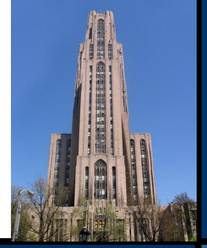
Abstract # 558



A Tale of Two Drugs in A Cocktail- Therapeutic Effect Twisted by Molecular Weight, Polarity and Volume Of Distribution

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ABSTRACT

Hypothesis / aims of study
Evidence grade of B and C undergirds the recommendation for the off-label bladder instillation of FDA approved drugs, Lidocaine and Heparin, respectively to manage the recalcitrant symptoms of Painful Bladder Syndrome/Interstitial Cystitis (IC) patients. While the aqueous solubility of the two drugs permits their easy mixing into a cocktail for bladder instillation, there is a huge disparity in the systemic uptake of heparin and lidocaine which escaped the attention of the community. Here, we clarify the scientific basis for the said disparity to shed light on the rapid onset of hypotensive effect within 2 minutes of lidocaine instillation in spinal cord injured patients (ref.2). We used standard pharmacokinetic analysis to demonstrate that the disparity in the systemic uptake of instilled heparin and lidocaine is predicated on the asymmetry of molecular weight, size, polarity, and volume of distribution (Vd).

Study design, materials and methods
Using model-independent pharmacokinetic equations, we analyzed the serum levels reported after bladder instillation in human subjects and then determined the extent of systemic dilution using Vd measured after intravenous administration of heparin and lidocaine. The divergence in the systemic uptake of instilled lidocaine and heparin was interpreted in light of their physiochemical properties listed on the public databases for drugs that are approved for human use:
https://druginfo.nlm.nih.gov/drugportal/ and
https://pubchem.ncbi.nlm.nih.gov

Results
Chemically, lidocaine is a synthetic xenobiotic and heparin is an endogenous glycosaminoglycan- a heterogeneous mixture of polysaccharide chains with molecular weights ranging from 6 to 20 KiloDaltons (KD) carrying anionic charge to bind with the clotting factors in the blood. Since the endogenous heparin complicates the exact determination of the dose fraction (F) for instilled heparin reaching the blood, we relied on the reported systemic uptake of the radiopharmaceutical, iodinated albumin (66.5Kd) after instillation in human subjects to estimate the systemic uptake of instilled heparin F= ~0.01% of the instilled dose. Because the molecular size of heparin is too large for penetration into the intracellular compartment, absorbed heparin exclusively resides in the blood volume to mirror the Vd of the clinical probe used for estimating the blood volume, iodinated albumin. Therefore, the Vd of heparin normalized to body weight at 0.05-0.1 liters/kg equals the estimated blood volume of ~7L for a 70kg adult. Since serum levels of heparin are not diluted beyond the blood volume, negligible serum levels of heparin accurately reflect the poor systemic uptake of instilled heparin. In contrast to heparin, the much smaller molecular weight of 234.4 Daltons for lidocaine facilitates its absorption from the bladder and extensive distribution into blood volume and extracellular fluid volume as well as the intracellular compartment because the unionized fraction of lidocaine diffuses across the cell membrane for a reversible binding with the sodium and hyperpolarization-activated cyclic nucleotide-gated channels to achieve a large Vd of 0.13-4.5 liters/kg (Table 1). Therefore, the mean Vd of 105L for lidocaine is 15 times higher than 7L for heparin in a 70kg adult. Fifteen times larger Vd of Lidocaine provides the context for interpreting the extent of distribution from lidocaine serum levels of 0.59±0.31ug/mL measured at 30min after instillation (10mL of 2%w/v solution)(ref.2) Using model-independent pharmacokinetic equations (F= Cmax * Vd/dose), we computed F= ~30% systemic uptake for instilled lidocaine comparable to instilled oxybutynin.

Interpretation of results
Lipinski proposed the Rule of Five for the absorption of drugs across cell membranes: molecular weight < 500, hydrogen bond donors < 5, number of hydrogen acceptors < 5, and an octanol-water partition coefficient (log P) < 5. The log P of -19.5 and 1.64 for heparin and lidocaine evinces their violation and compliance, respectively with the Rule of Five. Heparin is also negatively charged with topological polar surface area-area of all polar atoms- nitrogen and oxygen add up to 652 Å2 as opposed to just 32.3Å2 for lidocaine, an amphipathic molecule with pKa of 7.8 capable of generating the unionized fraction for rapid absorption across membranes to earn extensive distribution (Vd). Vd is a conceptual volume required for diluting the absorbed fraction of the drug to a concentration equivalent to the measured serum concentration. Since absorbed lidocaine gets diluted into Vd, approximately 15 times the blood volume, serum lidocaine levels can underestimate the true extent of lidocaine absorption. Instilled lidocaine causes hypotension within 2 minutes of instillation and the propensity for extensive dilution can mask the potential of absorbed lidocaine fraction to precipitate toxicity in vulnerable populations (ref.3). Moreover, rapid absorption and elimination of lidocaine questions the omission of earlier time points for blood sampling in reporting the safety of alkalinized lidocaine in IC patients

Concluding message
Here, we present evidence to demonstrate that the asymmetry in the physiochemical properties of two drugs in a cocktail predicts the asymmetry in the systemic uptake of ~0.01% and ~30% for heparin and lidocaine, respectively. These findings also elucidate the relevance of Lipinski's Rule of Five in the selection of permeability probes for understanding the drug absorption from the bladder and why the limited penetration of Evans Blue (960.8 Daltons) in rodent bladder does not predict the systemic uptake of up to 22% of the instilled dose for oxybutynin (357.48 Daltons) in human volunteers.

INTRODUCTION

- Off-label bladder instillation of FDA approved drugs, Lidocaine and Heparin for symptomatic management of Painful Bladder Syndrome/Interstitial Cystitis (IC) is backed by evidence grade B and C, respectively
- Aqueous solubility of heparin and lidocaine allows cocktail administration, but two drugs differ dramatically in systemic uptake (Table 1) owing to asymmetry in molecular weight, size, polarity, partition coefficient and volume of distribution (Vd)
- While local anesthesia/ analgesia for TURB and intradetrusor inj is achieved safely with instillation of lidocaine 2%, systolic blood pressure drops (BP↓) within 2 min of instillation (ref.1)
- Here, we analyzed whether instilled lidocaine is extensively diluted after rapid absorption ?

METHODS AND MATERIALS

- Using model-independent pharmacokinetic equations, we analyzed the reported serum levels after instillation in bladder of human subjects and then determined the extent of systemic dilution using Vd calculated after intravenous administration of heparin and lidocaine and their physiochemical properties listed on the public databases: https://druginfo.nlm.nih.gov/drugportal/ and https://pubchem.ncbi.nlm.nih.gov

Properties	Lidocaine	Heparin
Molecular weight (Daltons)	234.4	6000 to 20,000
Hydrodynamic diameter	3.95 Ångstrom	9 ± 1 Ångstrom
Volume of distribution (Vd)	0.13-4.5 liters/kg	0.05-0.1 liters/kg
Dose fraction (F) absorbed	23.4-30%	~0.01% of dose
Elimination rate (k_e)	-0.343 h^{-1}	-0.462 h^{-1}
Elimination half-life ($t_{1/2}$)	2.02h	1.5h
Systemic Clearance	36.01L h^{-1}	3.23 L h^{-1}
Log P	1.64	-19.5
pKa	7.8	5.1
Polar Surface Area	32.3 $Å^2$	652 $Å^2$
Formal charge	0 (amphipathic)	-1 (anionic)
Rotatable Bond Count	5	21
Hydrogen bond donors	1	15
Hydrogen acceptors	2	38

Table 1. Physiochemical properties are deterministic in absorption and distribution (Vd) of instilled drugs
While lidocaine complies, heparin violates Lipinski 's Rule of Five
Polar surface area (PSA)-area of all polar atoms- nitrogen and oxygen in the molecular structure

Acknowledgments: NCI grants CA252590; CA263243

RESULTS

- While lidocaine is a tertiary amine with pKa of 7.8 (an amphiphilic xenobiotic), heparin is a negatively charged glycosaminoglycan that binds with the endogenous clotting factors
- Since endogenous heparin complicates the determination of absorbed dose fraction (F), the F of instilled radio iodinated serum albumin (66.5KD) used as proxy for F of heparin ~0.01%
- Serum heparin levels accurately reflect the lower F of heparin because large size limits intracellular entry and volume of distribution-Vd- normalized to body weight of 0.05-0.1 liters/kg
- In contrast, Vd of lidocaine is 0.13-4.5 liters/kg =105L> 15 times of heparin Vd ~7L for a 70kg adult (Table 1; ref.1,2,4,7)
- With a mean Vd of 105L and reported C_{max} of 0.59±0.31ug/mL, F of instilled lidocaine ≥23% (F= C_{max}* Vd/dose) is comparable to oxybutynin, a tertiary amine (ref.8)
- Hence, low serum lidocaine levels masks the true F and blood sampled ≥ 25min post instillation (Fig.1A) generates erroneous reading of T_{max} = 30min(Fig.1A; ref.4) and >60min (ref.2) because unionized fraction of lidocaine is absorbed rapidly and immediately diluted in blood volume plus extracellular volume for reversible binding with Na and HCN channels in intracellular compartment

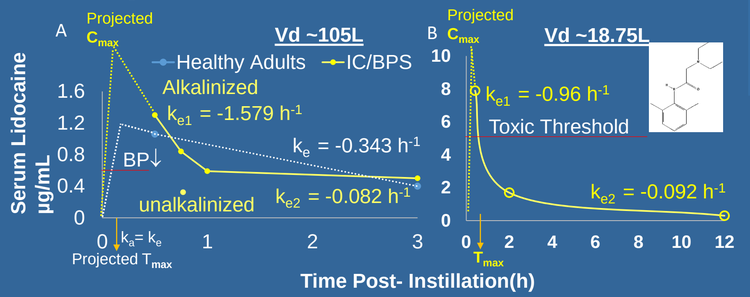

Figure 1. The rapid absorption of instilled lidocaine 2%in ~70kg adults (panel A; ref.2,4) and in a 12.5kg child (panel B;ref.3) is denoted by the steep slopes of the projected (dotted) lines before C_{max}. Equivalent F~23% results in lower and toxic serum levels in adults and child owing to dilution in larger adult Vd of ~105L and child Vd of ~18.75L, respectively. While blood sampling ≥25min post-instillation is tardy for determining IC/BPS related absorption rate (k_a) differences and true T_{max} (k_a=k_e) but terminal elimination rate (k_e) is slower for IC/BPS and in adults. The role of vasculature injured by surgery in lidocaine toxicity (panel B; ref.3) is negated by the minimal impact of Hunner lesion (IC/BPS) on F and by the dominance (71%vs 29%) of passive paracellular diffusion (across tight junctions) over intravascular uptake of I^{125} sodium iothalamate (635 Daltons) admixed in TURP irrigation fluids (ref.9). Plausibility of paracellular mode for lidocaine absorption is bolstered by a 3-fold rise in F with the extension of dwell time from 10 to 120min (ref.5) and accompanying dilation of tight junctions (ref.6,10).

DISCUSSION

- Pharmacodynamic evidence for rapid absorption of instilled lidocaine- ≥10mm Hg systolic BP↓ within 98.1± 59sec in spinal cord injured patients (ref.1)- questions the validity of pharmacokinetic evidence obtained from blood sampled ≥ 25min with C_{max} declining from T_{max} of 30 min (ref.4) and >60min (ref.2)
- Lidocaine applied topically to vagina and cervix achieves C_{max} of 0.5 ± 0.45 µg/mL at T_{max} of 5min with mild BP↓ (ref.7)
- Alkalinization increases lidocaine absorption by increasing the unionized fraction in bladder lumen (Fig.1A)
- Lidocaine complies with the Lipinski 's Rule of Five : < 500 Daltons, hydrogen bond donors < 5, number of hydrogen acceptors <5, and octanol-water partition coefficient (log P) < 5 to earn higher F and Vd than heparin (Table 1)
- Adult F with lower Vd leads to lidocaine toxicity in child (ref.3)

CONCLUSIONS

- Instilled lidocaine is rapidly absorbed from bladder with F ≥23% to be diluted in a large Vd~105L and blood sampled 5min post instillation can match BP↓ with the true T_{max}
- Lipinski 's Rule of Five explains F ~0.01% and Vd ~7L for heparin and the equivalence in F of lidocaine and oxybutynin (357.48 Daltons) at 5% capacity (ref.8), much higher than the F of Evans Blue (960.8 Daltons) at >90% bladder capacity (ref.10).

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