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Original Article

Does large volume of distribution of lidocaine masks its systemic uptake from bladder?

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Abstract: Purpose: To assess whether therapeutic and toxic effects of intravesical lidocaine are determined by coincident serum levels. Material and Methods: Published clinical trials and case studies on instilled lidocaine 1-2% that reported serum lidocaine levels were analyzed using model independent pharmacokinetic equations to compute the absorbed dose fraction (F) for linear regression with the respective dwell times. Results: Rapid absorption of intravesical lidocaine is evinced by the serum levels of 0.16±0.3 mg/L at 5 min in bladder cancer patients coinciding with the rapid onset of pain relief (<5 min) and blood pressure drop (≥10 mm Hg) in spinal cord injured patients. Serum levels at 5 min are raised five-fold by alkalinization for a tertiary amine with pKa of 7.8 and a linear rise in F with longer dwell time (r^2 = 0.80; P<0.005) conforms to passive, paracellular diffusion of amphiphilic lidocaine (log P of 1.68) around umbrella cell borders with absorption rate at least five times faster than the terminal elimination rate, and therefore the delay in blood sampling after instillation is unwarranted. A rapid resolution of therapeutic and toxic effects is predicated on the extensive dilution of absorbed lidocaine with a rapid distribution half-life of 3.6 min in body weight dependent Vd - 15 times larger than blood volume, 0.13-4.5 L/kg which necessitates dose adjustment in children. Conclusion: Whether rapid absorption of instilled lidocaine is complicated by an equally rapid and extensive dilution in body weight dependent Vd can be resolved by early blood sampling (<30 min) for: evidence-based medicine, avoidance of lidocaine toxicity in children and to educate the evolution of lidocaine solution to gel and devices.

Keywords: Lidocaine, volume of distribution, elimination, paracellular absorption

Introduction

Since 1949, the local anesthetic action of lidocaine has been employed in the urology offices for relieving acute pain of procedures: bladder mucosal biopsies [1], intradetrusor injections [2], bladder catheterization and cystoscopy [3]. Instilled lidocaine can also serve as a diagnostic screen for confirming bladder-centric chronic pain [4], hypersensitivity in detrusor instability [5] and for managing the intractable symptoms of interstitial cystitis/bladder pain syndrome (IC/BPS) alone or in cocktail with heparin [6-8].

Higson et al [5] was the first to realize that the pharmacokinetics and pharmacodynamics of instilled lidocaine, a tertiary amine with pKa of 7.8, complies with Henderson Hasselbalch equation. He was able to increase the fraction of absorbed lidocaine for diagnosing detrusor instability by raising the pH of 0.5% w/v lidocaine (80 mL) with 8.4% sodium bicarbonate ($NaHCO_3$) as a significant fraction of the absorbed lidocaine exist as unionized fraction above the pH of 7.4 which can transfer rapidly across the lipid bilayer of excitable cells (**Figure 1A**) [9] and then the slightly acidic pH of intracellular compartment generates a predominance of ionized fraction that binds with the inactivated state of Na+ channel to achieve a phasic block of action potential generation [9]. Intracellular fraction of lidocaine also binds with hyperpolarization cyclic nucleotide gated (HCN) channels [10] to raise the threshold potential and lengthen the refractory period of nerves.

Once absorbed systemically, lidocaine, a small molecule (234.4 Daltons) with pH sensitive amphipathic character, distributes rapidly not only into the blood volume (central compartment) but also into the extracellular fluid volume and into intracellular fluid volume with a

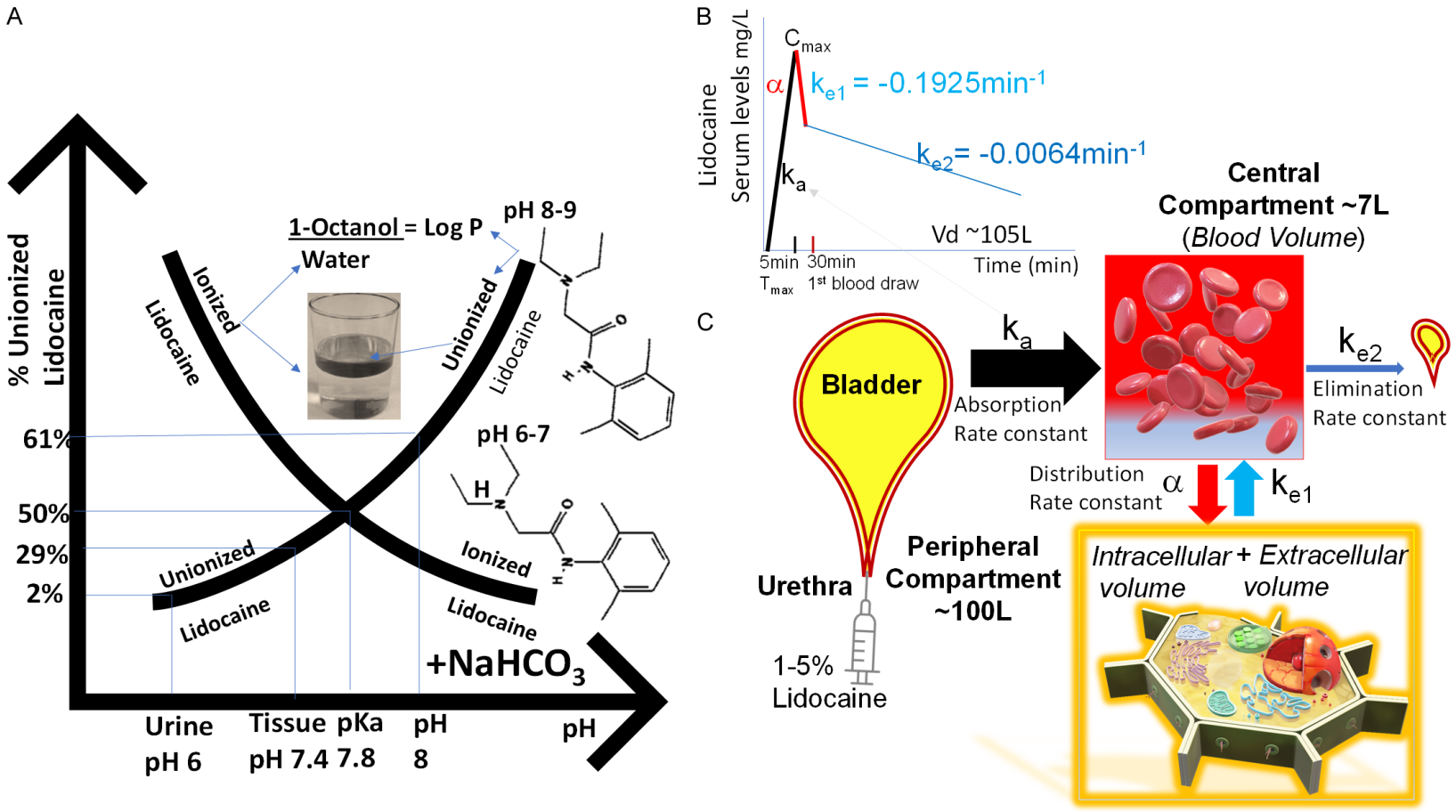

Figure 1. Schematic Illustration of Lidocaine's Pharmacokinetics: (A) *Alkaline pH increases absorption of Lidocaine having pKa of 7.8*: The schematic illustration for pH dependent predominance of unionized fraction at alkaline pH is expressed by pH > pKa = log [unionized lidocaine] > log [ionized lidocaine] in compliance with the Henderson Hasselbalch equation. As a result, alkalinization accelerates passive, paracellular diffusion of unionized lidocaine around umbrella cell borders to generate five-fold higher serum levels of lidocaine and two-fold higher intensity of pain relief. (B, C) Lidocaine also complies with Lipinski's rule of five with molecular weight of 234.4 Daltons and log P of 1.68 confers amphipathic character for a rapid absorption rate constant (k_a) and a rapid distribution rate constant of α = -0.1925 min^{-1} defines the rapid transfer of absorbed lidocaine from central compartment (~7 L) to much larger (~100 L) peripheral compartment and a large volume of distribution (Vd = central + peripheral compartment) of 0.13-4.5 Liters/kg. Thus, rapid onset of action as well as the rapid resolution of toxicity in low-body weight individuals is determined by a rapid distribution $t_{1/2}$ α of ~3.6 min into a large Vd composed of extracellular volume plus intracellular volume for intracellular binding with Na+ and HCN channels and large Vd also reinforces the role of body weight dependent dilution of F. The steepness of slope for the ascent (*thick black line of* B) and the descent (*thick red and thin blue line of* B), respectively of serum lidocaine levels not only proclaims that k_a is at least five times faster than k_e but also questions the rationale for delaying the blood sampling (0-25 min) and true C_{max} and true T_{max} when $k_a = k_e$ (elimination rate constant) is congruent with the rapid onset of action for instilled lidocaine. The differences in the magnitude of k_a and k_e are depicted by the thickness of lines in (B) and the color of the line in (B) depicts absorption, distribution, and elimination rate of instilled lidocaine in accordance with the color of corresponding arrows in scheme sketched out in (C).

distribution half-life of 3.6 min (**Figure 1B**, **1C**) [11]. Therefore, lidocaine absorbed into the central compartment is diluted into total body of water (42 L) and equilibrium binding with Na and HCN channels in heart and nerves (peripheral compartment) depletes the measurable serum concentration in central compartment and the resulting dilution is expressed by the proportionality factor of -volume of distribution (Vd)-0.13-4.5 liters/kg [11], or approximately 15 times the Vd of heparin ~7 L (= blood volume) for a 70 kg adult [12]. Hence, computation of the true absorbed dose fraction (F) = area under the serum concentration-time curve (AUC)/instilled dose (or systemic uptake from bladder) from low lidocaine serum levels requires corrections [13] for tissue binding and extensive dilution in the peripheral and central compartment, which is not necessary for instilled heparin-mean molecular weight 15,000 Daltons, negatively charged glycosaminoglycan [6-8]. Since the distribution of heparin is limited to only the central compartment of blood volume ~7 L and thus the negligible serum levels of heparin are congruent with its F without any correction.

Since lidocaine is topically applied on skin and epithelium of internal organs including bladder for localized anesthesia, a seminal report professed that F is inevitable for topical lidocaine and the report identified critical determinants of F: dose, histology, and organ's vascular supply [14]. Consequently, a rapid adjustment of blood flow [15] in the extensively interconnected capillary bed of urothelium and mucosa [16] can dramatically affect F, which sheds light on the question raised by the pediatric reports of lidocaine toxicity: why does lidocaine toxicity occurs at lower dose in bladder [17] than the dose applied topically on skin of young child [18, 19]. In that regard, while umbrella cells are renowned for their restricted transcellular permeability [20, 21], a rapid increase of mucosal blood flow [15] can dramatically accelerate the passive paracellular diffusion of instilled lidocaine [22] and breach the toxic threshold for serum lidocaine levels [17] much faster than transdermal lidocaine patch [23]. Past clinical studies also suggest that lidocaine serum levels are also sensitive to the increase in instilled volume or urinary retention [13] as bladder wall distended with longer dwell times causes the dilatation of tight junctions [22] to increase the paracellular diffusion of lidocaine.

Hence, we assessed whether variables of alkalinization and dwell time impacts the AUC and the systemic uptake from bladder (F) = AUC/instilled dose by computing the pharmacokinetic and pharmacodynamic data of 425 patients available from 14 published reports to support the premise that the rapid onset of action on pain [2] and on blood pressure [24] is predicated on rapid absorption of lidocaine [1] instilled in bladder and that the body weight dependent distribution (Vd) of adults [11] is a critical determinant in the dilution of lidocaine dose absorbed from bladder which prevents the lidocaine toxicity reported in individuals with significantly lower body weight [17, 25].

Materials and methods

We undertook this exercise to synthesize pharmacokinetic evidence for supporting the premise that the reported pharmacodynamics and toxicity of intravesical lidocaine are determined by coincident serum levels of lidocaine. Intravesical lidocaine is generally assumed to exert local anesthesia in the bladder and for multiplicity of reasons discussed later, very few studies measured serum lidocaine after instillation which has created a paucity of pharmacokinetic information on intravesical lidocaine.

We overcome the paucity of pharmacokinetic information by broadening the inclusion criteria: Published clinical studies and case reports with serum lidocaine levels for at least one time point after a single dose instillation to patients diagnosed with interstitial cystitis/painful bladder syndrome (IC/PBS), for transurethral resection of bladder tumor, neurogenic bladder patients and healthy volunteers. Although bladder malignancy and bladder inflammation are assumed to engender differences in intravesical absorption, that assumption is not supported by the published clinical evidence on equivalence in serum levels of thiotepa [26] as well as radio-iodinated albumin [27] in IC/BPS patients and in patients with superficial tumor.

Moreover, pathological processes associated with malignancy and inflammation are known to perturb tight junctions and increase the paracellular diffusion of small molecular weight drugs, like thiotepa [26] and lidocaine [13]. Therefore, different diseases were clubbed together in our analysis and instead of disease-based differences, we focused on dwell time or bladder distension as a key independent vari-

able affecting the dependent variable of systemic uptake from bladder (F) while eliminating age from the exclusion criteria: Based on our premise that serum levels of lidocaine are deterministic in the therapeutic effect of lidocaine, we excluded studies that measured the therapeutic effect of lidocaine after seven half-lives of a single lidocaine dose had elapsed. To simplify our analysis, we also excluded studies that administered multiple intravesical doses of lidocaine and studies that delivered multiple doses of lidocaine using polymeric device [28, 29].

Hence, our target population of interest is the entire patient population in urology who are generally exposed to a single dose of intravesical lidocaine. We used a standard formula *Equation* 4 for determining the F of instilled drugs, used in the past by others [26, 27, 30], the formula is derived from a standard formula used in loading dose calculations for intravenous route. Simply stated, F represents the fraction of instilled dose in bladder that is "loaded" into the systemic circulation.

Pubmed search using the terms "intravesical lidocaine" or "lidocaine bladder" revealed 140 results and we narrowed it down to 12 reports in English language that also reported serum levels of lidocaine at different time points after instillation of lidocaine as a solution in (**Table 1**).

Pharmacokinetic calculations

We used model independent equations to derive following pharmacokinetic parameters from serum levels reported in studies listed **Table 1**: rate of elimination (k_e), volume of distribution (Vd) and systemic clearance (CL) from elimination half-life ($t_{1/2}$) and percent dose absorbed (F) from the area under curve (AUC) and maximum serum levels (C_{max}):

Equation 1 - $t_{1/2} = 0.693/k_e$

Equation 2 - CL = ke* Vd

Equation 3 - CL = F. Dose/AUC [30, 31]

Equation 4 - $F = C_{max} \times Vd/\text{instilled dose}$

Equation 5 - $k_e = \ln (C_1/C_2)/(t_2 - t_1)$

Where ln is the symbol for natural log of reported serum levels of lidocaine (C_1 and C_2) at t_1 and t_2 timepoints for analyzing age related [17] or disease (IC/BPS) related [32] differences. We plotted serum lidocaine levels obtained from studies listed in **Table 1** to generate the archetypal serum-time concentration curve (**Figure 2A**, **2B**), characterized by the initial ascent in serum lidocaine levels (absorption phase) reaching the peak serum concentration (C_{max}) followed by the initial rapid descent (distribution phase-extensive distribution from central to peripheral compartment) and then slower decline of serum levels (terminal elimination phase from central compartment) (**Figure 1B**) conforming to two-compartment model kinetics of lidocaine (**Figure 1C**). The differences in the steepness of slope for ascending phase and declining serum levels (terminal downslope) hint that the rapid absorption rate constant (k_a) for intravesical lidocaine is at least five times faster than the elimination rate constant (k_e) (**Figure 1B**, **1C**).

Evaluation indicators for lidocaine with or without alkalization

To assess the differences in rapid absorption, distribution, and elimination of lidocaine with or without alkalization (**Figure 1A**), the blood sampling for the first 30 min after instillation must be more frequent than the subsequent 30-180 min time period (**Figure 2B**). The timing of blood sampled in the recommended fashion will be able to record all three slopes of AUC and faithfully capture the rapid absorption phase of alkalinized lidocaine (upslope) into central compartment followed by distribution (steeper downslope) and relatively slower elimination of lidocaine (shallower downslope). The differences in the rate of ascent and descent of plotted serum levels from 5 min to 180 min will be able to reveal the impact of alkalinization on the absorption phase (*differences in the rate of ascent*), distribution (*differences in the rate of rapid descent* immediately after C_{max} due to subject's body weight dependent change in Vd) and elimination (*differences in the rate of slow terminal decline*).

Statistical analysis

We used simple linear regression to assess the change in lidocaine serum levels with longer

Table 1. F of instilled lidocaine in published clinical studies

Study	Lidocaine dose (n = subjects)	Volume of Instillation	Dwell Time & Disease	Blood sampling points	Reported Serum levels	Absorbed Fraction (F) in %
Parsons et al 2015	333 mg + 252 mg $NaHCO_3$ (n = 14)	25 mL	45 min IC/BPS	45 min	0.17-0.84 μg/mL	26.4%
Parsons et al 2012	200 mg + 420 mg $NaHCO_3$ (n = 18)	15 mL	30 min IC/BPS	60 min	0.24-2.0 μg/mL Mean of 0.5 μg/mL	26.25%
Nickel et al 2009	200 mg + 8.4% $NaHCO_3$ (n = 19)	10 mL	60 min IC/BPS	every 30 min for 3 h	C_{max} 0.59±0.31 μg/mL	28.3-30.9%
Henry et al 2001	304-456 mg + 8.4% $NaHCO_3$ (n = 24)	18.4-22.8 mL	60 min Healthy and IC/BPS	every 30 min for 3 h	0.2-2.0 μg/mL C_{max} of 1.06 μg/mL	20.23%-23.47%
Clapp et al 1999	1000 mg (n = 1)	50 mL	15 min suprapubic pain and spasm	25-120 min	7.9 μg/mL (toxic >5 μg/mL)	28.4%
Amano et al 1995	400 mg (n = 29)	40 mL	15 min Bladder cancer	15 min	<0.2 μg/mL	5.25%
Birch and Miller 1994	400 mg (n = 11)	50 mL	60-120 min Urinary retention	60-1800 min	0.12-1.58 μg/mL	3.1-41.4%
Holmang et al 1994	400-800 mg (n = 30)	20-60 mL	7-10 min Bladder cancer	10 min	“negligible”	<1%
Pode et al 1993	750 mg (n = 10)	50 mL	5 min Bladder cancer	5, 10, 30 min	0.06-0.45 μg/mL	0.84-6.3%
Thrasher et al 1991-93	1000 mg (n = 35)	50 mL	7-10 min Bladder cancer	10 min	“negligible”	<1%
Giannakopoulos 1992	299 mg (n = 1)	65 mL	30 min IC/BPS		1.1-1.4 μg/mL	49.1%
Asklin and Cassuto 1989	200 mg (n = 1)	50 mL	IC/BPS		<5 μg/mL	-

Studies arranged in chronological order with F calculated from either AUC or highest reported serum levels in reported studies.

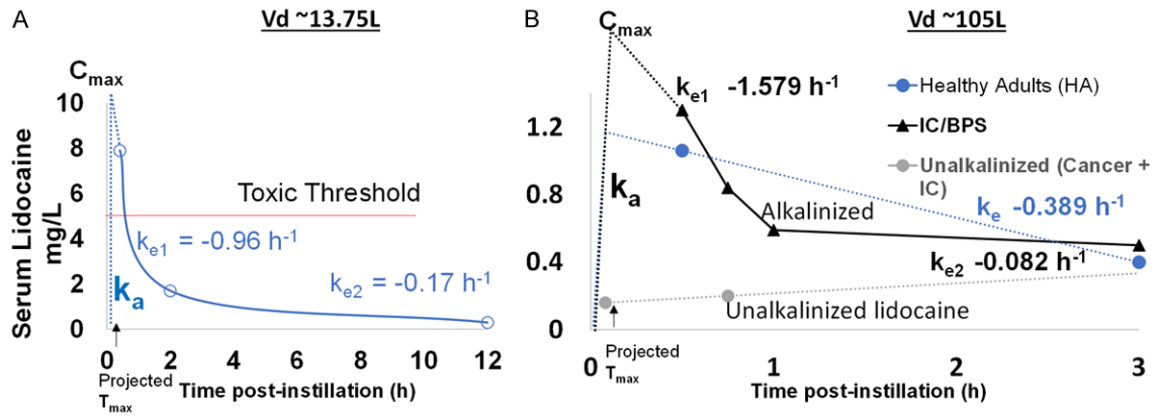

Figure 2. Impact of body weight (Vd), alkalinization and lesions on lidocaine's F-Rapid absorption of instilled lidocaine 2% w/v in 12.5 kg female child (A) and in ~70 kg adult females (B) is conspicuous from the steepness of the ascending slope of back-extrapolated (dotted) lines meeting the "true" C_{max}. The slope for the ascent of serum lidocaine levels was not only independent of age and disease but was also steeper than the downward sloping solid line denoting that the elimination phase (k_e) is at least several fold slower than absorption phase (k_a). Moreover, dose and dwell time only contributed slight differences in the serum levels of unalkalinized lidocaine at 5 and 45 min (B) in bladder cancer (750 mg for 5 min) and in IC/BPS patients (333 mg for 45 min), respectively but alkalinization significantly elevated the serum lidocaine levels relative to unalkalinized lidocaine at 5 min and at 45 min after instillation. The brief dip in the downslope immediately after C_{max} displays the distribution phase which vanishes quickly in adults due to extensive distribution in Vd ~105 L (B) but lasts longer in child (A) owing to 7-fold smaller Vd ~13.75 L to generate 10-13-fold higher $AUC_{0\text{-}12\ h}$ of 17.63 h. μg/mL than $AUC_{0.5\text{-}3\ h}$ of 1.825-2.313 h. μg/mL in adults. Moreover, rapid initial descent after C_{max} is denoted by a faster k_{e1} of -1.579 h^{-1} which suggests that concurrence of distribution and elimination heightens clearance of absorbed lidocaine in adults and a slower terminal elimination rate of -0.082 h^{-1} than -0.389 h^{-1} for healthy volunteers alludes to the reabsorption of excreted lidocaine in IC/BPS patients. Age-independent biexponential decline of serum levels conforms to two-compartment model kinetics and 97% of the absorbed dose is cleared within 4 h of instillation in child. Notice the differences in the scale for abscissa and ordinate in (A and B).

dwell times used in different clinical studies and to predict the extent of lidocaine absorption with different dwell times. Regression analysis was performed using the program PHStat on Excel. Whether the regression coefficient for the slope of the least squares line was significantly different from 0 at $P<0.05$ was assessed by Student's t test and 95% confidence interval (CI) of least squares line were calculated. The 95% CI of pharmacokinetic parameters were also used for comparing the pharmacokinetics of lidocaine with or without alkalinization and the differences in the systemic uptake and clearance of lidocaine by intravesical route [33] relative to other routes [34].

Results

Rapid absorption of instilled lidocaine-pharmacodynamic and pharmacokinetic evidence

A large body of clinical evidence supports that intravesical absorption of lidocaine, a tertiary amine with pKa of 7.8 [7, 8, 32, 33] conforms to Henderson Hasselbalch equation: pH = pKa + log [unionized lidocaine]/log [ionized lidocaine] [7, 8, 32, 33]. Just as the alkaline pH of blood accentuates the entry of unionized lidocaine into intracellular compartment, alkalinization of instilled lidocaine increases the unionized fraction in bladder lumen to accelerate intravesical absorption. This premise is supported by the findings of a recent randomized controlled trial [2] that compared the subjective acute pain relief following instillation of unalkalinized and alkalinized lidocaine.

The trial reported that 57 OAB patients reported ~50% higher pain relief immediately after instillation of 2% alkalinized lidocaine (20 mL + 10 mL of 8.4% $NaHCO_3$) than 59 OAB patients instilled with 2% lidocaine in 30 mL saline. The higher pain relief with 2% alkalinized lidocaine held in bladder of OAB patients for 5 min is also congruent with two-fold higher serum levels of 0.45±0.09 mg/L vs 0.20±0.05 mg/L measured 45 min post instillation of 2% alkalinized and unalkalinized lidocaine, respectively in a multicenter, crossover trial of 14 IC/

BPS patients [7] (**Figure 2B**). Importantly, 95% CI of 0.20±0.05 μg/mL for 2% unalkalinized lidocaine at 45 min in 14 IC/BPS patients overlaps with the 95% CI of 0.16±0.3 μg/mL for 1.5% unalkalinized lidocaine over the timeframe of 5-30 min in 40 bladder cancer patients [1, 35] (**Figure 2B**). While 95% CI of lidocaine serum levels overlapped, bladder cancer patients held 50 mL of 1.5% unalkalinized lidocaine for only 5 min and IC/BPS patients held 30 mL of 2% unalkalinized lidocaine for 30 min.

When we extrapolated lidocaine serum levels at 5 min in IC/BPS patients instilled with 2-2.5% alkalinized lidocaine [32] (**Figure 2B**), we noted that there is a fivefold elevation with respect to 0.16±0.3 μg/mL measured at 5 min with 1.5% unalkalinized lidocaine [1] as opposed to just two fold difference between alkalinized and unalkalinized lidocaine at 45 min [8]. Therefore, frequent blood sampling for first 30 min after instillation is critical for understanding the impact of alkalinization on absorption of lidocaine as there was hardly any difference in pain relief at 60 min with alkalinized and unalkalinized lidocaine in OAB patients [2].

A second multicenter crossover trial of 18 IC/BPS patients [7, 8] investigated the impact of alkalinization with extended dwell time only to infer that alkalinized lidocaine [2] accentuates the pain relief due to higher concentration of unionized fraction at alkaline pH (**Figure 1A**). Given the paucity of lidocaine serum levels to fully capture the ascent phase (**Figure 2B**) for alkalinized and unalkalinized lidocaine, immediate pain relief within 5 min of instillation [2] pharmacodynamically affirms that alkalinization accelerates the absorption of lidocaine. While C-fiber mediated systolic blood pressure drop of ≥10 mm Hg within 98.1±59 sec of instillation in a subset spinal cord injured patients [24] argues that either absorption of unalkalinized lidocaine in accelerated in neurogenic bladder or their baroreceptors become more sensitive to low serum levels of lidocaine.

Extrapolation of absorption phase: Unlike pharmacokinetics studies performed after topical application of lidocaine on nasopharyngeal [36] and vaginal [37] epithelium, lidocaine serum levels for the first 30 min after instillation were not recorded in IC/BPS patients [7, 8, 32, 33] and a range 0.06-0.45 μg/mL is reported for the timeframe of 5-30 min in adult bladder cancer patients [1, 35]. While the archetypal upward sloping phase for absorption phase of intravesical lidocaine could not be plotted from published serum levels in **Figure 2B**, k_a of instilled lidocaine is evinced by the steepness of upslope as well by the short time interval between the time of instillation and the projected C_{max}. Furthermore, rapid intravesical k_a can be also discerned from lidocaine serum levels of 0.16±0.3 μg/mL at 5 min in adult bladder cancer patients [1, 35] with 1.5% unalkalinized lidocaine being equivalent to lidocaine serum levels at 5 min [37] with 10% unalkalinized lidocaine sprayed on vagina and cervix. Therefore, equivalent lidocaine serum levels at >6 fold lower intravesical dose [1, 36, 37] argue that intravesical k_a is at least 5-times faster than vaginal k_a owing to the vast differences in the histology [14] and vascularity [15, 16] of urothelium and vaginal epithelium as well as urethral [3] and nasopharyngeal epithelium [36] exposed to same lidocaine concentration.

Distribution phase: The rapid distribution phase of absorbed lidocaine from central to peripheral compartment is graphed by the steep decline of serum levels immediately after C_{max}, defined by distribution rate constant (α = -0.1925 min^{-1} = 0.693/3.6 min) - derived from the reported distribution $t_{1/2}$ α of 3.6 min for injected lidocaine in anaesthetized adults [11, 38] - being equivalent to the initial elimination rate (k_{e1}) constant of -1.579 h^{-1} or (0.0263 min^{-1}) in IC/BPS patient. Because of delayed blood sampling post-instillation, distribution phase is partly captured by the rapidly declining serum levels (downward sloping) in published literature [17, 32].

Importantly, serum-time curves of **Figure 2A** and **2B** differ dramatically in the steepness of declining serum levels immediately after C_{max} as steep descent immediately transitions into slow decline in adults (**Figure 2B**) but steep descent lasts till 2 h in young child (**Figure 2A**), owing to the differences in volume of distribution (Vd) of young child and adults, respectively. A previous study on children less than 3 years old determined that Vd of lidocaine for that age-range is 1.1 L/kg [38] or just 13.75 L for body weight of 12.5 kg [38], seven-fold lower than the median adult Vd of 105 L calculated using the standard adult body weight of

70 kg and normalized adult Vd of 1.5 liters/kg [11].

While authors of the case report suspected extraordinarily higher extent of intravesical absorption of lidocaine by injured vasculature of bladder in young child [17], our analysis contends that amount of lidocaine absorbed by young child was comparable to adults ~23% but absorbed F of adults gets diluted in 7-fold larger adult Vd of ~105 L to generate 10-13-fold lower $AUC_{0.5\text{-}3\ h}$ of 1.825 and 2.313 h. μg/mL in healthy adults and IC/BPS patients, respectively than $AUC_{0\text{-}12\ h}$ of 17.63 h. μg/mL in child following 50 mL instillation of 2% lidocaine to relieve post-operative suprapubic pain of a 2.5-year-old female child [17].

Lidocaine toxicity and dilution (Vd): The lidocaine toxicity discussed above reproduced the toxic symptoms reported after administration of lidocaine for neonatal circumcision [18, 19]. Intriguingly, the toxicity in two case reports of children <3 years old of different genders was precipitated at nearly similar lidocaine serum levels, 8.3 μg/mL at 1 h post-application in neonate [18] and 7.9 μg/mL at 25 min (with time 0 designated as the start of instillation) in 12.5 kg female child [17]. Thus, our root cause analysis of lidocaine toxicity concurs with others on lower Vd of children and neonates, which makes them vulnerable to the exaggerated systemic exposure [19] $AUC_{0\text{-}12\ h}$ of 17.63 h. μg/mL compared to $AUC_{0.5\text{-}3\ h}$ of 1.825 and 2.313 h. μg/mL in adult healthy volunteers and in IC/BPS patients, respectively [32]. Thus, lidocaine toxicity in young child [17] resulted from the exaggerated systemic exposure of lidocaine due to lower Vd as 10-50 mL of 1-2% lidocaine is safely instilled in adult bladder cancer patients [1, 35] and in IC/BPS patients [7, 8, 33].

Elimination phase: Irrespective of the age of subject, the biexponential decline of lidocaine serum levels in **Figure 2A**, **2B** manifests two compartmental model of pharmacokinetics [11, 38] and depicts faster distribution and elimination phase with steep descent of serum levels post C_{max} and shallow terminal slope depicts slower elimination phase of lidocaine. The terminal shallow slope of declining serum levels in **Figure 2A**, **2B** is described by a slower, terminal elimination rate constant (k_{e2}) or β = -0.0064 min^{-1} in healthy volunteers [32, 33] and lidocaine serum levels at any time point can be given by $C(t) = A.\ e^{-ke1*t} + B.\ e^{-ke2*t}$. At later time points $k_{e1} >> k_{e2}$ (-0.1925 min^{-1} >> -0.0064 min^{-1}); $A.\ e^{-ke1*t}$ becomes very small relative to $B.\ e^{-ke2t}$ and C(t) can be approximated to the classic First order kinetic equation of: $C(t) = B.\ e^{-ke*t}$.

Importantly, the concave shape of plotted lidocaine serum levels in **Figure 2A**, **2B** indexes that the absorption, distribution, metabolism, and elimination of lidocaine conforms to First order kinetics with concentration dependent changes in k_e producing comparable serum levels (0.2-2 μg/mL) post instillation of 456 mg [32] and 200 mg dose [8] at 30 and 60 min, respectively in IC/BPS patients. Compliance with First order pharmacokinetics also permits back extrapolation [18], a method previously used to estimate C_{max} for explaining lidocaine toxicity in neonates [18, 19, 25]. Using standard pharmacokinetic techniques of "feathering" and back-extrapolation, we extrapolated to true C_{max} for estimating k_a to explain the instantaneous effect of instilled lidocaine on pain and blood pressure, irrespective of the age [4, 24]. While the acute pain of tumor resection in bladder cancer patients [1, 35] can be relieved with 5-10 min instillation of unalkalinized lidocaine (1-2% w/v) in the dose range of 400-750 mg, doubling of dwell time to 20 min [4] is warranted with a dose reduction of alkalinized lidocaine for the management of chronic bladder pain in IC/BPS patients [8, 33].

Lidocaine clearance: Despite differences in age and lesions, similar upslopes for the projected absorption phases prompted us to examine if slower distribution and clearance (CL) [17] precipitated the toxicity in younger population [17-19, 25]. The measurable lidocaine concentration in the central compartment declines with distribution into peripheral compartment ($\alpha = k_{e1}$) and elimination from the central compartment ($\beta = k_{e2}$). Accordingly, we first calculated k_{e1} with the formula: $k_{e1} = \ln(C_1/C_2)/(t_2 - t_1)$ using C_1 and C_2 of 7.9 μg/mL and 1.7 μg/mL at t_1 of 25 min and t_2 of 120 min **Figure 2A** [17].

k_{e1} = (ln (7.9)-ln (1.7))/(120-25) min = (2.066-0.530)/95 min = -0.016 min^{-1} or -0.96 h^{-1} and k_{e2} = ln (1.7)-ln (0.3)/10 h = 0.17 h^{-1}.

With the calculated k_{e1}, we determined the elimination $t_{1/2}$ $\beta = 0.693/k_e = 0.693/0.96 =$ 0.721 h or 43.31 minutes for instilled lidocaine,

which was comparable to the reported $t_{1/2}$ β of 58 min for intravenous lidocaine in children <3 years old [38]. However, delayed blood sampling (>25 min) in case report obviated the confirmation of the reported distribution $t_{1/2}$ α of 3.2 min in anaesthetized children [38]. Lidocaine's CL using the formula, ke* Vd, (0.96 h^{-1}*13.75 L) = 13.2 L h^{-1} was consistent with reported CL for <3 years old child [38], which is <10% of the computed CL of IC/BPS patients having a mean Vd of 105 L (1.579 h^{-1}*105 = 165.79 L h^{-1}). Using formula F = CL*AUC/Dose, we calculated that F = 23.2% = (13.2 L h^{-1}*17.63 h.mg/L)/1000 mg for 2.5 years old child [17]. Comparable F of lidocaine in child and adults (calculated below) supports our conclusion that lower Vd is responsible for the precipitation of lidocaine toxicity in child [17], and neonates [18] whereas seven-fold higher Vd leads to ten-fold lower lidocaine serum levels in adults [32, 33] (**Table 1**).

Intravesical pharmacokinetics of lidocaine in healthy adults and IC/BPS subjects

Several studies on IC/BPS patients that instilled equivalent doses of alkalinized lidocaine [7, 8, 32, 33] were compiled together for calculating k_{e1} = ln (1.3)-ln (0.59)/1-0.5 h = 0.789/0.5 = 1.579 h^{-1} and k_{e2} = ln (0.59)-ln (0.5)/2 h = 0.082 h^{-1}. Slower rate of terminal elimination phase implies that lidocaine excreted into urine is potentially reabsorbed in bladder of IC/BPS patients. We critically analyzed the pharmacokinetic parameters derived from 19 out of 102 adult IC/BPS patients instilled with alkalinized lidocaine in a multi-center study [33]. The adult $t_{1/2}$ β of 1.55±0.32 h [33] reported for instilled lidocaine in awake adults is longer than $t_{1/2}$ β of 43 min for intravenously injected lidocaine, measured in anaesthetized adults [38]. We computed mean k_e = 0.693/$t_{1/2}$ = 0.693/1.55 = -0.447 h^{-1} [32, 33] and then used mean Vd of 105 L to calculate mean CL = 46.93 L/h and F = (1.214 h.mg/L)*(46.93 L/h)/200 mg = 28.3% absorption. We also calculated F using *Equation 4:* F = (C_{max}*Vd)/dose by inserting the mean C_{max} of 0.59±0.31 mg/L reported by Nickel et al 2009 (**Figure 2B**) [33] into F = (0.59 mg/L*105 L)/200 mg results in 30.9% absorption. Therefore, for studies reporting only single value of lidocaine serum levels, we got a rough estimate of F using *Equation 4,* as listed in the rightmost column of **Table 1**.

Henry et al [32] instilled 5% alkalinized lidocaine after dilution for 60 min to 12 healthy volunteers and 12 IC/BPS patients (**Figure 2B**) but the delay in blood sampling, 30 min post-instillation resulted in a wide range of lidocaine serum levels from 0.66 to 1.71 μg/mL and 0.2-2.0 μg/mL with a mean C_{max} of 1.06 and 1.3 μg/mL in healthy volunteers and in IC/BPS patients, respectively. The pharmacokinetic parameters of intravesical lidocaine, not reported by Henry et al [32] were computed here. The k_e of lidocaine in healthy volunteers = ln (1.06)-ln (0.4)/(180-30) min = -0.389 h^{-1} was used to derive $t_{1/2}$ β = 0.693/0.389 = 1.78 h. Likewise, k_e for IC/BPS patients [32] = ln (1.3)-ln (0.5)/(180-30) min = -0.382 h^{-1} and $t_{1/2}$ β = 0.693/0.382 = 1.81 h falls in the 95% CI of 1.55±0.32 h reported by Nickel et al for IC/BPS patients [33]. Using mean body weight of 76 kg for healthy volunteers, we estimated mean Vd of 114 L and CL of 39.1 L h^{-1} and CL of 39.9 L h^{-1} was derived for IC/BPS patients having Vd of 105 L. F was 23.4% and 20.23% in healthy volunteers and IC/BPS patients, respectively.

Dwell time: While dwell time of just 5 min in bladder cancer patients (**Table 1**) generates serum levels of 0.06-0.45 mg/L [1, 35], that rises 3-fold [13] with the extended dwell time of 2 h in urinary retention patients. If we assume that urine flow rate to be 1 mL/min, then a rise in dwell time from 30 min [8] to 60 min doubles the distension of bladder wall by an additional volume of 30 mL [13, 33] as longer dwell time adds urine volume to already instilled volume of lidocaine and residual urine. Moreover, computational study [22] concurred with a cross over clinical trial [30] on intravesical thiotepa in revealing that dilatation of tight junctions following bladder distension by addition of 30 mL accelerated k_a of thiotepa. Therefore, acceleration of k_a with longer dwell time offsets the rapid distribution and elimination which raises serum levels.

Hence, we hypothesized that after adjusting for dose, increase in dwell time should increase F and accordingly, the predictor variable of dwell time (**Figure 3**) was linearly fitted with the dependent variable of F listed in **Table 1** using least squares linear regression analysis. The linear regression coefficient β of 0.355±0.1727 (95% CI) for the slope of Least Squares line between dwell time (**Figure 1C**) and F was significantly different from 0 (P<0.005, Student's t

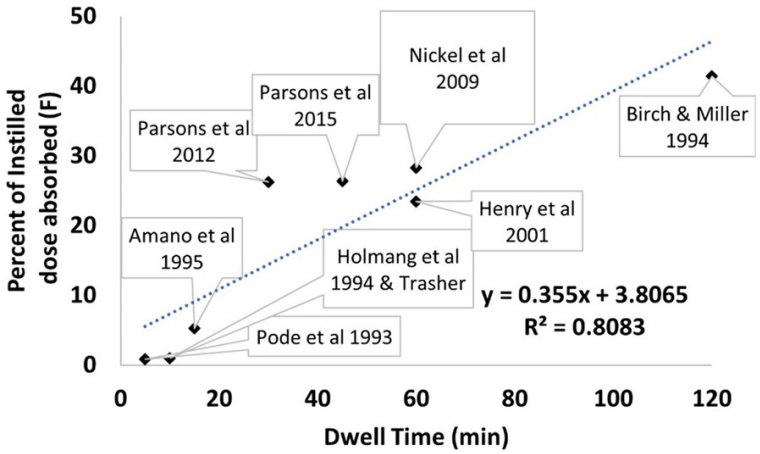

Figure 3. Dwell Time and F: As opposed to transcellular absorption of intravesical lidocaine, passive paracellular diffusion of instilled lidocaine is congruous with a 3-fold linear rise in F with the extension of dwell time to 120 min from 5 min. Because longer dwell time is bound to increase the dilatation of tight junctions >2x of Stokes-Einstein radius of 1.975 Ångstrom for lidocaine and accentuate the Stokesian diffusion rate of lidocaine through tight junctions and the extent of absorption (F) according to the predictive equation: F = 0.355 (dwell time) + 3.86065. The 95% CI of 0.355±0.1727 for the slope of the least squares line was significantly different from 0 (*P<0.005; Student's t test) and the coefficient of determination (r^2) of 0.80 implies that dwell time explains 80% of the variation in the reported serum levels of lidocaine with F rising 0.35% for every minute increase in dwell time and the predicted increase is independent of disease (bladder cancer, IC/BPS, or urinary retention) age, injured vasculature, and lidocaine dose in the range of 200-1000 mg. Dwell time of 60 min in IC/BPS patients was used by two different groups.

test). The coefficient of determination (r^2) = 0.8083 implies that the dwell time predicts 80% variation in F computed for different studies (**Table 1**) and a predictive relationship of dwell time is expressed by: F = 0.355 (dwell time) + 3.860. The independence of this predictive equation from disease and dose was empirically validated by 4-10-fold increase in lidocaine serum levels from 0.12 mg/L (n = 9) with dwell time of 1 h to 0.4-1.58 mg/L with dwell time of 2 h in in two urinary retention patients with indwelling catheters instilled with 400 mg lidocaine dose in 40 mL [13].

Discussion

Here, we synthesized pharmacokinetic evidence to support the premise that the rapid onset of action on acute bladder pain [2] and on blood pressure [24] of spinal cord injured patients is predicated on the rapid absorption of intravesical lidocaine as evinced by lidocaine serum levels of 0.16±0.3 mg/L at 5 min after instillation in bladder cancer patients [1, 35]. Moreover, a rapid resolution of therapeutic [24, 37] and toxic effect [17-19, 25] is determined by an equally rapid and extensive dilution of absorbed lidocaine in body weight dependent Vd [11, 38] - 15 times larger than blood volume [11, 38].

A rapid distribution ($t_{1/2}$ α 3.6 min) of absorbed lidocaine explains the short duration of evoked blood pressure drop [24, 37] and the lack of difference in the pain scores 60 min post instillation of alkalinized lidocaine and alkalinized lidocaine [2]. However, rapid distribution of absorbed lidocaine [38] questions the omission of blood sampling for first 25 min post-instillation in adult subjects [7, 8, 32, 33] as archetypal ascent of lidocaine serum levels [3, 37] denoting the absorption phase is missing from published graphs that only display the elimination phase of absorbed lidocaine.

Impact of pKa on C_{max}

The rapid pharmacokinetics and pharmacodynamics of instilled lidocaine are determined by its physiochemical properties of small molecular weight, amphiphilic nature and pKa of 7.8. By plotting serum levels at 5 min of bladder cancer patients instilled with unalkalinized lidocaine 750 mg in 50 mL [1] against serum levels recorded with alkalinized lidocaine [32], we could synthesize evidence that alkalinization of lidocaine elevates serum lidocaine levels by at least fivefold at 5 min as opposed to just twofold differences at 45 min [7] following instillation of alkalinized and unalkalinized lidocaine. A five-fold elevation in lidocaine serum levels at 5 min with alkalinization is congruent with a significant difference in the pain scores of OAB patients only at 5 min post-instillation of alkalinized and unalkalinized lidocaine [2] and not at 60 min. The difference in pain relief provides pharmacodynamic evidence corroborating our pharmacokinetic analysis that alkalinization accelerates rapid absorption [2, 4]. Therefore,

the reported pharmacokinetic T_{max} of 1.13± 1.09 h for alkalinized lidocaine [33] is erroneous and the blood sampling for first 30 min after instillation is critical for validating true T_{max} and verify the combined impact of alkalinization and lesions on k_a and true C_{max} in IC/BPS patients [11, 38]. The reported doubling of C_{max} with the intraurethral lidocaine dose from 400-800 mg [3] and the doubling of serum levels with the escalation of alkalinized lidocaine dose from 200 mg [33] to 456 mg [32] conforms to First order kinetics generating concentration dependent changes in k_a and k_e to double true C_{max} in accordance with intravesical pharmacokinetics of anticancer and antifungal drugs [30, 39, 40].

Unique vasculature of bladder mucosa and F

Without the first pass effect, the F of intravesical lidocaine is comparable to the F of 26-37% reported for oral lidocaine [34], which is not surprising considering that F of intravesical oxybutynin (357.48 Daltons) [41] is several fold higher than oral oxybutynin [41]. Moreover, vascularized urothelium with adjustable blood flow [15, 16] of human bladder generates higher lidocaine serum levels than the equivalent dose of lidocaine applied to skin [9], vagina [37], urethra [3] and nasopharynx [36]. Since intracavitary brachytherapy requires lidocaine spray at >6 times higher concentration than intravesical lidocaine [1, 35] only to generate comparable C_{max} of 0.50±0.45 mg/L at T_{max} of 5 min [37], we inferred that intravesical k_a is at least 5 times faster than vaginal k_a. The inference of rapid intravesical absorption is also corroborated by the coincidence of the computed pharmacodynamic T_{max} for instilled lidocaine and the insignificant drop in blood pressure following lidocaine spray on vagina and cervix [37]. Thus, based on available clinical evidence, k_a of instilled lidocaine (234.4 Daltons) is projected to be as rapid as the k_a for inert, diffusible, xenon gas (133 Daltons) because more than 1% of instilled dose of xenon is detectable in exhaled air of human subjects within <1 min of instillation [42].

Topical lidocaine and TEER

The lidocaine serum levels measured at 5 min after instillation also raises doubts on the purported inverse relationship between *ex vivo* measure of transepithelial resistance (TEER) and the permeability of epithelium to topically applied drugs (*in vivo*) because urothelium (without intact blood flow) reportedly exhibits higher TEER than vagina and skin *ex vivo* while *in vivo* systemic uptake of intravesical lidocaine is higher than lidocaine applied on skin [23] or vagina [37]. Therefore, the differences in the systemic uptake of lidocaine [32] and oxybutynin [41] from different epithelium not only emphasize the importance of histology and vascularity [14] in epithelial barrier function but also underlines that the magnitude of TEER only reflects the static component (histology) of bladder barrier function and the absence of blood flow impairs the dynamic component of urothelial barrier function in an *ex vivo* setup. With capillary density twice that of detrusor, mucosa containing urothelium traps drugs and dyes [20] that diffuse from lumen [43] and dilutes their potency in blood while incurring the risk of systemic toxicity [17] instead of permitting direct diffusion of instilled drugs to detrusor muscle [39]. We suspect that false perception of non-absorbable bladder mucosa [44] having high TEER may have misled pediatric urologists about the risk of systemic uptake from lidocaine instilled in bladder which resulted in toxicity [17].

Body weight dependent Vd and lidocaine toxicity

The authors of the case report on young child speculated on the role of exposed vasculature [17] in lidocaine toxicity without performing the due diligence of plotting the serum concentration- time curve for defining the temporal ascent and descent of serum lidocaine levels, as described in the methods section of manuscript. We finished that unfinished task in root cause analysis of lidocaine toxicity only to discover that pediatric urologists who authored the case report repeated the mistake of adult urologists [7, 8, 32, 33] in missing the rapid absorption phase by taking the first blood sample at 25 min after instillation, after the young child exhibited classical signs of lidocaine toxicity.

Furthermore, when we compared the plotted serum levels of child with the reported lidocaine serum levels in IC/BPS patients having bleeding Hunner lesion [32], we noted that the extrapolated "true" C_{max} [17] occurred around the same time in child and adults. Moreover,

comparable slopes for the back-extrapolated [18] lines for the ascending phase of serum levels before C_{max} argues that k_a of child and adult was comparable, which rules out any differences in the rate of lidocaine absorption in child as well as dismisses the role of exposed vasculature in lidocaine toxicity as speculated by pediatric urologists [17]. Furthermore, lidocaine serum levels of 0.16±0.3 mg/L at 5 min in adult bladder cancer patients before the tumor resection [1] argues that passive paracellular diffusion of the lidocaine is rapid enough without any injury to the vasculature. The Stokesian diffusion of lidocaine (234.4 Daltons and log P of 1.68) for systemic uptake from injured or uninjured bladder is expected to be even faster than the extravascular uptake of I^{125} sodium iothalamate (635 Daltons) from resected prostate of human subjects [45].

Moreover, instead of differences in ascending phase of serum concentration-time curve, we noted dramatic differences in the duration of initial rapid descent between child and adults, which underlies that lower body weight of children lowers the Vd [17] and the lower dilution of absorbed lidocaine quickly breaches the toxic threshold in young child [32, 33] but 7-fold higher Vd [11] leads to ten-fold lower lidocaine serum levels in adults. Thus, our root cause analysis of lidocaine toxicity identifies lower Vd (0.22 L/kg) of children vs 0.13-4.5 L/kg in adults as the F of instilled lidocaine in child was comparable to F in adults with bladder malignancy [46-48] or bladder inflammation [7, 32, 33, 49]. Other groups also reached similar conclusions to explain lidocaine toxicity in young individuals [18, 25].

Paracellular diffusion and dwell time

A linear rise of lidocaine serum levels with dwell time and its linear regression with F [13] corroborates that passive paracellular diffusion of instilled xenobiotics including lidocaine conforms to the principle of Stokesian diffusion-rate being inversely related to the size of drug molecule. Therefore, lidocaine with Stokes-Einstein radius of 1.975 Angstrom is expected to diffuse twice as fast as Fluorescein molecule with Stokes-Einstein radius of 3.5 Angstrom through the tortuous gap of tight junctions of human bladder distended to 50 mL [20]. Moreover, bladder distension dependent visual penetration of instilled Trypan blue dye having Stokes-Einstein radius of ~13 Angstrom validates the positive relationship of Stokesian diffusion with widened tight junctions. Therefore, a 3-fold linear rise in F with dwell time extended from 5 to 120 min argues that gap in tight junctions becomes wide enough for two molecules of lidocaine to diffuse together instead of just one molecule, analogous to the traffic flow rate increasing from one lane to two-lane highway.

Apart from distension, paracellular diffusion is also sensitive to inflammatory cytokines [43] mediated dilation of tight junctions leading to increased reabsorption of excreted salicylate in cats [31] and of excreted lidocaine in IC/BPS patients indexed by slower k_{e2} of 0.082 h^{-1} in IC/BPS patients compared to faster k_{e2} of -0.380 h^{-1} in healthy volunteers. Therefore, paracellular diffusion pathway around umbrella cell borders traced by paramagnetic dyes [43] and fluorescein [20] is more plausible than the transcellular absorption of instilled lidocaine, speculated by others [32].

Moreover, systemic absorption of instilled xenon [42] in patients with inflamed bladder and in catheterized patients illustrates the relative sensitivity of paracellular diffusion to inflammation over bladder distension, which is relevant in interpreting the differences in lidocaine's F in urinary retention [13] and IC/BPS patients at equivalent dwell times [32, 33]. However, there is a downside to longer dwell time as the addition of urine over the period of dwell time dilutes the instilled concentration of lidocaine and predictably lower mucosal concentration [39] of lidocaine can explain the lower C_{max} in cat [50] and of thiotepa in humans [30]. The effect of urine dilution with longer dwell time can be mitigated by restricted water intake or with reduced urine production by desmopressin [51] as reported for instilled mitomycin.

Elimination

While lidocaine serum levels at 45-min and 60-min post instillation [7] suggest a doubling of F with alkalinization, a lack of difference in pain score at 60 min [2] pharmacodynamically affirms that alkalinization does not impact k_e of lidocaine. Since calculated CL of 0.78 L/min [32, 33] falls within 95% CI of 0.77±0.07 L/min for oral [34] or intravenous routes [11, 38], we deduced that CL of lidocaine is route independent but differs with age and disease

(**Figure 1B**) in accordance with slower CL of instilled salicylate in cystitis relative to healthy cats [31]. Considering adult $t_{1/2}$ of ~90 min [11, 33], future cross over trial design can be refined with the incorporation of faster lidocaine washout in just 24-48 h instead of weeks [7].

Efficacy of cocktail and contraption (device)

While instilled lidocaine solution provided symptomatic relief for weeks to IC/BPS patients [32, 33], a recent study on lidocaine delivery by device failed to live up [28] to the promise shown a decade earlier [29]. A 500-1000 fold difference in the mean serum levels of lidocaine with contraption and cocktail [6-8, 32, 33] underscores the importance of pharmacokinetics in understanding the therapeutics and raises following questions: what should be the target serum lidocaine concentration for symptomatic relief in IC/BPS patients? Did the device underperform because it underperformed in sustaining the target concentration of lidocaine? Future studies should draw blood levels <5 min after instillation to truly determine the impact of rapid distribution, instilled volume, instilled concentration, and urine dilution with longer dwell time on lidocaine serum levels.

Conclusion

The pharmacokinetic evidence synthesized here supports the premise that the rapid onset of action is predicated on the rapid absorption of intravesical lidocaine, while a rapid resolution of therapeutic and toxic effect is determined by an equally rapid and extensive dilution in body weight dependent Vd. The rapid dilution in large Vd can mask the rise in serum levels and foster a misperception about poor intravesical absorption of lidocaine. We generated clinical evidence to support paracellular diffusion of lidocaine as opposed to transcellular absorption by linear regression of dwell time with F of intravesical lidocaine. Urothelial vasculature offsets the limited surface area available for paracellular absorption in bladder compared to gastrointestinal epithelium and therefore, frequent blood sampling for first 30 min post-instillation is critical for: evidence-based medicine, avoidance of lidocaine toxicity in low body weight individuals (neonates and children) and for guiding the evolution of lidocaine solution into gel and devices.

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Disclosure of conflict of interest

None.

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