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Review – Voiding Dysfunction

New Frontiers in Intravesical Therapies and Drug Delivery

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Article info

Abstract

Objectives: The intravesical route permits site-specific delivery of drugs with a reduced side-effect profile as compared to oral delivery systems, either by avoiding first-pass metabolism or by obtaining a local effect. We investigated mechanisms related to urothelium permeability and new physical and chemical developments in intravesical drug delivery that potentially permit successful treatment of several bladder dysfunction.

Methods: A literature review.

Results: Pharmacologic agents increasing urothelial permeability and useful for clinical purposes have been described, such as dimethylsulfoxide, protamine sulphate, chitosan, and nystatin. Among physical approaches, electromotive drug administration appears to be more effective than intravesical passive diffusion in delivering drugs through the urothelium into deeper layers of the bladder. Experimental and clinical reports demonstrated that electric current significantly increases the transport of local anaesthetics, mytomicin C, oxybutynin, resiniferatoxin, epinephrine, and dexamethasone. Among new chemical approaches, cell-penetrating peptides posses the ability to translocate macromolecular drugs across membranes of urothelial cells. The therapeutic benefits of sustained delivery afforded by thermosensitive hydrogel, which forms a depot for hydrophilic and hydrophobic drugs, have been demonstrated by delivering anti-inflammatory drugs. Liposomes improve the aqueous solubility of several hydrophobic drugs such as taxol, amphotericin, and capsaicin.

Conclusions: Electromotive drug administration, new in situ delivery systems, and bioadhesive liposomes may make it possible to extend intravesical therapy and drug administration to many bladder diseases. Research to expand knowledge of the chemical and physical properties of the bladder and processes regulating drug transport across biologic membranes is needed to make this a reality.

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1. Introduction

The direct administration of drug solutions into the bladder overcomes systemic adverse effects of drugs used for bladder disease. Commonly used for the treatment of superficial bladder cancer, intravesical drug administration, for example, oxybutynin, has also been used to treat neurogenic detrusor over-activity [1]. The variability of the results obtained in different clinical studies with intravesical oxybuty-nin can be attributed to several factors related to the properties of the urothelium as well as the char-acteristics of the therapeutic agents.

Recent observations of several receptors for different neurotransmitters (cholinergic, adrener-gic, purinergic, and vanilloid receptors) at the level of the urothelial cells suggest that the target sites for pharmacologic modulation of bladder dysfunction should be readily available. In any event, the ideal chemical and physical conditions for each instilled drug solution must still be standardised. Urine is frequently hypertonic and differs markedly with respect to blood potassium and pH. Changes in intravesical ions, osmolality, and pH can alter urothelial permeability, increasing or decreasing drug penetration into the bladder wall.

Furthermore, it seems that a crucial point to obtain successful drug penetration is the vehicle of the drug solution to increase urothelial permeabil-ity. Normal saline, ethanol at different concentra-tions, glucidic solvents, or liposomes with hydrogel, have been used for capsaicin and resiniferatoxin (RTX) intravesical delivery, with different success rates [2–5].

As things currently stand, we do not know the best vehicle for each intravesical drug nor do we know the ideal bladder conditions to perform useful intravesical treatment. Indeed, a better knowledge of urothelial permeability and of new systems of delivery could help to optimise intravesical treat-ments.

This review examines the mechanisms under-lying drug transport into the bladder wall and discusses exciting new frontiers for intravesical therapy.

2. Bladder urothelium: permeability and drug diffusion

The main function of the urinary bladder is to store urine while maintaining the composition of the urine similar to that produced by the kidneys. The urothelium allows the urinary bladder to minimise alterations in the composition of the urine.

Urothelial cells have different properties to per-form this function. First of all, the urothelium should expose a minimum surface to intravesical volume to avoid large movements of urine compo-nents across the bladder wall. The geometry of the bladder, which resembles a sphere, is ideal for obtaining a minimum epithelial surface area with respect to urine volume. Thus, the amount of movement of substances between the urine and blood is reduced. Urothelial cells should be impermeable to all substances present in the urine or blood. Movement across the urothelial cells occurs via two parallel pathways: the ''transcellular pathway'' (through the cells) and the ''paracellular pathway'' (through the tight junctions and lateral intercellular spaces) [7]. Tight junctions and cell membranes should be impermeable to urine or blood components, as well as to any drug contained in both compartments. Modifications of either cellular or tight junction permeability alter the efficacy of the barrier properties of the urothelium.

3. Passive permeability

For prolonged periods, the mammalian bladder is able to maintain large gradients for water, small nonelectrolytes, ions, protons, and ammonium between the urine it stores and blood. It is well known that the bladder has a small but finite passive permeability to most substances (electrolytes and nonelectrolytes) found in the urine and blood [9]. It is possible to measure the ion permeability of an epithelium by calculating the transepithelial electric resistance, which is caused by the parallel arrange-ment of cell resistance and tight junction resistance [10]. Based on the magnitude of this resistance, epithelial cells are divided into two categories: leaky and tight epithelial cells. The bladder epithelium is considered a tight epithelium [11], which has the highest recorded transepithelial resistance of all epithelia measured to date. The lack of ''uroplakins'' or urothelial plaques (protein particles packed hexagonally in the apical surface of the urothelium) does not affect the function of the tight junctions between umbrella cells, but does increase urea and water permeability [8].

In essence, the apical membrane of the bladder urothelium contributes 80% of the resistance to water flow of the epithelium as well as >95% of the resistance to fluxes of urea, ammonia, and protons. If there is appreciable permeation of these sub-stances through the tight junctions, then the apical membrane provides an even higher proportion of the resistance across the epithelium [12].

4. The "blood–urine barrier"

An essential requirement for normal bladder function is that urine components should not jeopardise the barrier properties of the bladder [6]. Changes within the physiologic range for urine pH or calcium or urea concentrations do not alter the barrier function of the urothelium, as determined from measurements of the transepithelial resistance. Consequently, acid pH, low Ca^{++}, or high urea increase the ion permeability of the urothelium [8]. In experimental studies, urine seems to be able to influence the volume–pressure response of the bladder; bladder capacity can be reduced by administering intravesical solutions of isotonic KCl, hypertonic NaCl, and pH 5 [9]. It can be increased by administration of hypotonic NaCl, isotonic mannitol, and pH 8 [9]. Furthermore, extracellular K^+ and hyperosmolality directly depolarise smooth muscle cells and generate increased activity of the detrusor, whereas hypo-osmolality produces opposite changes [9].

5. Agents that alter urothelial permeability

Several pharmacologic agents, which increase bladder urothelial permeability and can be used for clinical purposes, have been described.

A number of nonphysiologic factors cause alterations of the urothelial barrier function. Bacterial products, such as amphotericin B, nystatin, polymyxin B, and possibly β-hemolysin, as well as positively charged proteins released from eosinophils and found in sperm (histones and protamine), increase the ion permeability of the urothelium by interacting with the apical membrane.

Acetate, propionate, butyrate, or succinate at pH 4.4, but not at pH 5.0, also alter the transepithelial permeability of rabbit urothelium [9]. The increase in transepithelial permeability due to volatile fatty acids is rapid (minutes) and is due, in part, to an increase in the permeability of the apical membrane to sodium and chloride [13].

5.1. Chitosan

Chitosan is a polysaccharide composed of glucosamine and N-acetylglucosamine. It is regarded as a biocompatible, biodegradable, and nontoxic polymer. Chitosan can induce desquamation of pig urothelium, which removes all diffusion barriers: glycosaminoglycans, membrane plaques, and tight junctions of umbrella cells. This ability has been proven in vitro on nasal, buccal, vaginal, and urinary bladder mucosa of different animals, thus making this polymer a promising agent in the development of controlled drug delivery systems [14].

5.2. Antibiotics

Nystatin and gramicidin eliminate the apical membrane as a resistive element for water diffusion. Nystatin is incorporated into the lipid bilayers of sterol-containing biologic membranes and creates aqueous pores. This effect rapidly increases with the addition of the detergent Triton X-100 [15].

5.3. Protamine sulphate

An ideal model of urothelial injury would involve selective damage to the surface of urothelial or umbrella cells. On the basis of its potential to damage the surface glycosaminoglycan layer of urothelial cells, protamine sulphate (PS) has been instilled into bladders in vivo and the effects on bladder function have been evaluated [16,17]. It was demonstrated that exposure to PS in vivo causes a clear-cut disruption of the bladder permeability barrier, which starts within 1 h of exposure and recovers during days 2–5 [18]. PS bladder damage can be avoided by the addition of intraperitoneal melatonin or intravesical defibrotide [19,20].

5.4. Dimethyl sulfoxide

Widely used to treat interstitial cystitis, dimethyl sulfoxide (DMSO) is a solvent with anti-inflammatory and bacteriostatic activity; it produces analgesia and nerve blockade, diuresis, cholinesterase inhibition, vasodilation, and muscle relaxation. DMSO also has the unique capability to penetrate living tissues without causing significant damage. It has been used to enhance bladder absorption of chemotherapeutic agents such as cisplatin, pirarubicin, and doxorubicin [21,22]. In addition, DMSO is approved by the US Food and Drug Administration for the treatment of interstitial cystitis and up to 50% (vol/vol) DMSO can safely be instilled in the bladder of patients.

6. Recent developments in physical approaches

Drugs absorption through the bladder wall and drug concentrations at the target site (detrusor) are important determinants of efficacy, but passive diffusion (PD) of drugs across the urothelium is complex and not easily defined.

Many factors, including pressure and concentration gradients, time of exposure, partition coefficient, molecular weight and chemical structure, pH degree of ionisation, and urinary output rate, interact to produce different transport rates.

It has been observed that recruitment of electrokinetic forces accelerates drug administration rates across biologic membranes and into underlying tissues [23]. The term ''electromotive drug administration'' (EMDA) describes the transport of all water-soluble drugs under the influence of an electric field and, unlike PD, is most effective when dealing with an ionised drug, where the rate of drug transport is proportional to the intensity of the applied current, which largely overrides all other variables [23,24].

The idea of using electric current to allow transcutaneous drug penetration can probably be attributed to the work done by Veratti in 1747 [25]. The concept of iontophoresis was first described in the mid-18th century. However, it was not until Leduc's experimentation in 1908 that researchers realised the importance of the differences between positive and negative ions and adopted this technique for therapeutic uses. In recent years, iontophoresis has been used for local anaesthesia of the skin [26], to administer corticosteroids to joints and tendons involved in inflammatory processes [27], and for regular transcutaneous administration of drugs [28].

EMDA has been recently applied in the treatment of bladder pathologies and dysfunctions. Laboratory and clinical studies have been conducted on intravesical electromotive delivery of oxybutynin [29,30], mitomycin C (MMC) [31–33], RTX [34,35], verapamil and dexamethasone [36], bethanecol [37], and lidocaine and epinephrine [38] (Tables 1 and 2).

Laboratory studies have been performed, first of all, to identify a sensitive method to determine tissue concentrations of different drugs after either PD or electromotive administration (Table 1).

Massoud et al. found that high-performance liquid chromatography (HPLC), equipped with a diode-array spectrophotometric detector, an electrochemical detector and reversed-phase column,

Table 1 – Laboratory studies of drug administration by EMDA or passive delivery

Authors [ref]	Aims to assess	Tissue/material	Results	Advantages/problems
Lugnani et al. [24]	Lidocaine + epinephrine penetration with EMDA	Cadaveric human bladder	Staining extends into the muscolaris in all bladders	EMDA may have applications to treat bladder diseases
Gurpinar et al. [25]	Methylene blue penetration with EMDA	Dog bladder	Significant submucosal and muscolaris methylene blue penetration	EMDA may have applications to treat bladder diseases
Di Stasi et al. [41]	(a) MMC concentrations after passive diffusion or EMDA (b) Effects of EMDA on tissue viability and on MMC structure	Human bladder	EMDA/MMC reduces variability in drug delivery rate	Tissue undamaged and viable, no modification in drug structure
Di Stasi et al. [40]	Oxybutynin concentrations after both passive delivery or EMDA	Human bladder	After EMDA: mean oxybutynin tissue concentrations significantly higher	Tissue undamaged and viable, no modification in drug structure
Di Stasi et al. [42]	MMC concentration-depth profiles after passive diffusion or EMDA	Human bladder	EMDA significantly enhances MMC transport into all bladder wall layers	Tissue undamaged and viable, no modification in drug structure
Massoud et al. [39]	Oxybutynin extraction and determination by HPLC	Human bladder	EMDA significantly enhances oxybutynin penetration	Simple and cost effective; no internal standard required
Di Stasi et al. [38]	(a) Stability of lidocaine and epinephrine over time (mass spectrometry) (b) Transport rates with passive diffusion or EMDA	Pig bladder	Lidocaine and epinephrine remain stable for 1 d; EMDA accelerates lidocaine and epinephrine transport	In vitro results support clinical studies
Di Stasi et al. [35]	Stability of RTX stock solution by HPLC	Plastic material/glass	RTX stock solutions: better stability if stored at ≤4 °C in the dark	Material for RTX storage is not important
Di Stasi et al. [34]	RTX concentrations of after passive delivery or EMDA	Pig bladder	RTX bladder concentrations significantly higher	Large coefficient of variation with both techniques

EMDA = electromotive drug administration; MMC = mitomycin C; HPCL = high-performance liquid chromatography; RTX = resiniferatoxin.

was a useful method to determine tissue concentrations of oxybutynin [39]. The procedure was then applied for tissue extraction and the determination of other agents (Table 1).

The objectives of experimental studies were also to analyse the effects of electric current both on bladder tissues and on the chemical structure of the drug being used. Di Stasi et al. observed that EMDA did not alter the chemical structure of RTX, lidocaine and epinephrine, oxybutynin, or MMC and did not induce any damage to the exposed bladder tissues [34,38,40–42], thus making this method a promising tool for the treatment of detrusor overactivity and superficial bladder cancer and for inducing local anaesthesia. Furthermore, through in vitro studies the authors demonstrated that EMDA significantly increased the transport rates of several drugs into the bladder wall, as compared to simple PD. Two recent laboratory studies investigated both the transport rates of RTX into pig bladder wall after either PD or EMDA and the best conditions for the stability of RTX stock solutions [34,35]. These authors showed that the application of electric current significantly reduced the variability in transport rates of RTX as compared to PD and that glass storage in the dark and at low temperatures did not alter the stability of the drug [34,35]. These results could allow better results with RTX intravesical treatment.

From a clinical standpoint (Table 2), EMDA has been demonstrated to significantly increase the transport rates of several drugs into the bladder wall, as compared to simple PD [32,43–45]. Stenzl et al. found that five of six patients were tumour free after a follow-up of 10–16 mo, after electromotive administration of δ-aminolevulinic acid (δ-ALA) solution [44]. In this study, δ-ALA was used for the photodynamic diagnosis and therapy of superficial bladder tumours. The response rate in high-risk superficial bladder cancer was improved with increased bladder uptake of MMC following electromotive administration [32]. Intravesical electromotive administration of both 5 and 15 mg oxybutynin significantly increased cystometric bladder capacity and significantly reduced the first volume for the onset of uninhibited detrusor contractions, and duration and maximum pressure of these contractions, in patients with neurogenic detrusor overactivity [29,30]. Clinical reports demonstrated that intravesical EMDA of local anaesthetics produced sufficient anaesthesia to allow transurethral resection of bladder tumours [45,46], to perform botulinum toxin A injections into the detrusor muscle [47], to administer intravesical capsaicin [48], and to determine cystodistention in the treatment of refractory interstitial cystitis and chronic noninfectious cystitis [49–51].

6.1. Side-effects

Fatal side-effects have never been reported during or after treatment with EMDA. Hinkel and Pannek reported systemic neurologic alterations after EMDA in two older patients treated for chronic noninfectious cystitis, probably related to epinephrine systemic absorption [52]. No clinical evidence of lidocaine toxicity has been reported, and serial serum lidocaine levels measured in a few patients were innocuous [46]. No haematologic toxicity was observed after application of MMC by PD or EMDA [31,32], and no systemic side-effects were observed after oxybutynin 15 mg with EMDA application [30]. The most frequently reported side-effect is the appearance of a transient skin erythema at the site of abdominal electrode or a tingling sensation on the abdomen during treatment (Table 2).

6.2. Costs

It has been reported that, compared to spinal or general anaesthesia, the local anaesthesia induced by lidocaine with EMDA saves around 15% of the costs [47]. This treatment modality allows clinicians to perform bladder distention also in an office setting, with equivalent results to distention under general anaesthesia and potentially less morbidity and lower costs [53,54]. The cost per patient was about $146 Cdn less with electromotive intravesical lidocaine than with conventional general/spinal anaesthesia [45]. Overall, the cost of the technique includes purchasing a generator ($\cong$ Euro 2500.00), a specially designed electrode ($\cong$ Euro 250.00), and anaesthetics and other medications. The current generator can usually be used for at least 100 treatments before needing replacement or repair.

7. Recent developments in chemical approaches

A number of substances have been developed to increase drug transport across the bladder wall. Sasaki reported that intravesical instillation of saponin before administering anticancer drugs (4′-O-tetrahydropyranyldoxorubicin [THP]) can cause vacuolisation and swelling of superficial cells, and the concentration of THP in bladder tissues was significantly higher than that of untreated animals. In any case, no difference was found in plasma [55,56].

Table 2 – Clinical trials of intravesical drug administration by EMDA or passive delivery

Authors [ref]	Trials (no. of patients)	Indications	Intravesical drug/ surgical procedure	Results	Side-effects
Lugnani et al. [24]	Controlled (22)	Bladder anaesthesia before surgery	Lidocaine and epinephrine/EMDA	Pain in 16/22 patients	In all patients: transient erythema of abdominal skin
Gurpinar et al. [25]	Prospective (6)	Refractory interstitial cystitis	Lidocaine and epinephrine + cystodistention	Symptoms improved in 4 patients	Tingling sensation on the abdominal skin
Stenzl et al. [44]	Prospective (6)	Superficial bladder cancer: to evaluate the effects of δ-ALA in photodynamic diagnosis and therapy	PD/δ-ALA vs. EMDA/δ-ALA and photodynamic therapy	5 patients were tumor free for to up 16 mo	No complications occurred
Riedl et al. [49]	Prospective (17)	Noninfectious chronic cystitis	Lidocaine and dexamethasone + cystodistention	No pain in 11 patients; partial resolution in 4	No complications occurred
Rosamilia et al. [51]	Prospective (21)	Refractory interstitial cystitis	Lidocaine and dexamethasone + cystodistention	No pain in 25% of patients at 6 mo and in 63% at 2 mo	No complications occurred
Fontanella et al. [46]	Prospective (91)	Bladder and urethral anaesthesia before surgery	EMDA/lidocaine and adrenaline	No pain in 111 interventions	Transient erythema of abdominal skin
Brausi et al. [43]	Prospective multicenter controlled (28)	Superficial bladder cancer	Passive/MMC (13 patients) vs. EMDA/MMC (15 patients)	EMDA/MMC: CR: 41% vs. 41.6%; less recurrence, longer disease-free interval	After EMDA/MMC: severe chemical cystitis in 2/15 patients; cutaneous rush in 1/15
Dasgupta et al. [48]	Prospective (8)	Refractory neurogenic detrusor overactivity	EMDA/lidocaine and epinephrine (before intravesical capsaicin)	Successful CR: 75% of patients; increase in functional bladder capacity from 3 to 8 mo	No complications
Riedl et al. [50]	Prospective (13)	Refractory interstitial cystitis	EMDA/lidocaine and dexamethasone + cystodistention	No pain in 62% of patients for 4.5 mo; mean bladder capacity increased by 166%	Transient erythema of abdominal skin
Jewett et al. [45]	Prospective multicenter (94)	Bladder cancer, BPH, interstitial cystitis	No anaesthesia (18 patients) vs. EMDA/lidocaine before bladder biopsy (27 patients); EMDA/lidocaine for: transuretral resection of bladder cancer (43 patients), hydrodistension and BPH (6 patients)	No pain in EMDA groups	Tingling sensation during treatment; mucosal blanching at the bladder neck
Colombo et al. [33]	Prospective (80)	Superficial bladder cancer	Passive/MMC (36 patients) vs. MMC/thermochemotherapy (29 patients) vs. EMDA/MMC (15 patients)	CR: (a) Passive/MMC: 27% (b) Thermochemtherapy/ MMC: 40% (c) EMDA/MMC: 66%	Local toxicity more severe after thermochemotherapy
Di Stasi et al. [29]	Prospective (10)	Refractory neurogenic detrusor overactivity	Oral oxybutynin vs. passive/oxybutynin vs. EMDA/oxybutynin + pharmacokinetic studies (oxybutynin)	After EMDA/oxybutynin: significant improvements in urodynamics	Transient erythema of abdominal skin in most patients

Table 2 (*Continued*)

Authors [ref]	Trials (no. of patients)	Indications	Intravesical drug/ surgical procedure	Results	Side-effects
Di Stasi et al. [30]	Prospective (12)	Refractory neurogenic detrusor overactivity	Oral oxybutynin vs. passive/oxybutynin vs. EMDA/oxybutynin + pharmacokinetic studies (oxybutynin and N-desethyloxybutynin)	After EMDA/oxybutynin: significant improvements in urodynamics	Transient erythema of abdominal skin in most patients
Riedl et al. [37]	Prospective (25)	Detrusor hypocontractility	EMDA/bethanecol	EMDA/bethanecol predicts success of oral therapy in 86% of patients	Bladder discomfort and pain in few cases
Di Stasi et al. [31]	Multicentre randomised controlled (108)	Superficial bladder cancer	Passive/MMC (36 patients) vs. EMDA/MMC (36 patients) vs. passive/BCG (36 pts)	CR: (a) Passive/MMC: 28% (b) EMDA/MMC: 53% (c) BCG: 56%	No complications with EMDA
Schurch et al. [47]	Prospective (38)	Refractory neurogenic detrusor overactivity	Passive/lidocaine + Botox (10 patient) vs. EMDA/lidocaine + Botox (28 patients)	Mean pain score: 4.0 vs. 0.5, respectively	After EMDA/lidocaine: slight or no pain during Botox injections
Hinkel et al. [52]	Case report (1)	Chronic noninfectious cystitis	EMDA/lidocaine + epinephrine + dexamethasone	Success	No complications
Rose et al. [54]	Prospective (21)	Refractory interstitial cystitis	Passive/lidocaine + cystodistention (10 patients) vs. EMDA/lidocaine (11 patients) + cystodistention, in the office	After EMDA/lidocaine: 135% increase in bladder capacity	Failure
Rose et al. [53]	Retrospective (21)	Refractory interstitial cystitis	EMDA with cystodistention in the office vs. general anaesthesia	No significant difference	Pain persistence
Di Stasi et al. [32]	Prospective randomised	High-risk superficial bladder cancer	Passive/BCG vs. BCG + EMDA/MMC	BCG + EMDA/MMC longer disease-free interval, less recurrence, progression, and disease-specific mortality	No systemic complications

EMDA = electromotive drug administration; δ-ALA = δ-aminolevulinic acid; PD = passive diffusion; MMC = mitomycin C; CR = complete response; BPH = benign prostatic hyperplasia; BCG = bacillusCalmette-Guérin.

Certain peptides called cell-penetrating peptides or protein transduction domains have been shown to posses the ability to translocate macromolecular drugs across the blood–brain barrier and membranes of other cells [57]. However, these peptides are not cell selective and thus represent a poor choice for systemic use.

One of the authors of the present study (M.B.C.) examined the effect of short-length transactivators of transcription peptides, deriving from immunodeficiency virus, for the intravesical administration of macromolecular drugs such as peptide nucleic acids (PNAs). PNAs have been used for their "antisense" effect in various studies; in other words, they bind to RNA and completely block transcription [58]. PNAs show superior binding properties and higher stability in biologic fluids such as urine, over a wide pH range, as compared to traditional oligonucleotides and ribozymes [59].

7.1. Sustained drug delivery

Sustained intravesical delivery of drugs can ensure the continuous presence of the drug in the bladder without needing intermittent catheterisation, and drug concentration in the bladder would be constant without any peaks and valleys. It is also plausible to expect increased efficacy with increased duration of direct contact between the drug and the abnormal urothelium [60].

A simple and sensible approach for sustained intravesical drug delivery is prolonged infusion into the bladder. This technique has often been applied to achieve slow and sustained release of drugs inside the bladder. Prolonged instillation of RTX was recently demonstrated as a feasible procedure for treating interstitial cystitis [61]. RTX was infused through a suprapubic 5F mono-pigtail catheter for 10 d at the flow rate 25 μl/h with the help of an infusion pump. Patients were evaluated 30 d after the end of infusion and after 3 mo. A 30% decrease in frequency and a 3-fold reduction of nocturia was observed, with a significant reduction of pelvic pain for at least 6 mo after the end of infusion. A similar approach was previously applied for local therapy of prostaglandins in the treatment of cyclophosphamide-induced cystitis in patients [62,63]. A 100-ml irrigation of 5 μg/ml prostaglandin E$_2$ (PGE$_2$) into the bladder for 3 h completely freed a 40-yr-old patient of all symptoms within 24 h [64].

Forming a drug depot inside the bladder appears to be an attractive option over prolonged infusion. Aqueous solutions of poly(ethylene glycol-b-[DL-lactic acid-co-glycolic acid]-b-ethylene glycol) (PEG-PLGA-PEG) triblock copolymers form a free-flowing solution at room temperature and become a viscous gel at body temperature of 37 °C [65]. Its formulation does not require organic solvent, and the products from bioerosion of the biocompatible polymer are nontoxic PEG, glycolic acid, and lactic acid [66]. Thermosensitive hydrogel formed by PEG-PLGA-PEG has been used for in situ gel formation for a depot of hydrophobic and hydrophilic drugs following subcutaneous administration in rats [67]. The triblock copolymer was used for sustaining the residence time of hydrophobic drugs in rat bladder after its instillation at room temperature. The kinetics of drug excretion were studied by fluorescence measurement of urine after instilling fluorescein isothiocyanate-loaded hydrogel. The increased urine concentration over a period of time implies increased penetration into the bladder tissue. The therapeutic benefit of sustained delivery afforded by thermosensitive hydrogel was demonstrated by delivering misoprostol, an anti-inflammatory drug. It was able to protect the bladder against cyclophosphamide-induced cystitis [68].

7.2. Liposomes

Liposomes were first studied in England in 1961 by Bangham [69] and, since then, they have become a versatile tool of study in biology, biochemistry, and medicine. Liposomes are artificial spherical vesicles consisting of an aqueous core enclosed in one or more phospholipid layers, used as drug carriers and loaded with a great variety of molecules such as small drug molecules, proteins, nucleotides, and even plasmids [70]. Previously, liposomes were shown to improve the aqueous solubility of hydrophobic drugs such as paclitaxel (Taxol) and amphotericin; a recent report by the laboratory of one of the authors in the United States discussed the use of liposomes as vehicles for capsaicin and evaluated their potential as a vehicle for intravesical delivery in rats [71]. Liposomes were able to deliver capsaicin with efficacy similar to that of ethanolic saline, but toxicity to the bladder was drastically reduced [72].

Liposomes are versatile drug delivery vehicles due to the flexibility of their compositions. Liposomes were used for intracellular delivery of anticancer drugs and biologics into the bladder cancer cell line. Use of multilamellar liposomes proved favourable in cell culture studies and the antiproliferative capacity of interferon α (IFN-α) in resistant bladder cancer cell lines was improved by using liposomes as a delivery vehicle. Instillation of liposomes encapsulated radiolabelled IFN-α or radiolabelled liposomes into mouse bladder was able to

achieve localised therapy with negligible penetration to other organs.

Earlier it was reported that liposomes can form a film on the cell surface and have been tested as possible therapeutic agents to promote wound healing. Such reports prompted evaluation of empty liposomes devoid of any drug in a rat model of bladder hyperactivity. Liposomes alone were able to partially reverse the high urinary frequency induced by PS/KCl. These observations suggested that liposomes might enhance the barrier properties of a dysfunctional uroepithelium and increase resistance to irritant penetration.

8. Conclusions

The lower urinary tract is ideally suited for minimally invasive intravesical therapy that would limit the risk of systemic side-effects. Although treatment with intravesical passive delivery of drugs is commonly used today in patients on intermittent catheterisation, new physical approaches such as EMDA or in situ delivery systems and bioadhesive liposomes may expand intravesical therapy and drug administration to many bladder diseases. New agents modulating bladder neurotransmitters and neuroreceptors are being discovered, and they may be appropriate for advanced intravesical therapy. Research to expand the knowledge of chemical and physical properties of the bladder and processes regulating drug transport across biologic membranes is needed to make this a reality.

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Editorial Comment

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This comprehensive article on intravesical therapies reviews the less accessible, nonmedical literature for the urologist and links the information to clinical practice and empirical therapies for which I offer my congratulations. The physical and chemical properties of the urothelium are worth further study in the future and empirically found applications need confirmation in randomised trials so that a larger introduction into clinical practice is possible. Improving anaesthesia of the bladder is useful for general urologic practice. In functional urology, interstitial cystitis and the overactive bladder are demanding indications for any improvement in the intravesical route (botulinum toxin, resiniferatoxin, dimethyl sulfoxide, oxybutynin, etc). Electromotive drug administration (EMDA) is not routinely used in clinical practice and intraluminal drug delivery devices need confirmation in the literature along with pertinent indications. New chemical approaches are discussed but are still considered experimental. This review is hopefully the impetus for a large series of studies, publications, and new developments.