PIVOtAL: Pharmacokinetic Interactions Between ValprOic Acid and Lorazepam: A Qualitative Systematic Review of Literature and Retrospective Chart Review to Identify Site-Specific Practices

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Background

- Lorazepam (LZP) is a short-acting benzodiazepine often used concurrently with valproic acid (VPA), a broad-spectrum antiepileptic drug, to treat epilepsy and psychiatric disorders
- Proposed pharmacokinetic (PK) interaction: inhibition of LZP glucuronidation via direct inhibition of uridine 5'-diphosphate-glucuronosyltransferases (UGT) enzymes by VPA
- LZP plasma clearance shown to ↓ and area under the plasma drug concentration-time curve (AUC) ↑ presumably due to ↓ glucuronidation in combination with VPA
- Lack of clinical studies to demonstrate mechanism of interaction is secondary to UGT inhibition
- Limited evidence on other PK pathways
- **Objectives:**
  - Summarize current evidence on VPA/LZP PK interaction
  - Assess clinical significance and identify site-specific practices

Outcomes

Qualitative Systematic Review:

- Data on PK properties of VPA and LZP (i.e. absorption, distribution, metabolism, and elimination)

Retrospective Chart Review:

- **Primary:**
  - *Frequency* of intervention when VPA/LZP are prescribed concomitantly
  - *Types* of interventions made
- **Secondary:**
  - *Rationale* for therapy intervention
  - *Adverse outcomes* experienced

Methods

- **Qualitative Systematic Review:**
  - A systematic search of MEDLINE, EMBASE, CINAHL, ISI Web of Science and PsychINFO (until Mar 2015)
    - Search terms: (valproic acid OR valproate sodium OR divalproex sodium) AND lorazepam AND (pharmacokinetics OR drug metabolism OR metabolism OR metabolic pathway)
    - Inclusion criteria: English, in vitro and in vivo human studies, PK data
- **Retrospective Chart Review:**
  - Convenience sample size (N=30) admitted from Sept 08-14

Inclusion	Exclusion
• ≥ 18 years of age • Admitted to psychiatry or neurology • Prescribed VPA and LZP concomitantly	• LZP prescribed as needed but not given • ESRD[a] (eGFR[b] <15mL/min or dialysis)

[a]ESRD, end-stage renal disease; [b]eGFR, estimated glomerular filtration rate

Results of Retrospective Chart Review

Table 1: Baseline Characteristics	N = 30
Female n (%)	8 (27%)
Age (mean ± SD[a], years)	41.4 ± 15.1 (19-76)[e]
eGFR (mean ± SD, mL/min)	85.4 ± 22.1 (27-120)
Albumin level (mean ± SD, g/L)	39.0 ± 4.9 (27-48)
Total PO[b] VPA dose/day (mean ± SD, mg)	1083.3 ± 492.8 (500-2500)
Maximum total PO/SL[c] LZP dose/day (mean ± SD, mg)	3.0 ± 1.8 (1-10)
Maximum total IM[d] LZP dose/day (mean ± SD, mg)	0.3 ± 0.9 (0-4)
Most Responsible Psychiatric Diagnosis	**%**
Bipolar disorder	43
Schizophrenia	33
Polysubstance abuse	30
Alcoholism	23
Depression	22
Anxiety disorder	10
Common Concurrent Medications	**%**
Antipsychotic	93
Antidepressant	30
Benzodiazepine	27
Zopiclone	20
Anticonvulsant	3

[a]SD, standard deviation; [b]PO, oral; [c]SL, sublingual; [d]IM, intramuscular, [e]range of values

Figure 1: Frequency and Types of Intervention

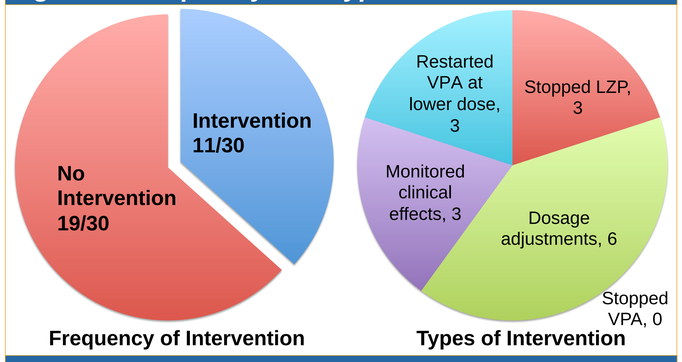

Figure 2: Rationale for Intervention

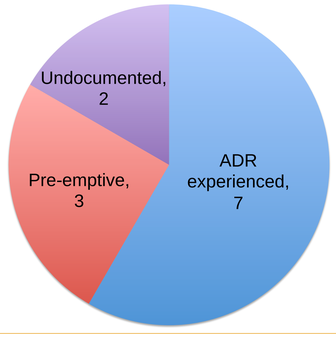

Figure 3: Adverse Outcomes Experienced

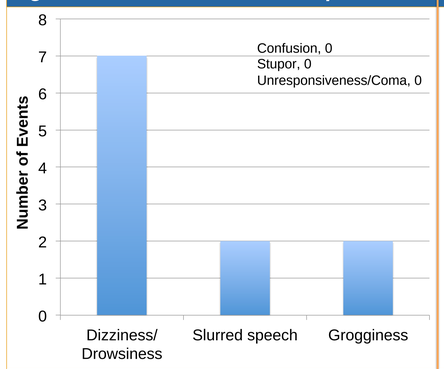

Figure 4: Search Strategy

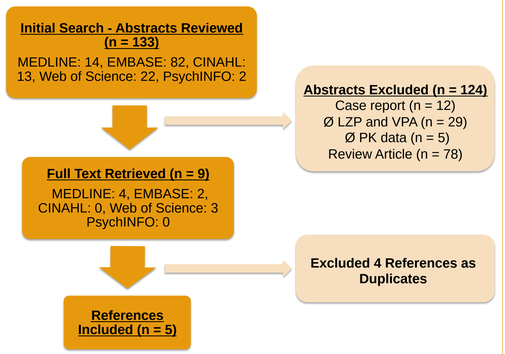

Table 2: Results of Qualitative Systematic Review

PK Parameters	LZP Monotherapy		LZP (PO/IV) + VPA	
	PO[a]	IV[b]	PO	IV
Absorption: AUC (ng*h/mL)	218-953.6[1-3]	563.1-1029.4[1]	261.0[3]	Ø data
	• Absorption of LZP does not seem to be affected by coadministration with VPA			
Distribution: Vd[c] (L/kg)	1.08-1.46[2,3]	0.84-1.30[1,4,8]	1.59[3]	Ø data
	• No evidence of significant effect on distribution			
Metabolism: Fraction of dose as glucuronide metabolite (%)	71.9-80.0[1-5]	68.5-85.0[1,4,8,9]	↓68.0[3] (SS?)[d]	↓62.0[9] (NS)[e]
	• Appears to be a trend towards ↓ in fraction excreted as LZPG[f]			
Excretion: Plasma clearance (mL/min/kg)	1.07[3]	0.52-1.10[1,4,8-11]	↓0.87[3] (SS?)	↓0.31-0.93[9-11] (p < 0.05)
LZPG Formation clearance (mL/min/kg)	0.86[3]	0.40[9]	↓0.58[3] (p < 0.05)	↓0.17[9] (p < 0.05)
Elimination $t_{1/2}$[g] (h)	11.1-17.2[1-7]	11.0-15.9[1,4,8,9]	↑21.4[3] (SS?)	↓10.7[9] (NS)
	• LZP clearance reported to ↓ with VPA, which may explain reduction in LZPG formation clearance and fraction excreted as glucuronide metabolite • Despite ↓ in plasma clearance, lack of data to determine effects on $t_{1/2}$			

[a]PO, oral; [b]IV, intravenous; [c]Vd, volume of distribution; [d]SS, statistically significant; [e]NS, not statistically significant; [f]LZPG, lorazepam glucuronide; [g]$t_{1/2}$, half-life

Conclusions

- Minimal evidence proving mechanism of PK interaction
- However, resources continue to cite drug interaction as "major" requiring "therapy modification" and supported by evidence of "excellent" reliability[12]
- Negligible renal clearance of LZP→ plausible explanation for ↓ clearance may be inhibition of hepatic metabolism
- Evidence of intersubject variability possibly due to UGT enzyme polymorphism[10,11]→ ↑ risk of ADRs
- Small number of patients (N = 8/30)→ transient, non-life threatening ADR suspected to be secondary to VPA/LZP interaction
  - Difficult to draw causal relationship due to polypharmacy
- Consider using lowest effective dose of LZP when coadministered with VPA
  - Patients who experienced ADRs received mean dosage of 4 mg LZP PO/IM per day
  - Most patients (N = 16/22) without ADRs received < 2 mg LZP PO/IM per day
- Close patient monitoring required to avoid oversedation when VPA/LZP used concomitantly, especially if there are other risk factors for serious CNS depression

References

(1) Greenblatt DJ, Shader RI, Franke K, MacLaughlin DS, Harmatz JS, et al. Pharmacokinetics and bioavailability of intravenous, intramuscular, and oral lorazepam in humans. J Pharm Sci 1979a;68:57-63. (2) Kyriakopoulos AA. Bioavailability of lorazepam in humans. In: Gottschalk and Merlis, editors. Pharmacokinetics of psychoactive drugs: blood Levels and clinical response. New York: Spectrum; 1976:127-139. (3) Samara EE, Granneman RG, Witt GF, Cavanaugh JH. Effect of valproate on the pharmacokinetics and pharmacodynamics of lorazepam. J Clin Pharmacol 1997;37:442-50. (4) Greenblatt DJ, Allen MD, Locniskar A, Harmatz JS, Shader RI. Lorazepam and kinetics in the elderly. Clin Pharmacol Ther 1978b;26:103-13. (5) Greenblatt DJ, Schillings RT, Kyriakopoulos AA, Shader RI, Sisenwine SF, et al.. Clinical pharmacokinetics of lorazepam. I. Absorption and disposition of oral ^{14}C-lorazepam. Clin Pharmacol Ther 1976;20:329-41. (6) Verbeeck R, Tjandramaga TB, Verberckmoes R, de Schepper PJ. Biotransformation and excretion of lorazepam in patients with chronic renal failure. Br J Clin Pharmacol 1976;3:1033-39. (7) Greenblatt DJ, Allen MD, MacLaughlin DS, Huffman DH, Harmatz JS, Shader RI. Single- and multiple-dose kinetics of oral lorazepam in humans: the predictability of accumulation. J Pharmacokinet Biopharm 1979c;71:159-79. (8) Greenblatt DJ, Corner WH, Elliott HW, Shader RI, Knowles JA, Ruelius HW. Clinical pharmacokinetics of lorazepam III. Intravenous injection. Preliminary results. J Clin Pharmacol 1977a;17:490-4. (9) Anderson GD, Gidal BE, Kantor ED, Wilensky AJ. Lorazepam-valproate interaction: studies in normal subjects and isolated perfused rat liver. Epilepsia 1994;35:221-5. (10) Chung J, Cho J, Yu K, Kim J, Jung H, Lim K, et al. Effect of the genotype on the pharmacokinetics, pharmacodynamics, and drug interactions of intravenous lorazepam in healthy volunteers. Clin Pharmacol Ther 2005;77(6):486-94. (11) Chung JY, Cho JY, Yu KS, Kim JR, Lim KS, Sohn DR, et al. Pharmacokinetic and pharmacodynamic interaction of lorazepam and valproic acid in relation to UGT2B7 genetic polymorphism in healthy subjects. Clin Pharmacol & Ther 2007;83(4):595-600. (12) Lorazepam and valproic acid. In: Lexi-Comp, Inc. (Lexi-Interact). Lexi-Comp, Inc.; Accessed: 19 Feb 2015.

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