)
Dexamethasone Na Phosphate (2 mg/mL)	7.8 (7.5)	7.6 (7.6)	7.5 (7.5)
Diazepam (5 mg/mL)	Precipitated	Precipitated	Precipitated
Fosphenytoin (25 PE/mL)	8.8 (8.6)	8.6 (8.6)	8.5 (8.5)
Lorazepam (1 mg/mL)	7.6 (7.2)	7.0 (7.5)	6.9 (6.9)
Magnesium Sulfate (100 mg/mL)	5.5 (5.8)	6.2 (6.7)	6.5 (6.8)
Mannitol (15%)	7.6 (6.9)	6.6 (7.0)	6.6 (6.9)
Methylprednisolone Na Succinate (5 mg/mL)	7.8 (7.6)	7.7 (7.8)	7.6 (7.5)
Midazolam (2 mg/mL)	Precipitated	Precipitated	Precipitated
Pentobarbital Sodium (5 mg/mL)	8.6 (8.5)	8.5 (8.6)	8.3 (8.5)
Phenytoin Sodium (50 mg/mL)	Precipitated	Precipitated	Precipitated
Thiopental Sodium (25 mg/mL)	10.7 (10.6)	10.4 (10.3)	10.2 (10.2)
Ranitidine Hydrochloride (25 mg/mL)	7.1 (6.9)	7.0 (7.0)	6.9 (7.0)
Valproate Sodium (Depacon)		6.7 (7.2)	6.9 (7.2)

D5W, dextrose in 5% water; NS, normal saline
Selected drugs, diluted to the described concentration with either D5W or saline, were admixed at room temperature with valproate (2 or 20 mg/mL), diluted in the same manner. The pH values of the resulting solutions were recorded using a calibrated Ag/AgCl$_2$ electrode, as described in "Methods." Data represent the mean of duplicate determinations for each drug and vehicle combination.

termined by the light obscuration method using a HIAC/Royco liquid particle counter[w] according to the USP 788 criteria for large-volume injections which sets the limits for particle counts at no more than 25 particles > than or equal to 10 μm in size and no more than 3 particles > than or equal to 25 μm in size per milliliter.[14]

Chemical compatibility

Levels of valproate in the drug admixtures were determined by reversed-phase, high performance liquid chromatography (HPLC) analysis[x] using a modification of the method published by Kushida.[15] This was chosen in preference to the USP assay for valproic acid, which employs GC separation with FID detection and requires almost 1 hour per analysis. [16] Briefly, samples (25 μL) were separated on a C_{18} column (4 μm, 100 mm × 5 mm i.d., 50°C)[y] using a mobile phase consisting of methanol/tetrahydrofuran/phosphate buffer (44/1/55%, v/v) at 1.5 mL/min. The column eluate was monitored by photodiode detector (190-400 nm)[z], and the valproate peak (220 nm) was quantified both by peak area and height. With the exception of mannitol and magnesium sulfate, which both possess no chromophores, all of the admixing agents and their excipients were also detectable by absorbance over similar wavelengths. Samples were injected within 5 minutes following admixture and were reassessed at 15 and 30 minutes.

In all experimental conditions, the two admixed drugs were compared to each component drug alone, in its original manufactured concentration or in the appropriate dilution vehicle. Results are expressed as the average of duplicate samples of each time point for each dilution vehicle. The coefficient of variation on valproate peak area or peak height was calculated as (standard deviation/mean)/100%, in the normal manner.

RESULTS AND DISCUSSION

Physical compatibility

Patients with epilepsy or head trauma are commonly treated with one of the drug options listed in Table 1.These drugs were tested in the present study for compatibility with valproate at 2 or 20 mg/mL. In some cases, the drug is formulated

Table 2. Extent of Particle Formation in Solutions of Valproate Sodium (2 or 20 mg/mL) Admixed with Common Anticonvulsant Medications in D5W or Normal Saline

ADMIXED DRUG*	PARTICLE COUNT: ≥ 10 μm (≥ 25 μm)			
			ADMIXED DRUG PLUS	
	DILUENT	DRUG ALONE	VPA 2 mg/mL	VPA 20 mg/mL
Atracurium Besylate (0.2 mg/mL)	D5W	4.0 (0.1)	2.7 (0.2)	15.4 (0.2)
	NS	0.4 (0)	1.7 (0)	0.5 (0)
Dexamethasone (2 mg/mL)	D5W	3.3 (0.1)	3.5 (0.1)	2.4 (0.1)
	NS	0.4 (0)	1.8 (0)	2.3 (0)
Fosphenytoin (25 PE/mL)	D5W	4.2 (0.2)	3.6 (0.1)	4.7 (0.1)
	NS	1.2 (0.1)	1.1 (0)	0.8 (0)
Lorazepam (1 mg/mL)	D5W	3.2 (0.1)	3.6 (0.1)	3.1 (0)
	NS	0.6 (0.2)	0.6 (0)	0.2 (0.1)
Magnesium (100 mg/mL)	D5W	2.5 (0.2)	3.0/(0)	0.7/(0.1)
	NS	0.6 (0)	1.1 (0.1)	0.5 (0)
Mannitol (15%)	D5W	0.9 (0)	1.1 (0)	2.3 (0.2)
	NS	0.4 (0)	1.1 (0.1)	0.7/0.1
Methylprednisolone (5 mg/mL)	D5W	8.8 (0.1)	4.6 (0.1)	12.3 (0.1)
	NS	11.6 (0.2)	7.6 (0.2)	6.6 (0.1)
Pentobarbital (5 mg/mL)	D5W	0.9 (0.1)	2.0 (0.1)	7.8 (1.1)
	NS	0.3 (0)	0.7 (0.3)	0.4 (0.1)
Thiopental (25 mg/mL)	D5W	16.3 (0.1)	6.7 (0.1)	9.0 (0.1)
	NS	3.8 (0)	6.0 (0)	7.3 (0.1)
Ranitidine (25 mg/mL)	D5W	0.9 (0.1)	2.8 (0)	1.0 (0.1)
	NS	4.0 (0)	5.4 (0.1)	3.6 (0.1)

VPA, valproate; D5W, dextrose in 5% water; NS, normal saline
Selected drugs, diluted to the described concentrations with either D5W or saline, were admixed at room temperature with valproate (2 or 20 mg/mL) diluted in the same manner. The number of particle counts/mL of the diluted drugs, alone and in combination with the valproate solutions, were determined using a HIAC/Royco liquid particle counter, as described in "Methods." Data represent the mean of duplicate determinations for each drug and vehicle combination.

with the aid of a surfactant, such as propylene glycol, and/or the pH of the solution is adjusted in the manufacturing process to maintain drug solubility or stability. In instances in which the valproate (D5W or NS) admixture spurs a significant change in pH or an aqueous dilution, precipitation is possible. This was indeed the case with Diazepam, Midazolam, and Phenytoin, each of which formed an overt precipitate upon admixture. However, the precipitation phenomenon could be duplicated simply by aqueous dilution or by pH adjustment with 1N acid or alkali, in the absence of concurrent valproate, thereby indicating that dilution or pH change was the instigator, rather than the presence of the secondary drug product *per se*.

Whereas the pH of the remaining admixtures varied between valproate and either mannitol (pH 6.6) or thiopental (pH 10.2), depending upon the concurrent agent, none of these pairings resulted in the formation of an overt precipitate, evolution of gas, or a color change during the 30-minute study period. Admixture of valproate with magnesium sulfate or mannitol would be anticipated to be the most problematic, given the acidic nature of these two admixtures. Valproate sodium, as the drug product, is the water-soluble salt of valproic acid, produced by pH adjustment to 7.6 with sodium hydroxide and/or hydrochloric acid. In an increasingly acidic milieu, valproic acid has the tendency to precipitate, producing a film or haze. Whereas this phenomenon was clearly evident with an undiluted drug product (100 mg/mL), it was not detected visually or by particle counting at the dilutions employed in these studies. Nevertheless, precipitation of valproate sodium upon admixture with these agents in other concentration combinations remains a very real possibility.

Table 2 displays the particle counts of the various admixing drugs, alone and in combination with valproate at 2 or 20 mg/mL. As would be expected prior to the addition of valproate, all of

Table 3. HPLC Analysis of the Valproate Sodium Peak in Admixed Solutions of Valproate Sodium (2 or 20 mg/mL) with Medications that are Frequently Used in Patients With Epilepsy or Head Trauma

	VPA 2 mg/mL		VPA 20 mg/mL	
	AREA D5W (NS)	HEIGHT D5W (NS)	AREA D5W (NS)	HEIGHT D5W (NS)
ADMIXED DRUG*				
Atracurium Besylate (0.2 mg/mL)	2.19 (1.05)	1.63 (3.67)	0.46 (0.39)	0.42 (0.24)
Dexamethasone (2 mg/mL)	0.64 (1.18)	0.73 (0.92)	0.67 (0.36)	0.48 (0.44)
Diazepam (5 mg/mL)	—	—	—	—
Fosphenytoin (25 PE/mL)	0.54 (0.49)	1.14 (1.33)	0.2 (1.09)	0.67 (0.27)
Lorazepam (1 mg/mL)	0.17 (1.37)	0.71 (1.36)	0.85 (0.35)	0.87 (0.35)
Magnesium (100 mg/mL)	0.36 (0.12)	1.47 (0.5)	0.84 (0.39)	0.47 (0.33)
Mannitol (15%)	0.83 (0.97)	1.29 (1.06)	0.98 (0.36)	0.97 (0.49)
Methylprednisolone (5 mg/mL)	0.47 (0.03)	1.05 (1.4)	0.47 (0.5)	0.82 (0.46)
Midazolam (2 mg/mL)	—	—	—	—
Pentobarbital (5 mg/mL)	0.12 (0.18)	0.50 (0.64)	0.20 (0.51)	0.38 (0.09)
Phenytoin (50 mg/mL)	—	—	—	—
Thiopental (25 mg/mL)	0.4 (0.45)	1.71 (1.10)	0.17 (0.10)	0.79 (0.13)
Ranitidine (25 mg/mL)	0.27 (1.39)	1.44 (1.43)	0.41 (0.3)	0.7 (0.5)

VPA, valproate; D5W, dextrose in 5% water; NS, normal saline
Selected drugs, diluted to the described concentration with either D5W or saline, were admixed at room temperature with valproate (2 or 20 mg/mL) diluted in the same manner. The resulting solutions were analyzed by reversed-phase HPLC, as described in "Methods", immediately upon admixture and again 15 and 30 minutes later. Data represent the variability in area or height of the valproate chromatographic peak over these temporal determinations, and are the mean of duplicate determinations.

the diluted drugs met the requirements of the USP < 788 > particulate matter test. Upon admixture with valproate there were no significant changes in particle counts for any of the concurrent drugs, thereby confirming the visual analysis that no detectable component precipitation had occurred. As the admixture of valproate with Diazepam, Phenytoin and Midazolam resulted in overt precipitation, for the reasons noted above, none of these admixtures warranted analysis using the HIAC/Royco system.

The HPLC analysis of admixed drugs is shown in Table 3 and a representative panel of three-dimensional photodiode plots for Fosphenytoin (25 PE/mL) /Depacon is shown in Figure 1. The valproate peak area and peak height coefficients of variability (220 nm) for the three consecutive analyses (5, 15 and 30 minutes) were very small and showed no detectable reduction in the size of the peak over this period. Chromatographic results were unaffected by dilution of the drugs in D5W versus NS, and replicate studies produced comparable data. Assessment of the automated HPLC equipment for reproducibility, using 10 sequential injections of valproate solution, revealed a variability coefficient of 0.64% and 1.56% for area and height, respectively.

No attempt was made to quantify changes in the UV absorption of the concurrent drugs, which in most instances exhibited significantly greater UV absorption than Depacon. For many agents, additional polar UV absorbing peaks relating to benzyl alcohol or other pharmaceutical additives were also discernible (see Figure 1). Regardless, no additional UV absorbing peaks (190-400 nm) were formed temporally in the presence of valproate, and there were no discernible changes either in the retention time or in the UV spectrum (190-400 nm) of the valproate peak during the observation period.

CONCLUSION

Diazepam, phenytoin, and midazolam all precipitated in the presence of a pH environment that was substantially different from that found in their commercial vials. Conversely, all of the remaining drugs and IV solutions proved chemically and physically compatible with valproate at 2 or 20 mg/mL. No combination produced measurable particle forma-

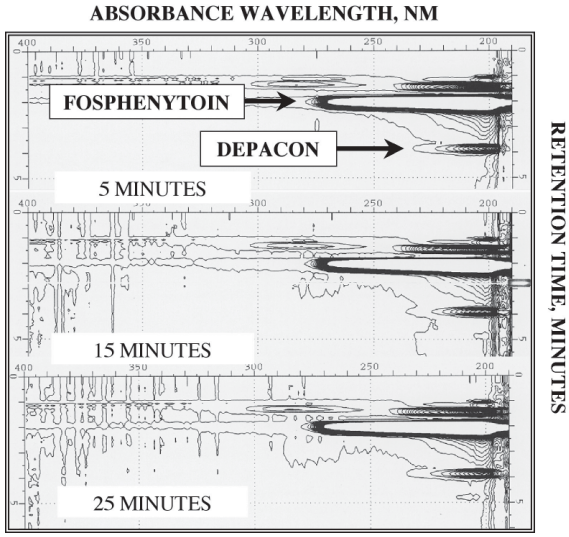

Figure 1. Temporal HPLC Photodiode Array Analysis of Valproate Sodium (Depacon; 20 mg/mL) Admixed with Fosphenytoin (25 PE/mL).

tion, detectable Tyndall effect or gas evolution, loss of valproate titer (by HPLC), or formation of additional UV-absorbing peaks. Therefore, based upon these studies, valproate appears safe for IV Y-site administration in conjunction with these common seizure control agents at the concentrations described.

[a] Abbott Laboratories, North Chicago IL, lot 79 949Z7
[b] Abbott Laboratories, North Chicago IL, lot 74 691-DK
[c] American Reagent Laboratories, Shirley NJ, lot 0354
[d] Abbott Laboratories, North Chicago IL, lot 77-353-DK
[e] Parke Davis Div Warner Lanbert, Ann Arbor MI , lot 18636A
[f] Wyeth Laboratories, Philadelphia PA, lot 041094
[g] American Reagent Laboratories, Shirley NJ, lot 0717
[h] Abbott Laboratories, North Chicago IL, lot 69-040-DK
[i] Pharmacia Upjohn, Kalamazoo MI, lot 02F JK
[j] Bedford Laboratories, Bedford OH, lot 232364
[k] Abbott Laboratories, North Chicago IL, lot 74858Z721
[l] Elkins-Sinn, Cherry Hill NJ, lot 050184 (no longer marketed in the US)
[m] Abbott Laboratories, North Chicago IL, lot 77-405-DK
[n] Glaxo Wellcome, Research Triangle Park NC, lot 1ZP1468
[o] Baxter Healthcare, Deerfield IL, lot C399584
[p] Baxter Healthcare, Deerfield IL, lot PS089516
[q] Fisher Scientific, Fairlawn NJ, lot 011803
[r] Aldrich Chemical Co, Milwaukee WI, lot MO 03034MO
[s] Beckton Dickinson & Co. Franklin Lakes, NJ 1 mL syringe (p/n 309623), 10 mL syringe (p/n 309604) and 18G $1^{1/2}$ sterile needle (p/n 305196)
[t] Dolan Jenner Industries Model 180 FiberLite
[u] Fisher Scientific, Pittsburgh PA, standard polymer-body liquid-filled combination electrode
[v] Fisher Scientific, Pittsburgh PA, SB101-500 and SB107-500 certified buffers
[w] Pacific Scientific Instruments, Grants Pass OR
[x] Waters Associates, Milford, MA, model 712 WISP and twin model 515 pumps
[y] Waters Associates, Milford MA, Nova Pak column lot T2105X01
[z] Waters Associates Model 990 Photodiode detector

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