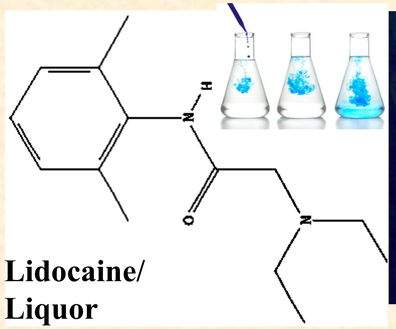
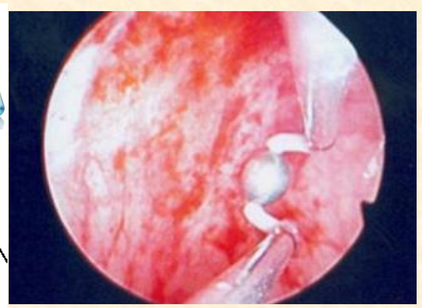
Abstract # 24345

Hunner Lesion Obeys Michaelis-Menten Kinetics In Delaying The Elimination of Drugs

Pradeep Tyagi , Anirban Ganguly, Naoki Yoshimura, Jonathan Kaufman[2], Michael Chancellor[2], Christopher Chermansky

Department of urology, University of Pittsburgh; Lipella Pharmaceuticals





IC/BPS; Tyagi et al J Urol. 2012;187(6):2243-8.

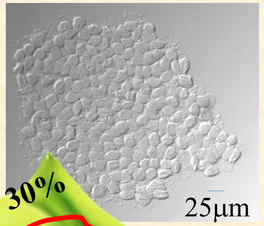


Figure 1: Since polygonal umbrella cells (70%) of luminal surface have restricted permeability, tight Junctions (30%) of luminal surface can be treated as paracellular ports of entry for lidocaine-capacity limited- amenable to Michaelis-Menten kinetics

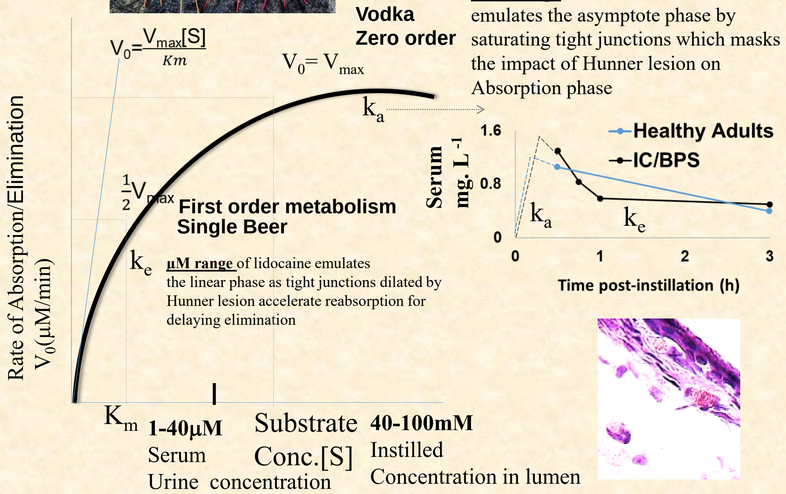


Figure 2. Michaelis-Menten Kinetics- The contrasting impact of Hunner lesion (IC/BPS) on the rate of absorption and elimination of lidocaine, fluorescein and salicylate conforms to Michaelis –Menten Kinetics. Restricted transcellular absorption leaves only the capacity limited, passive paracellular diffusion (across tight junctions) as the viable route for systemic uptake which is affirmed by a 3-fold rise in systemic uptake with tight junctions widened by prolonged dwell time of 120min from 10min (ref.5).

BACKGROUND

- We recently reviewed the pharmacokinetic basis for the use of instilled lidocaine as local anesthetic/ analgesic for TURB and intradetrusor inj[1]
- We were puzzled by the published lidocaine serum level plots in which the impact of Hunner lesion in interstitial cystitis/painful bladder pain syndrome (IC/BPS) patients[2] is much more easily discernible on elimination (downslope) than on the absorption (upslope) of instilled lidocaine
- The delayed elimination due to bladder reabsorption is not unique to lidocaine as orally ingested fluorescein[3] and instilled or injected salicylate[4] in animals also challenge the assumption of bladder as a non-returning (one-way traffic) compartment for drugs excreted into urine after **Absorption →Distribution → Metabolism → Excretion (ADME)**
- While Henderson Hasselbalch equation explains the accentuation of lidocaine anesthesia at 5min[5] following accelerated absorption but principle governing delayed elimination of lidocaine and other drugs is unclear
- Michaelis Menten Kinetics been previously used to elucidate the non-linear metabolism (M of ADME) of ethanol[6], phenytoin, and paclitaxel
- Here, we distilled the published clinical evidence[1-4] to probe whether the apparent ceiling effect in intravesical absorption and First order reabsorption of lidocaine and fluorescein from urine by dilated tight junctions[7] of Hunner lesion(Fig.1) is amenable to Michaelis Menten Kinetics

METHODS

- Published clinical studies on IC/BPS and healthy controls[1-2,5] were analyzed to examine the impact of Hunner lesion on intravesical absorption and renal elimination of lidocaine, fluorescein[3] and salicylate[4]
- Whether the differential impact of Hunner lesion on absorption at instilled concentration and reabsorption at low urine concentration is amenable to Michaelis Menten Kinetics

RESULTS

- The instillation of 2% alkalinized lidocaine in healthy controls and IC/BPS patients generated an overlap in the published C_{max} range of 0.66 - 1.71 mg/L (7.2micromolar)[2] and 0.2 to 2.0 mg/L (8.5 micromolar), respectively at Tmax ~30min.
- The overlap is consistent with the comparable upslope[1] or absorption rate constant (k_a) before C_{max} in stark contrast to the significant differences in the downslope post C_{max} between IC/BPS patients and healthy controls [2]
- Slower elimination rate constant (k_e) of -0.082h^{-1} in IC/BPS patients relative to -0.380 h^{-1} for healthy volunteers alludes to the reabsorption of lidocaine in urine being accentuated by Hunner lesion
- Thus, application of the linear phase of Michaelis Menten Kinetics to urinary reabsorption is consistent with the demonstrated linearity between urine and mucosal concentration [8]

INTERPRETATION

- Umbrella cells covering 70% of bladder luminal surface [7] are renowned for their transcellular impermeability, drugs like lidocaine are exclusively absorbed and reabsorbed like fluorescein across tight junctions, covering ~30% of luminal surface [3](Fig.1),
- The limited number of tight junctions or ports of entry can be conceptualized as enzymes mediating lidocaine diffusion, and therefore the widening of tight junctions by distension[9] and inflammation[4] is bound to accelerate absorption/reabsorption(Fig.1)
- Thus, the variability in lidocaine reabsorption and the ceiling effect during absorption between controls and IC/BPS subjects manifest Michaelis-Menten kinetics of lidocaine if one considers that instilled concentration of 1-2% w/v lidocaine (45-85mM) achieves the maximum absorption[10] rate (k_a) analogous to the maximum enzyme activity (beyond V_{max}) depicted by the asymptote phase of Michaelis-Menten curve (Fig.2)
- The ceiling effect of V_{max} at 45-85mM obscures any additional increase in k_a rate from the widening of tight junctions by inflammation secondary to Hunner lesion which is easily discernible from flatter elimination slope of IC/BPS patients at lower urinary concentration in micromolar range

CONCLUSIONS

- The differential impact of Hunner lesion on absorption (45-85mM) and elimination(<0.01mM) manifests compliance with the asymptote and linear phases of Michaelis-Menten kinetics, respectively.
- Higher concentration saturates tight junctions (entry ports on bladder luminal surface) to obscure any impact of tight junctions widened by inflammation secondary to Hunner lesion, which is discernible at lower urine concentration (<0.01mM)
- Thus, delayed clearance of lidocaine in IC/BPS patients relative to controls is amenable to Michaelis-Menten kinetics just as healthy adults are more likely to be inebriated with vodka (40% ethanol) than with single beer (5-10% ethanol)

REFERENCES

1.Tyagi et al. Does Large Volume of Distribution of Lidocaine Masks Its Systemic Uptake From Bladder? Am J Clin Exp Urol. 11(2):121-135 2023.. 2. Henry et al. Absorption of alkalized intravesical lidocaine in normal and inflamed bladders: a simple method for improving bladder anesthesia. J Urol, 165: 1900, 2001 3. Buffington et al. Excretion of fluorescein in the urine of women with interstitial cystitis. *J Urol* 158, 786-9 (1997). 4. Au, et al. Evidence of significant absorption of sodium salicylate from urinary bladder of rats. J Pharmacol Exp Ther 258, 357-64 (1991).
5. Pereira et al. Alkalinized lidocaine solution as a first-line local anesthesia protocol for intradetrusor injection of onabotulinum toxin A: Results from a double-blinded randomized controlled trial. Neurourol Urodyn . 2020 ;39(8):2471-2479. 6. Büsker et al. Population Pharmacokinetics as a Tool to Reevaluate the Complex Disposition of Ethanol in the Fed and Fasted States.J Clin Pharmacol. 63(6):681-694. 2023 7. Staehelin, et al.: Lumenal plasma membrane of the urinary bladder. I. Three-dimensional reconstruction from freeze-etch images. J Cell Biol, 53: 73, 1972 8. Gao, X., Au, J.L., Badalament, R.A. & Wientjes, M.G. Bladder tissue uptake of mitomycin C during intravesical therapy is linear with drug concentration in urine. Clin Cancer Res 4, 139-43 (1998). 9. Birch, B. R., Miller, R. A.: Absorption characteristics of lignocaine following intravesical instillation. Scand J Urol Nephrol, 28: 359, 1994. 10. Solinsky et al. Onset of the action of intravesical lidocaine after spinal cord injury. Neurourol Urodyn, 39: 376, 2020 .

Acknowledgments: NIH grants CA252590; CA263243, DK108937