1. ハンナー潰瘍を認める場合，経尿道的潰瘍切除術（TUR: transurethral resection）を行うと症状の改善に有効である。これは，炎症反応が起こっている潰瘍部位を切除することで炎症促進因子が除去されることによると考えられている。逆に潰瘍を認めた場合は，可及的に潰瘍を切除すべきであり，これを残して治療を終えると症状が術後も遺残する一因となる。
2. 有効性については，本治療を実施した約50％の症例で症状が改善し，その効果は約6ヵ月で消失する。
3. 作用機序としては，膀胱壁の血流や神経末端への影響が推測されており，さらには拡張によって膀胱粘膜における成長因子が調整され，症状改善に繋がっていると考えられている。

② 症状コントロールのための治療～疼痛～

1. 膀胱痛に対して鎮痛剤を用いているが，最もよく用いられるのが即効性のあるジクロフェナクやロキソプルフェンをはじめとした非ステロイド系鎮痛剤である。
2. 疼痛コントロール不良の場合，癌性疼痛のようにコデインなどの弱オピオイド，さらには強オピオイド（モルヒネ製剤，ペンタゾシンなど）を用いることがあるが，実際には膀胱刺激症状に対しては効果が低く，期待するほどの鎮痛効果が得られない場合が多い。
3. コントロール困難な痛みを伴う場合，多くは潰瘍型間質性膀胱炎であり，その場合にはTUR・TUCを含めて膀胱水圧拡張術を検討したほうがよい場合が多い。

処方例

1) ロキソニン（60）　3錠　分3　症状の程度により調整
2) ボルタレン座薬（25，もしくは50mg，症状の程度と患者の状態で選択）　1～3回肛門内挿入
3) トラムセット　2カプセル　分2

なお，症状詳記を記載する必要があるが，上記にても症状コントロール不良の場合，トラマールや麻薬を用いることもある。

③症状コントロールのための治療～頻尿・尿意切迫感～

1. 間質性膀胱炎は膀胱粘膜の原因不明の炎症の結果として頻尿・膀胱痛などの膀胱刺激症状をきたしているので，炎症を除去しないで抗コリン剤を用いると排尿筋の収縮力を低下させるばかりでむしろ症状を悪化させる。
2. したがって，当科では少なくとも初療から頻尿の治療目的に抗コリン剤を用いることはしていない。
3. 疼痛がコントロールされているものの頻尿症状が遺残している場合，半減期の短い抗コリン剤もしくは，膀胱平滑筋弛緩薬を用いる。

処方例
1) ステーブラOD錠 (0.2)　1錠分1もしくは2錠分2 (症状の程度で選択)
2) ブラダロン (200)　3錠分3　(症状の程度で調整可)

④仮説に基づいた治療

(1) トシル酸スプラタスト

1. IgE産生，ヘルパーT細胞によるIL-4やIL-5の産生を抑える働きがあり，本邦では喘息などのアレルギー性疾患に対する抗アレルギー薬として用いられている。
2. 間質性膀胱炎の治療でも応用され，症状の改善が報告されている。

処方例
1) IPDカプセル (100)　3カプセル　分3

(2) 三環系抗うつ薬

1. うつ病を合併した患者にamitriptylineを用いたところ，間質性膀胱炎の症状が改善したことから，間質性膀胱炎の治療への応用がなされた。
2. 機序としては，amitriptylineはserotoninやnoradrenalineの再取り込みを抑制し，中枢神経の痛み刺激の伝導を抑えるとともに

histamineH1受容体をブロックして肥満細胞の活動を抑制し，間質性膀胱炎症状の改善に寄与していると考えられる。

処方例
1）トリプタノール（30～75mg） 分3 （状態に応じて適宜調整）

（3）シメチジン

1. histamineH2受容体阻害薬で，肥満細胞の増加とcimetidineに対する反応性との間に関連を認めなかったが，6ヵ月の内服による症状の改善が報告されている。

（4）ステロイド

1. 副作用の問題から一般的には用いられていないが，Soucyらは難治性の間質性膀胱炎患者にステロイド療法を行い，有意な疼痛コントロールが得られたと報告している。
2. 重症例に限ってではあるがステロイド療法介入の余地が示唆されており，当科でも潰瘍型の中でも症状増悪を繰り返している症例についてステロイド療法を導入している。ただし，副作用の問題があるので長期処方は望ましくないことを念頭に治療を行う必要がある。

処方例
1）セレスタミン 1～6錠 分3
2）通常は用いないが，症例によってはプレドニンを用いる。

（5）抗ヒスタミン薬

1. 強力な炎症性メディエーターを含む肥満細胞の活性化を抑制することで間質性膀胱炎の症状を改善していると考えられている。

（6）Pentosan polysulfate（経口剤）

1. 経口摂取でその3～6%が尿中に排泄され膀胱粘膜のバリアであるGAG層の欠損を修復し，効果を示すと考えられている。
2. 海外ではその有用性が示されているが，本邦ではPentosan polysulfateは未承認で，変形性膝関節症治療薬として第Ⅰ相臨床試験が開始されたところである。

なお，これらの薬剤で明確な効果の示されたものはPentosan polysulfateに限られ，しかも，その効果に疑問を呈する研究もある。したがって，内服治療は効果の不確定な治療のひとつとして，あくまでも補助的に用いるべきである。

⑤ 膀胱内注入療法・膀胱壁内注入療法

- 膀胱内注入療法・膀胱壁内注入療法は直接膀胱内/膀胱壁内に薬剤を注入し，直接的な効果を期待した治療法である。
- いずれも現時点ではエビデンスレベルの高い治療ではないため，膀胱水圧拡張術などで治療しても症状の寛解が得られない難治症例を対象としている。
- また保険適応となっていないため行う場合は施設の倫理委員会の審査を経た形で行うことが望ましい。

(1) ムコ多糖類(ヘパリン，ヒアルロン酸，硫酸コンドロイチン，Pentosan polysulfate)

1. 尿路上皮表面の破壊されたGAG層の修復を目的にムコ多糖類の膀胱内注入。
2. Parsonsらは56%の患者で症状の軽減を認めたと報告しているが，まだヘパリンを含め，いずれのムコ多糖類でも有効性の確証が得られていないのが実情である。
3. 疼痛の軽減を目的として局所麻酔薬であるリドカインを膀胱内に注入することもあるが，短時間で効果が期待できる半面，効果が持続しないため，一般的には行われていない。
4. 筆者らの施設では，ヘパリンとリドカイン双方の長所を生かす目的でヘパリン・リドカイン混合液膀胱内注入療法を行っているが79%の患者で症状の改善を認めており，その有効性が期待される。

(2) DMSO (Dimethyl sulfoxide)

1. 当科では現在用いていないが，間質性膀胱炎の治療に古くから用いられている。作用機序は不明であるが，炎症抑制，筋弛緩，鎮痛，コ

ラーゲンの分解，肥満細胞の脱顆粒などの作用があるとされる。

(3) A型ボツリヌス毒素

1. 末梢の神経筋接合部における神経終末内でのアセチルコリン放出抑制により神経筋伝達を阻害し筋弛緩作用を示す。
2. 泌尿器科領域では過活動膀胱の治療に用いられているが，最近インターロイキン1を抑制することでNGF分泌を抑制することが判明し，症例は少ないが間質性膀胱炎での応用が報告されている。

⑥ 外科的手術(膀胱拡大術，膀胱全摘除術・尿路変向術)

1. 種々の保存的治療で症状のコントロールがつかない症例は特に明確な適応基準や定められた術式はないが，膀胱摘除術・尿路変更術もしくは膀胱部分切除術・回腸利用膀胱拡大術の適応となる。
2. ただし，膀胱拡大術に関しては膀胱三角部を残すことから賛否が分かれており，術式の選択においては症状遺残の可能性などを含めて勘案し，慎重に検討を進める必要がある。
3. なお，近年の報告では膀胱摘除術・回腸導管造設術が最も選択されている術式となっている。
4. 治療効果は，Rossbergerらによると潰瘍型の間質性膀胱炎患者では82%で症状の寛解が得られたのに対して非潰瘍型の間質性膀胱炎ではわずか23%であった。ほかにもPeekerらも同様の報告をしており，治療効果は潰瘍の有無によって規定されており，この点においても間質性膀胱炎は潰瘍の有無で病態が異なる可能性が示唆されている。

D ここが診療のポイント

1. 間質性膀胱炎の症状はバリエーションに富んでおり，その診断は基本的には同様の症状をきたしうる疾患の除外診断を行いながら行っていく。その中で要となるのは問診である。

② 併存症としての膠原病や抗がん剤などの使用が間質性膀胱炎症状を引き起こしている場合があり，既往症や薬剤使用歴の聴取は重要である。

③ 現在，間質性膀胱炎の診断基準，治療方針に関して確立されたものは無いが，わが国では，日本間質性膀胱炎研究会が刊行した「間質性膀胱炎診療ガイドライン」に基づいた診療が行われている。

④ 最終的な診断は，治療を兼ねて行う膀胱水圧拡張術での膀胱粘膜所見による。
すなわち，膀胱水圧拡張術が現時点では，間質性膀胱炎診療の要となる医療行為である。

⑤ 膀胱水圧拡張術後は基本的に患者の状況に応じて適宜薬剤を調整し，症状が自制内で無くなった場合において次の侵襲的な治療を検討する。

セルフアセスメント

問題

70歳女性，頻尿と膀胱痛を主訴に受診。これまでに同様の症状を訴えて複数の医療機関を受診し，治療を受けるも改善が無かったとのこと。前医では抗コリン剤を処方されたが，症状は改善するどころか排尿回数は変わらずに，むしろ膀胱の違和感が悪化したという。
1日排尿回数は30回前後，1回平均排尿量は50mℓ。尿は漏れないが，我慢すると違和感や痛みが強くなり，排尿すると軽快するという。尿検査，超音波検査では明らかな異常を認めず。尿培養は陰性，尿細胞診はClass2であった。
この症例の診断において最も重要と思われる検査はどれか。

(a) 尿流動態測定検査
(b) CT
(c) 外来での膀胱鏡
(d) 膀胱粘膜生検
(e) 尿流測定検査

解説　蓄尿で，膀胱痛を訴える典型的な潰瘍型の間質性膀胱炎の症例である。
患者は蓄尿で痛みを感じるため，経験的に痛みを感じる前に排尿するようにし，そのために頻尿となることが多い。ただし，過活動膀胱と違い，膀胱粘膜の炎症によって膀胱知覚が過敏となっているため，抗コリン剤など蓄尿を促す薬剤を用いるとむしろ症状の増悪をもたらすことが多い。
また，頻尿と膀胱痛を訴える場合の鑑別疾患としては，女性の場合，膀胱結石，膀胱癌などがあげられる。とくに膀胱上皮内癌との鑑別は重要である。
以上を総合すると，間質性膀胱炎に類似する疾患は大方除外され，間質性膀胱炎を考えるが，その診断においては①膀胱粘膜の観察と②病理組織学的な悪性疾患の否定が最終的に重要である。
この点を勘案して検査を計画すると良い。

a. 尿流動態検査	×	間質性膀胱炎診断においてはそれほど重要な意味を持たない。また検査自体が侵襲的であり，通常は行わない。
b. CT	×	全く不要な検査ではないが，すでに超音波検査で尿路のスクリーニングをしており，プライオリティの高い検査ではない。
c. 外来での膀胱鏡検査	×	間質性膀胱炎では痛みを訴えることが多く，また悪性疾患の否定のため生検が推奨されることも勘案すると麻酔下での膀胱鏡検査，粘膜生険を行うことが望ましい。なお，間質性膀胱炎を疑う場合は，膀胱水圧拡張術の手順に準じて検査を進めるとよい。(注水→内部観察→排水時の粘膜変化の観察→生検)
d. 膀胱粘膜生検	○	
e. 尿流測定検査	×	排尿状態を知る補助的な検査ではあるが，「最も」重要な検査ではない。

解答 (d)

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Original Article

On- and post-treatment symptom relief by repeated instillations of heparin and alkalized lidocaine in interstitial cystitis

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Abbreviations & Acronyms
AVV = average voided volume
DMSO = dimethyl sulfoxide
FVC = frequency volume chart
GAG = glycosaminoglycan
GRA = global response assessment
HBS = hypersensitive bladder syndrome
IC = interstitial cystitis
NGF = nerve growth factor
NIDDK = National Institute of Diabetes and Digestive and Kidney Diseases
NSAIDs = non-steroidal anti-inflammatory drugs
NUIC = non-ulcer type IC
OSSI/OSPI = O'Leary and Sant's symptom index and problem index
UF = urinary frequency
UIC = ulcer type interstitial cystitis
VAS = visual analog scale (for pain)

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Objectives: To examine outcomes of intravesical instillations of heparin and alkalized lidocaine in patients with interstitial cystitis.

Methods: Patients with interstitial cystitis refractory to conventional therapies were given a solution of 20 000 U heparin, 5 mL 4% lidocaine and 25 mL 7% sodium bicarbonate, intravesically, weekly for 12 weeks consecutively. The treatment was regarded as "effective", when patients rated "slightly improved" or "better" on a seven-graded scale of global response assessment. Other assessment measures included O'Leary and Sant's symptom index and problem index, visual analog scale for pain, and frequency volume chart variables.

Results: A total of 32 patients were enrolled in the study. The average age was 63.3 years. All participants had received hydrodistension 2.2 times on average, and fulfilled National Institute of Diabetes and Digestive and Kidney Diseases criteria. The therapy was effective in 60.0% of the patients at the fourth instillation, in 76.7% at the last instillation, and 90.0%, 46.7% and 16.7% at 1, 2 and 6 months after the last instillation, respectively. Most of other assessment measures improved significantly at the fourth instillation and further beyond until the end of therapy. On termination of therapy, the efficacy gradually diminished, yet mostly maintained statistical significance by 2 months post-instillation. No severe adverse events occurred.

Conclusions: A 12-week course of weekly intravesical instillations of heparin combined with alkalized lidocaine is safe and effective in relieving symptoms in interstitial cystitis patients. The effect of the treatment is maintained for 6 months. Further studies are required to optimize the number of instillations and maintenance intervals in order to maximize the therapeutic potential of simple or combined instillations in the management of interstitial cystitis.

Key words: heparin, interstitial cystitis, intravesical instillation, lidocaine.

Introduction

IC is characterized by a particular symptom complex with no identifiable causes.[1] The symptom complex, HBS, is defined as bladder hypersensitivity, usually associated with urinary frequency, with or without bladder pain.[2] No current treatments have a significant impact on symptoms over time, and as a result, patients are subject to numerous treatment modalities; from invasive to holistic therapies.[3–5]

One of the possible etiologies for IC is chronic and persistent deficiency of the GAG layer, which allows penetration of urine into the interstitial layer of the bladder, thereby causing inflammatory reactions.[6,7] Heparin, a family of sulfated polysaccharide resembling GAG, is believed to bind the defect of the GAG layer on bladder surface. According to the previous reports, intravesical heparin therapy is effective in approximately half of the patients; however, it cannot produce immediate relief of IC symptoms.[7] In contrast, immediate symptom relief can be attained by intravesical lidocaine therapy. The safety and

improved absorption of alkalized lidocaine was confirmed in IC patients, although the effects of alkalized lidocaine disappear within a few days.[8] Combination of heparin and alkalized lidocaine successfully attained immediate and sustained improvement; however, the patients were followed only for 2 weeks post-treatment, and backgrounds (i.e. age, sex, with or without ulcer) predictive of favorable response have not been explored.[9]

We tested the efficacy of 12-weekly intravesical instillations of a combination of heparin and alkalized lidocaine in patients with IC, and evaluated therapeutic outcomes up to 6 months after the last instillation. In addition, we examined the difference in therapeutic response according to their backgrounds.

Methods

Patients

Patients with IC refractory to conventional therapies were enrolled in the study. IC was diagnosed by three conditions: (i) lower urinary symptoms, such as urinary frequency, bladder hypersensitivity and/or bladder pain; (ii) bladder pathology proven endoscopically by Hunner's ulcer and/or mucosal bleeding after over-distension; and (iii) exclusion of confusable diseases, such as infection, malignancy or calculi of the urinary tract.[2] According to cystoscopic findings on hydrodistension, patients were categorized into two groups; UIC and NUIC. Symptoms were assessed by OSSI/OSPI. Scores six or more for both indices, despite present therapies (i.e. hydrodistension or oral drugs), were required for enrolment. At enrolment, patients' age at therapy, age at onset of IC, duration of IC symptoms, sex, number of hydrodistensions undergone before the therapy and distended bladder volume at the primary hydrodistension were recorded. Patients with an allergy to lidocaine, continuous macrohematuria, active urinary tract infection and hemorrhagic diathesis were excluded.

The protocol of the study was approved by our Institutional Review Board (#2205), and was fully explained to the patients before a written informed consent was obtained.

Therapeutic protocol

All patients were intravesically given a solution of 20 000 U heparin (Ajinomoto, Tokyo, Japan), 5 mL 4% lidocaine (Astrazeneca, Osaka, Japan) and 25 mL 7% sodium bicarbonate (Otsuka, Tokyo, Japan) weekly for 12 weeks consecutively at our outpatient clinic using an 8-Fr urethral catheter. The acidity of the solution was pH 7.5. At each treatment, patients voided before instillation, and were instructed to hold urine for 30 min after instillation. The solution was prepared under sterile conditions immediately before every instillation. Adverse events were monitored by urinalysis and interviewing patients.

Table 1 Patients' demographics

No. (male/female)	32 (3/29)
Mean age (years)	63.3 ± 13.8 (range 35–82)
Age at onset of IC (years)	60.0 ± 14.4 (range 25–74)
Duration of IC (years)	4.7 ± 3.5 (range 1–13)
Type of IC (UIC/NUIC)	17/15
Past treatment	
Hydrodistension	32 2.21 times on average (range 1–7)
Distended bladder volume at primary hydrodistension (mL)	570.0 ± 230.0 (range 200–1200)
DMSO instillation	10
Medicine	
Suplatast tosilate	18
Tricyclic antidepressant	11
NSAIDs	14
Others	6

Evaluation items

We used GRA as the primary outcome measure. Participants rated their symptoms on a seven-grade scale ranging from markedly worse (−3) to markedly improved (+3) compared with the baseline. Efficacy was classified as "effective" when participants reported slight (+1) to marked improvement (+3) on the GRA, otherwise efficacy was considered to be "not effective" or as "symptom recurrence" if it was during the follow-up period.[10]

Other assessments included OSSI/OSPI, VAS for pain and FVC variables. The efficacy was evaluated after the first, fourth and 12th instillations, and 1, 2 and 6 months after the last instillation. Withdrawal from the study without completing the treatment course was counted as drop-out.

Statistical analysis

Therapeutic outcomes were compared with the baseline values. For its skewed distribution, signed Wilcoxon's rank sum test for paired samples was carried out to compare the values of average voided volume, daytime urinary frequency and nocturnal urinary frequency. For other variables, Wilcoxon's signed rank test was used. Patients' background factors associated with therapeutic efficacy at the fourth instillation and 2 months post-therapy were examined by χ^2-test and Fisher's exact test. $P < 0.05$ was considered significant. All calculations were carried out with SPSS, version 18.0 (SPSS, Chicago, IL, USA).

Results

A total of 32 participants (29 women and 3 men) were enrolled in the study (Table 1). The mean age was 63.3 years (range 35–82 years). All participants were compatible with the NIDDK criteria.[11] Of them, 17 were categorized as UIC, and 15 as NUIC. All patients had received hydrodistension

Table 2 Global therapeutic response ($n = 30$)

	During therapy			Post-therapy		
	Week 1	Week 4	Week 12	1 Month	2 Months	6 Months
Responders†	10	18	23	27	14	5
Non-responders‡	20	12	7	3	16	25
Response rate (%)	33.3	60.0	76.7	90.0	46.7	16.7

†GRA: +1, +2 or +3. ‡GRA: 0, −1, −2 or −3.

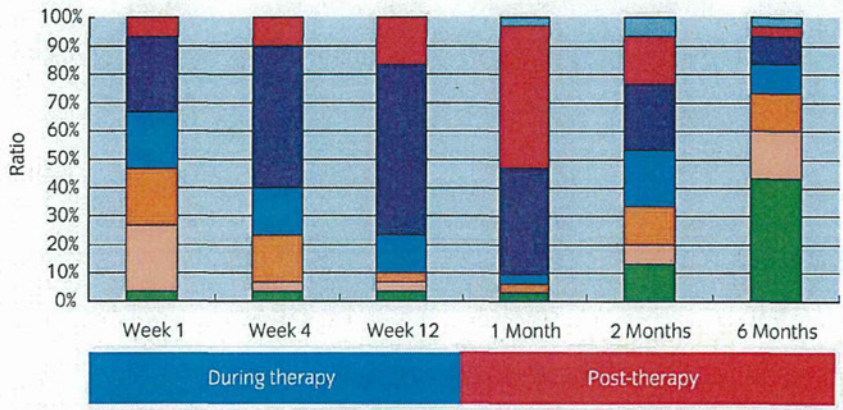

Fig. 1 Global response assessment for efficacy of heparin and alkalized lidocaine instillation. Patients with IC refractory to conventional therapies received a solution of 20 000 U heparin, 5 mL 4% lidocaine, and 25 mL 7% sodium bicarbonate intravesically weekly for 12 weeks consecutively. The patients were followed up at 1, 2 and 6 months post-instillation without further treatment. The efficacy was graded as "marked improved" (GRA +3), "moderately improved" (GRA +2), "slightly improved" (GRA+1), "no change" (GRA 0), "slightly worsened" (GRA −1), "moderately worsened" (GRA −2) or "marked worsened" (GRA −3). ■, GRA = +3; ■, GRA = +2; ■, GRA = +1; ■, GRA = 0; ■, GRA = −1; ■, GRA = −2; ■, GRA = −3.

at least once before instillation, with 2.2 times on average (range 1–7). Prior treatments included suplatast tosilate ($n = 18$), tricyclic antidepressant ($n = 11$), DMSO instillation ($n = 10$) and/or NSAIDs ($n = 14$). A total of 30 patients completed the treatment protocol and post-treatment follow up to 6 months, whereas two patients discontinued the therapy because of symptoms worsening at the fourth or sixth instillation.

According to GRA, responders gradually increased with advancement of the therapy (Table 2, Fig. 1); the response rate was 33.3% after the first instillation, 60.0% after the fourth and 76.7% after the 12th, and 90.0% 1 month after the last instillation. On the termination of instillation, the rate declined to 46.7% at 2 months and 16.7% at 6 months. Post-hoc analysis indicated ulcer type IC, onset age younger than 60 years and bladder volume at primary hydrodistension less than 500 mL as prognostic factors for better therapeutic response at the fourth instillation (Table 3); however, no factors were identified for efficacy at 2 months post-therapy. Other variables showed significant improvement during the therapy (Table 4). OSPI reached a significant level of improvement as early as at the fourth instillation ($P = 0.033$), and it was pronounced at the 12th instillation ($P < 0.001$). VAS for pain showed a significant reduction after the fourth instillation from the baseline ($P = 0.024$) and thereafter. Average voided volume significantly increased from the fourth therapy ($P = 0.029$). Urinary frequency decreased significantly at the fourth therapy for daytime frequency ($P = 0.003$) and for night-time frequency ($P = 0.001$). During post-therapy follow up, all the variables showed gradual deterioration with time; however, significant improvement lasted until 2 months after the termination of instillation. There was no significant difference at 6 months after the last instillation, except for nocturnal frequency, compared with the baseline.

As for side-effects of the therapy, no adverse events requiring additional intervention were observed. Two patients discontinued the therapy because of poor benefit. Minor side-effects included bladder pain ($n = 18$), gross hematuria ($n = 4$) and urinary tract infection ($n = 3$), all of which were self-limited. Gross hematuria was observed only on the day of instillation and not associated with systemic coagulation disorder (data not shown).

Additionally, 70% of patients reported slight bladder discomfort lasting for approximately 1 day every time after the administration, which also could be tolerated and decreased

Table 3 Univariate analysis of overall response factors at fourth therapy and 2 months post-treatment

	Univariate analysis					
	Fourth therapy			2 months post-treatment		
	OR	CI (95%)	*P*-value	OR	CI (95%)	*P*-value
Ulcer						
Ulcer/non-ulcer	8.250	1.154–59.003	0.039*	1.167	0.224–6.081	0.855
Sex						
Male/female	4.667	0.352–61.831	0.269	0.750	0.541–1.040	0.217
Age						
≥65 years/<65 years	0.500	0.087–2.886	0.657	1.250	0.233–6.715	0.795
Age at onset						
≥60 years/<60 years	0.121	0.017–0.867	0.039*	0.857	0.164–4.467	0.855
Duration of IC						
≥5 years/<5 years	1.500	0.266–8.449	0.685	1.167	0.224–8.081	0.855
Distended bladder volume						
≥500 mL/<500 mL	0.083	0.011–0.641	0.023*	1.250	0.233–6.715	0.795
Past hydrodistension						
≥2/once	0.686	0.119–3.963	0.673	2.4	0.444–12.980	0.414

*P-value <0.05.

Table 4 Therapeutic effects by symptom measures (mean ± SD, $n = 30$)

	Baseline	During therapy			Post-therapy		
		Week 1	Week 4	Week 12	1 Month	2 Months	6 Months
OSSI	13.4 ± 3.7	12.9 ± 3.4	10.9 ± 3.9	8.3 ± 3.6**	8.8 ± 4.0**	9.4 ± 4.4*	9.3 ± 5.3
OSPI	11.8 ± 4.2	11.5 ± 4.0	8.6 ± 4.2*	6.9 ± 3.3**	6.5 ± 3.6**	7.0 ± 3.9**	7.1 ± 4.5
VAS	5.8 ± 2.7	5.5 ± 2.4	3.4 ± 2.4**	3.5 ± 2.5*	3.3 ± 2.3**	3.8 ± 2.9*	3.5 ± 2.7
AVV1 (mL)	93.8 ± 65.5	108.2 ± 61.6	130.3 ± 61.8*	143.9 ± 72.9*	129.8 ± 66.4**	106.1 ± 72.4	118.6 ± 102.9
UF2 (day)	27.1 ± 36.6	19.3 ± 13.4**	14.4 ± 3.7**	13.4 ± 4.6**	14.6 ± 4.5**	15.1 ± 4.2*	15.0 ± 6.5
UF2 (night)	4.3 ± 2.7	3.6 ± 2.8**	2.7 ± 2.0**	2.3 ± 2.4*	2.3 ± 1.6**	2.1 ± 1.4*	2.0 ± 1.3*

*$P < 0.05$ versus baseline, **$P < 0.005$ versus baseline.

with continuation of the therapy. This discomfort was not related to therapeutic effect (data not shown).

Discussion

Intravesical therapy with a combination of heparin and alkalized lidocaine was first reported by Parsons.[9] The solution consisting of 40 000 U of heparin, 8 mL 2% lidocaine and 3 mL 8.4% sodium bicarbonate was given three times per week for 2 weeks. At the initial administration of the solution, 94% of patients (33 of 35 patients) reported immediate relief of both pain and urgency. However, patients were followed until 48 h after the last therapy, when 80% of them reported sustained relief of the symptoms. Another study by Welk used 10 000 U of heparin, 8 mL 2% lidocaine and 4 mL 8.4% of sodium bicarbonate for 23 female IC patients complaining of dyspareunia.[12] Patients were treated with the solution three times per week for 3 weeks. Three weeks after the therapy, 65% of patients reported a successful outcome of IC symptoms. Most of the efficacy parameters, including OSSI, OSPI, frequency, voided volume, Pelvic Pain Urgency Frequency score and Female Sexual Function Index pain domain score, showed significant improvement, supporting the effectiveness of the therapy. A double-blind, crossover, placebo-controlled trial showed that a single instillation of the solution can provide significant and immediate relief of IC symptoms up to 12 h.[13] These three studies demonstrated well the short-term efficacy, especially for pain, of intravesical therapy with a combination of heparin and alkalized lidocaine. However, they presented little data for outcomes post-administration.

Based on previous studies and the short-term efficacy of heparin instillation, we carried out the present study to assess the long-term outcomes of combined instillations, confirming the efficacy comparable with three previous studies. According to GRA, responders increased with advancement of the therapy; 33.3% after the first therapy, 60.0% at the fourth therapy and 76.7% at the 12th therapy. Once improved, there was no deterioration in efficacy during therapy. At the

first week, all the parameters showed slight improvement, yet not at a significant level, whereas Parsons and Welk reported quicker responses to the therapy. The reason for the difference might be because of the difference in the study design; the previous two studies gave the solution three times per week, whereas ours was given weekly. We designed the interval according to the capacity of our outpatients' clinic and patients' convenience. However, almost all of the parameters reached a significant level of improvement at the fourth instillation. No specific backgrounds were identified as predictive factors, although patients with the ulcer type of IC, younger onset age and smaller bladder volume at primary hydrodistension were likely to be better off earlier. As these factors are related to the ulcer type of IC, the subtyping might be responsible for the responsive difference. During the post-instillation period, the response rate was maximized (90.0%) at 1 month, 46.7% at 2 months and 16.7% at 6 months; the therapeutic effect lasted an average of 4.1 months after the last therapy. Other parameters similarly showed slight deterioration. These facts suggest that repeated administration of the solution could recover the damaged GAG layer of the bladder mucosa, and that the recovery deteriorates in due time. In other words, the current therapy would not be a curative, but palliative, treatment for IC. Also suggested is the necessity for regular maintenance therapy, with 1–4 months as a possible interval.

The therapy was well tolerated. A common side-effect was bladder discomfort after instillation, which occurred to 60.0% of patients after every instillation. Two patients discontinued the therapy because of worsening symptoms, amplified with instillation. The bladder discomfort might be explained by catheterization, alkalinity of the solution, stimulation of bladder mucosa by agents and/or natural course of the disease. Though discomfort itself might not affect the therapeutic effect, it should be solved by further study. Another adverse event was gross hematuria; however, it was self-limited and observed only on the day of instillation.

The limitations of the present study should be mentioned. It was a single-armed, open-label trial with a small number of patients. The efficacy of a single agent, heparin or lidocaine, remained unevaluated; heparin instillation alone might be effective.[13] In addition, the therapeutic outcomes were assessed by subjective questionnaires, but not by objective measures, such as urine NGF level.[14] Further studies should be explored to determine: (i) composition of the solution; (ii) duration of induction therapy; (iii) interval of maintenance therapy; and (iv) therapeutic assessment by objective outcome measures.

Twelve weekly intravesical instillations of heparin combined with alkalized lidocaine safely achieved symptom relief in most IC patients, which diminished in 6 months post-treatment. Younger age and the presence of ulcers are predictive of a quicker response. Further studies are required to optimize the patient selection, the number of instillations and the maintenance interval to maximize the therapeutic potential of this therapy in controlling IC symptoms.

Conflict of interest

None declared.

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Short Communication

Admissions related to interstitial cystitis in Japan: An estimation based on the Japanese Diagnosis Procedure Combination database

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Abbreviations & Acronyms
IC = Interstitial cystitis
DPC = Diagnosis Procedure Combination
JUA = Japanese Urological Association

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Abstract: We estimated the incidence of admissions related to interstitial cystitis in Japan using a national administrative claims database, the Diagnosis Procedure Combination database, which included information for 53.6% of urological training hospitals certified by the Japanese Urological Association. "Admissions related to interstitial cystitis" was defined as those cases whose ICD-10 code for the main reason for admission was N301 (interstitial cystitis) between 2007 and 2009. Among 8.42 million inpatient cases, 784 female and 212 male patients with interstitial cystitis were identified. The ratio of females to males was 3.69 and the median age was 67 years (range 5–92 years). The admission incidence (per 100 000 person-years) in females and males was estimated to be 1.35 (95% confidence interval 1.25–1.46) and 0.37 (0.31–0.42), respectively. This incidence is low compared with other reports. Possible reasons for this finding include racial difference, clinical examination methods, lack of outpatient data and poor healthcare coverage of interstitial cystitis.

Key words: bladder, epidemiology, incidence, interstitial cystitis, Japan.

Introduction

Interstitial cystitis (IC) is a chronic disease of the urinary bladder characterized by lower urinary tract symptoms, such as urinary frequency, bladder hypersensitivity and/or bladder pain and resultant serious impairment of quality of life.[1]

Although the National Institute of Arthritis, Diabetes, Digestive and Kidney Disease proposed the diagnostic criteria of IC for research use in 1988,[2] it has not been widely used in the clinical setting because of its strictness and complicacy. To promote research activity and medical care of IC in Japan and East Asia, the Clinical Guidelines for IC were established by the Society of Interstitial Cystitis of Japan in 2007.[1]

Estimation of the incidence or prevalence of IC in the general population is difficult because of its rarity. Although several articles estimating the incidence or prevalence of IC have been published,[3–10] many of them were based on restricted sample populations (i.e. office visitors and nurses' cohort) or scoring questionnaire research and few focused on male patients. To our knowledge, just three articles from the USA have been published to estimate the male and female incidence or prevalence of IC in the general population based on clinical diagnosis.[5,9,10]

The present study evaluated the incidence of admissions related to IC in both the male and female general population in Japan, using the Diagnosis Procedure Combination (DPC) database, which is a nationwide administrative database.

Methods

The DPC database

The DPC database is a case-mix inpatient claims database.[11–14] During our study period of 2007–2009, the database contains annually approximately 2.6 million inpatient cases from approximately 850 hospitals from July to December (6 months per each year), which represents approximately 44% of all acute care inpatient hospitalizations in Japan. Given the anonymous nature of the data collection process, informed consent was not required. Study approval was obtained from the Institutional Review Board in the University of Occupational and Environmental Health.

Japanese Urological Association-certified hospitals

The Japanese Urological Association (JUA) is the professional urological association in Japan. The JUA certifies urological specialists and hospitals where the teaching system is ensured (JUA-certified hospitals).

Study samples

In the DPC database, one disease should be assigned to "the main reason for admission" category. We defined "admissions related to IC" as those cases whose ICD-10 code for the main reason for admission was N301 (IC), and we identified them from the DPC database in 2007–2009.

Estimation of prevalence of IC

We estimated the incidence of admissions related to IC based on stratified hospital bed volume. First, we collected the number of beds in all JUA-certified hospitals and hospitals that had joined the DPC database. Hospitals were stratified with bed volume categories. The estimated annual number of IC cases (Yi) and the 95% confidence intervals (CI) were calculated with the following equation using Wald confidence intervals for the population proportion:[13]

$$Yi/Ni = pi \pm Z\sqrt{pi(1-pi)/(ni \times 1.5)}$$

where Ni is the number of beds in all JUA-certified hospitals, ni is the number of beds in JUA-certified hospitals that joined the DPC database, $pi = Xi/(ni \times 1.5)$ (Xi is the observed number of IC cases in JUA-certified hospitals that joined the DPC database between July and December, 2007–2009), and $Z = 1.96$.

Results

Among 8.42 million inpatients in the study population, we identified 996 admissions related to IC (Table 1). The ratio of females to males was 3.69 and the median age was 67 years (range 5–92 years). Almost all patients (95.3%) were hospitalized in JUA-certified hospitals. A vast majority of patients underwent cystoscopic intervention. Although they were minor, cystectomies and augmentation cystoplasties were also selected for therapy.

Table 1 Distribution of male and female interstitial cystitis patients from the Diagnosis Procedure Combination database

Total	Males	Females
	212 (100.0%)	784 (100.0%)
Age (years)		
≤19	4 (1.9%)	9 (1.1%)
20–29	5 (2.4%)	29 (3.7%)
30–39	7 (3.3%)	42 (5.4%)
40–49	9 (4.2%)	47 (6.0%)
50–59	26 (12.3%)	95 (12.1%)
60–69	65 (30.7%)	215 (27.4%)
70–79	75 (35.4%)	268 (34.2%)
80–89	20 (9.4%)	76 (9.7%)
≥90	1 (0.5%)	3 (0.4%)
Median (IQR)	67 (59–76)	67 (57–74)
Year		
2007	80 (37.7%)	263 (33.5%)
2008	58 (27.4%)	242 (30.9%)
2009	74 (34.9%)	279 (35.6%)
JUA hospital	200 (94.3%)	750 (95.7%)
Intervention		
Cystoscopic interventions including hydrodistension	176 (83.0%)	706 (90.1%)
Augmentation cystoplasty	2 (0.9%)	2 (0.3%)
Simple cystectomy	1 (0.5%)	2 (0.3%)
Implantation of spinal cord stimulation apparatus	3 (1.4%)	1 (0.1%)
Missing or others	30 (14.2%)	73 (9.2%)

IQR, interquartile range; JUA, Japanese Urological Association.

Table 2 shows the distribution of hospitals and IC cases stratified with bed volume categories. Overall, the DPC database covered 53.6% of JUA-certified hospitals and 63.4% of those beds. The estimated annual number of IC cases per year was 886 in females and 231 in males. According to the Population Census Data, the population of Japan in 2008 was approximately 65.44 million females and 62.25 million males; therefore, the incidence of admission related to IC (per 100 000 person-years) in females and males was estimated as 1.35 (95% CI 1.25–1.46) and 0.37 (0.31–0.42), respectively.

Table 2 Estimated incidence of admissions related to interstitial cystitis in Japan

Bed volume	JUA-certified hospitals (2007–2009)		JUA-certified hospitals that joined the DPC database (2007–2009)				No. IC patients in the DPC database for 1.5 years [*Xi*]†		Estimated annual no. IC patients (95% confidence interval) [*Yi*]‡	
	n	No. of beds [*Ni*]	*n*		No. of beds [*ni*]		Males	Females	Males	Females
≥800	62	60 768	50	80.6%	50 278	82.7%	42	183	34 (24–44)	147 (126–169)
600–799	107	72 437	80	74.8%	54 394	75.1%	31	115	28 (18–37)	102 (83–121)
400–599	336	161 951	224	66.7%	109 834	67.8%	41	165	40 (28–53)	162 (137–187)
200–399	512	153 265	269	52.5%	81 480	53.2%	94	273	118 (94–142)	342 (302–383)
≤199	231	30 486	46	19.9%	7406	24.3%	4	48	11 (0–22)	132 (95–169)
Total	1248	478 907	669	53.6%	303 392	63.4%	212	784	231 (198–263)¶	886 (819–952)¶
Total population in 2008 (100 000 persons)									622.5	654.4
Incidence (per 100 000 person-years)									0.37 (0.31–0.42)	1.35 (1.25–1.46)

†Data were collected from six months (July to December) of each 3 years (2007–2009). ‡$Yi/Ni = pi \pm 1.96 \times \sigma i$, where $pi = Xi/(ni \times 1.5)$, $\sigma i^2 = pi\,(1 - pi)/(ni \times 1.5)$. ¶$\Sigma\, Yi = \Sigma\,(Ni \times pi) \pm 1.96 \times (\Sigma\, Ni \times \sigma i^2)^{0.5}$. DPC, Diagnosis Procedure Combination; IC, interstitial cystitis; JUA, Japanese Urological Association.

Discussion

In the present study, we used a large administrative database and identified IC with a registered ICD-10 code. A similar method was used in two previous studies using Kaiser Permanente Northwest, a health maintenance organization in Portland, Oregon, USA. Clemens *et al.*[9] reported that "the prevalence" of IC during 1998–2002 was 197 and 41 per 100 000 in females and males, respectively, when IC was defined as the ICD-9 code 595.1, and Patel *et al.*[5] reported that "the incidence" of IC during 2002–2005 was 15 per 100 000 in females (no male patients were identified). Therefore, there is a 10-fold discrepancy between our results and those of Patel *et al.*

The incidence of IC varies widely, even though IC is diagnosed by clinical examination. Robert *et al.* analyzed Olmsted Country cohort data (1976–1996) and reported that the incidence of IC diagnosed through cystoscopic intervention was 1.6 and 0.6 per 100 000 in females and males, respectively.[10] Leppilahti *et al.* carried out a clinical examination in Finnish people who scored high points in the O'Leary-Sant IC symptom and problem index (OLS) questionnaire, and concluded that the prevalence of probable IC in women was 230 per 100 000 and that of possible/probable IC was 530 per 100 000.[8]

Recently, several questionnaires measuring the severity of IC, such as the OLS, have been developed. According to some OLS-based surveys, the prevalence of possible IC or painful bladder syndrome (per 100 000 females) is estimated to be 575 in the USA,[7] 306 in Austria,[6] 265 in Japan[4] and 261 in Korea.[3] These data suggest that there is some racial discrepancy between Asia, European countries and the USA, but the differences seem not so largely radical to solely explain the 10-fold gap. This implies that several IC patients remain undiagnosed and untreated in Japan.

Although the Clinical Guidelines for IC were released in January 2007 in Japan to promote research and clinical activity for IC,[1] the number of patients did not increase (Table 1). We consider there to be two possible reasons for this finding. First, racial variants and differences in database background could be attributed to our low IC incidence. In particular, the DPC database did not contain outpatient cases and our result of "incidence of admission related to IC" did not directly represent overall IC incidence. A previous report described that hydrodistension can be safely carried out under local anesthesia without hospitalization.[15] Second, Japanese national health-care insurance does not currently cover hydrodistension. Special approval from authorities is required to carry out hydrodistension (this restriction was lifted in April 2010).

Finally, we showed that the DPC database is highly represented in the urological field. The database coverage rate is approximately 35% of whole acute care beds,[13] but by restriction to JUA-certified hospitals, it increased to 53.6%. This high coverage enables accurate clinical assessment.

There are several limitations in the present study. First, the definition of IC was only based on an ICD-10 code in the administrative database. Neither chart reviews nor scoring questionnaires were available in the database. Second, because the present study was based on administrative claims data, the validity and reliability of the written diagnoses were limited, resulting in underestimation.

The incidence of admission related to IC from the DPC database (per 100 000 person-years) is estimated as 1.35 in

females and 0.37 in males. Possible reasons for this low incidence include racial difference, clinical examination methods, lack of outpatient data and poor health-care coverage for IC.

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Conflict of interest

None declared.

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Effects of TRPV4 Cation Channel Activation on the Primary Bladder Afferent Activities of the Rat

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Aims: Transient receptor potential vanilloid 4 (TRPV4) may affect afferent pathways innervating the bladder. We investigated the effects of GSK1016790A (GSK) and RN1734, a TRPV4 agonist and antagonist, respectively, and P2X-purinoceptor antagonists (TNP-ATP and PPADS) on cystometry (CMG), and the effect of GSK on single afferent fiber activities (SAAs) of the rat bladder and its relationship with capsaicin (Cap)-sensitivity. **Methods:** Conscious female Sprague–Dawley rats were used for CMG measurements. In SAA measurements, under urethane anesthesia, SAA was identified by electrical stimulation of the pelvic nerve and by bladder distention. Cystometric parameters were measured before and after intravesical drug instillation. In SAA measurements, response with saline instillation served as baseline. Then, GSK was instilled three times, and finally Cap was instilled to investigate the relationship with Cap-sensitivity. **Results:** Intravesical GSK-instillation transiently decreased bladder capacity and voided volume, which were counteracted by RN1734, TNP-ATP, and PPADS. In SAA measurements, Aδ-fibers (n = 7) were not affected by either GSK or Cap. Based on the Cap-sensitivity, C-fibers could be divided into two subtypes: Cap-insensitive (n = 14) and Cap-sensitive (n = 8). In the Cap-insensitive C-fibers, GSK significantly increased the SAAs during the first instillation, but the increase attenuated with time, whereas GSK did not significantly affect the Cap-sensitive C-fibers. **Conclusions:** The present results suggest that activation of TRPV4 in the bladder, probably urothelium, facilitates the micturition reflex by activation of the mechanosensitive, Cap-insensitive C-fibers of the primary bladder afferents in rats. *Neurourol. Urodynam. 31:148–155, 2012.* © 2011 Wiley Periodicals, Inc.

Key words: afferent nerves; desensitization; rats; transient receptor potential (TRP); urinary bladder

INTRODUCTION

The transient receptor potential vanilloid subfamily (TRPV) contains six proteins in mammals, and they are commonly divided into two subgroups based on sequence homology, functional similarities, and Ca^{2+}-selectivity; TRPV1–V4 and V5/6.[1] The subgroup of TRPV1–V4 members are weakly Ca^{2+}-selective cation channels, modulated by various intracellular signals and activated by temperature.[2,3] Expression of the TRPV1, V2, and V4 has been reported in human and rat/mouse urinary bladders.[4–10] Moreover, TRPV1 has been exploited clinically to desensitize bladder afferents and reduce bladder overactivity.[11] On the other hand, TRPV4 is sensitive to osmotic and mechanical stimuli, such as cell stretching or fluid flow.[12] Some previous studies show that TRPV4 may be modulated by calmodulin (CaM) and adenosine triphosphate (ATP), C-terminal CaM binding potentiating the current and Ca^{2+}-dependent CaM binding to the N-terminal desensitizing the current.[13–16]

Several researchers reported that TRPV4 is implicated in the regulation of urothelial ATP release that modulates the sensitivity of bladder afferent nerves.[7,8,17–19] In our previous study, the activation of the bladder mechanosensitive afferents induced by exogenous ATP was mainly through capsaicin (Cap)-insensitive (probably TRPV1-independent) C-fibers in the rat.[20] Therefore, it is conceivable that TRPV1 and TRPV4 have a role in the bladder afferent transduction via a different pathway.

In the present study, we focused on the afferent function of TRPV4, and investigated the effects of intravesical administration of GSK1016790A (GSK), a TRPV4 agonist, which has at least 300-fold greater potency for activating TRPV4 than 4α-PDD,[21] on single fiber activities of the primary bladder mechanosensitive afferent nerves.

MATERIALS AND METHODS

Animals

Forty-eight adult female Sprague–Dawley rats weighing 180–234 g were used. The rats were maintained under standard laboratory conditions with a 12:12 h light:dark cycle, and free access to food pellets and tap water. The protocol was approved by Animal Ethics Committees of The University of Tokyo Graduate School of Medicine and in line with NIH guidelines for the care and use of experimental animals.

Cystometry (CMG) Measurements

Rats were anesthetized with 30 mg/kg intraperitoneal pentobarbital sodium. A polyethylene catheter (Clay-Adams PE-50; Parsippany, NJ) was inserted in the bladder through the dome, and secured. After the operation, each rat was housed single in a cage.

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Continuous CMG was performed on conscious rats 4 days after surgery. Each rat was placed without any restraint in a metabolic cage (3701M081; Tecniplast, Buguggiate, Italy) for at least 1 hr to adapt to the environment. The bladder catheter was connected to a pressure transducer (DX-100; Nihon Kohden, Tokyo, Japan) and microinjection syringe pump (KDS100; Muromachi, Tokyo, Japan) via a three-way tap. Saline at room temperature was continuously infused into the bladder at a rate of 0.08 ml/min. The basal pressure (BP; cmH_2O), micturition threshold (MT; cmH_2O), peak pressure (PP; cmH_2O), and voided volume (VV; ml) were recorded continuously on data acquisition program (Windaq; DATAQ Instruments Inc., Akron, OH). Bladder capacity (BC; ml) was calculated as intercontraction interval (ICI) × saline infusion rate into the bladder. All parameters were averaged for 20 min (10–30 and 40–60 min after drug administration), and investigated before and after drug instillation.

Afferent Measurements

The rats were anesthetized with urethane (1.5 g/kg intraperitoneally). Body temperature was maintained by a heated blanket at 38°C. Single afferent fiber measurements were performed as described before.[20,22,23] In brief, the left pelvic nerve was dissected from surrounding tissue proximal to the major pelvic ganglion. A pair of silver electrodes was placed around the pelvic nerve. A polyethylene catheter (Clay-Adams PE-50) was inserted in the bladder. Both L6 dorsal roots were cut close to their entrance to the spinal cord after the laminectomy. Fine filaments were dissected from the left L6 dorsal root and placed across shielded bipolar silver electrodes. Clearly different unitary action potentials of afferent fiber originating from the bladder were identified by electrical stimulation of the pelvic nerve and bladder distention with saline. These action potentials were discriminated by the Spike2 (CED, Cambridge, UK) impulse shape recognition program. Conduction velocity (CV) was calculated from the latency of response to electrical stimulation and the conduction distance between stimulation and recording sites, which was based on our anatomical data. Fibers were grouped based on CV. Those with a CV < 2.5 m/sec were considered to correspond to unmyelinated C-fibers and those with CV ≥ 2.5 m/sec to thinly myelinated Aδ-fibers.[24]

Protamine sulfate (PS) solution (10 mg/ml, 0.3 ml) was instilled intravesically and kept in the bladder for 60 min just before the measurement. Single fiber afferent activity was recorded during constant filling CMG with saline at 0.08 ml/min. Filling continued until an intravesical pressure of 30 cmH_2O was reached. The afferent activity caused by pelvic nerve stimulation was also recorded before and after bladder filling and confirmed to correspond with that caused by bladder filling.

At the beginning of the experiments, recording was repeated consecutively three times, at 5 min intervals to evaluate the reproducibility. The third recording served as the baseline value. After that, GSK was instilled three times according to the same time schedule as before GSK instillation; all three cycles of recording were used to evaluate the time-dependency and reproducibility of the drug effect. Then finally, Cap was instilled to investigate the relationship with Cap-sensitivity. The bladder was not washed out between each of multiple instillations.

Unitary afferent activity was evaluated in relation to intravesical pressure and volume. The relationship of nerve activity to pressure or volume was established by comparing nerve activity and intravesical pressure at 1-sec intervals. These values were then averaged at 5 cmH_2O interval of pressure or by dividing into five equal parts of volume in the filling phase. Average unitary activity was totaled as a function of intravesical pressure or volume. Afferent nerve activity is expressed as a percentage of baseline activity, integrated for the whole filling phase. Since the stimulation substance instillation into the bladder increased the afferent activity approximately 150% as significant changes in our previous studies,[20,22,23] "Cap-sensitive" or "Cap-insensitive" afferent activities were classified based on both pressure and volume increases of more or less than 150% from baseline, respectively, when the bladder was instilled with Cap.

Drugs

Protamine sulfate, GSK1016790A (*N*-((1*S*)-1-{[4-((2*S*)-2-{[(2,4-dichlorophenyl) sulfonyl]amino}-3-hydroxypropanoyl)-1-piperazinyl]carbonyl}-3-methylbutyl)-1-benzothiophene-2-carboxamide),[21,25] and Cap were purchased from Sigma–Aldrich (St. Louis, MO). RN1734 (2,4-dichloro-*N*-isopropyl-*N*-(2-isopropylaminoethyl) benzenesulfonamide)[26] and PPADS (pyridoxal phosphate-6-azo (benzene-2,4-disulfonic acid)) were purchased from Tocris Bioscience (St. Louis, MO). TNP-ATP (2′,3′-*O*-(2,4,6-trinitrophenyl-)ATP) solution was purchased from Molecular Probes (San Diego, CA). GSK and RN1734 were dissolved in *N,N*-dimethylacetamide (DMA), and Cap was dissolved in absolute ethanol as a stock solution. These drugs were stored at −80°C and subsequent dilutions of the drugs were made on the day of the experiment using saline. TNP-ATP and PPADS were diluted/dissolved in saline. PS was dissolved in distillated water. All drugs were instilled intravesically. The doses were chosen according to previous studies in the mouse/rat and our pilot study.[7,20,21,26]

Statistical Analysis

All data are expressed as mean ± SEM. Results were analyzed using two-way ANOVA followed by Tukey's test for multiple comparisons before and after drug instillation. P values <0.05 are considered statistically significant.

RESULTS

CMG Measurements

Instillation of the vehicle (0.4% DMA) did not affect cystometric parameters (data not shown). Instillation of GSK significantly reduced BC and VV at 10–30 min; however, the effects were attenuated 40–60 min after instillation (Table I and Fig. 1A).

Instillation of RN1734, TNP-ATP, and PPADS induced no significant changes in cystometric parameters, although BC and VV tended to be increase and PP tended to decrease. When instilled in combination with RN1734, TNP-ATP, or PPADS GSK did not affect any of the cystometric parameters (Table I and Figs. 1A and 2).

Afferent Measurements

In a pilot study, we have investigated whether the both Aδ- and C-fiber afferent activities were influenced by 1 hr PS-exposure but no significant differences were found between before and after PS-exposure (Aδ-fibers; n = 7, base: 100%, after PS-exposure: 95% and 102% based on pressure and volume, respectively. C-fibers; n = 6, base: 100%, after PS-exposure: 102% and 98% based on pressure and volume, respectively).

TABLE I. The Effects of Intravesical Application of GSK1016790A (GSK), RN1734, TNP-ATP, and PPADS on Cystometric Parameters

Parameter	Saline	10–30 min after instillation of GSK	40–60 min after instillation of GSK
GSK1016790A (3×10^{-6} M, TRPV4 agonist), n = 6			
Base pressure (cmH_2O)	3.13 ± 0.56	2.61 ± 0.89	2.71 ± 0.54
Micturition threshold (cmH_2O)	9.61 ± 1.26	7.43 ± 0.50	8.15 ± 1.05
Peak pressure (cmH_2O)	43.54 ± 5.54	42.23 ± 3.44	45.05 ± 5.64
Bladder capacity (ml)	1.42 ± 0.23	0.75 ± 0.25*	1.14 ± 0.11
Voided volume (ml)	1.44 ± 0.22	0.84 ± 0.26*	1.20 ± 0.13

Parameter	Saline	10–30 min after instillation of RN1734	40–60 min after instillation of RN1734	10–30 min after instillation of GSK and RN1734	40–60 min after instillation of GSK and RN1734
GSK1016790A (3×10^{-6} M, TRPV4 agonist) and RN1734 (10^{-5} M, TRPV4 antagonist), n = 6					
Base pressure (cmH_2O)	3.38 ± 0.44	3.09 ± 0.42	3.18 ± 0.54	2.8 ± 0.41	3.68 ± 0.57
Micturition threshold (cmH_2O)	8.21 ± 0.73	8.86 ± 1.98	9.77 ± 2.12	8.85 ± 0.75	10.17 ± 1.41
Peak pressure (cmH_2O)	47.69 ± 3.10	42.45 ± 2.99	46.06 ± 3.28	42.02 ± 2.28	49.83 ± 3.37
Bladder capacity (ml)	1.32 ± 0.22	1.30 ± 0.19	1.69 ± 0.27	1.63 ± 0.07	1.39 ± 0.29
Voided volume (ml)	1.33 ± 0.23	1.36 ± 0.19	1.63 ± 0.27	1.60 ± 0.08	1.44 ± 0.30

Parameter	Saline	10–30 min after instillation of TNP-ATP	40–60 min after instillation of TNP-ATP	10–30 min after instillation of GSK and TNP-ATP	40–60 min after instillation of GSK and TNP-ATP
GSK1016790A (3×10^{-6} M, TRPV4 agonist) and TNP-ATP (3×10^{-5} M, $P2X_3$ antagonist), n = 6					
Base pressure (cmH_2O)	1.97 ± 0.56	2.68 ± 0.32	2.79 ± 0.54	2.28 ± 0.25	2.26 ± 0.44
Micturition threshold (cmH_2O)	12.27 ± 1.89	9.66 ± 1.00	11.95 ± 1.32	9.04 ± 1.55	7.29 ± 0.91
Peak pressure (cmH_2O)	41.42 ± 3.48	36.77 ± 2.61	35.43 ± 3.64	37.73 ± 3.68	38.74 ± 5.26
Bladder capacity (ml)	1.31 ± 0.18	1.00 ± 0.17	1.44 ± 0.13	1.33 ± 0.13	1.16 ± 0.24
Voided volume (ml)	1.43 ± 0.17	1.13 ± 0.15	1.59 ± 0.09	1.44 ± 0.17	1.16 ± 0.23

Parameter	Saline	10–30 min after instillation of PPADS	40–60 min after instillation of PPADS	10–30 min after instillation of GSK and PPADS	40–60 min after instillation of GSK and PPADS
GSK1016790A (3×10^{-6} M, TRPV4 agonist) and PPADS (3×10^{-5} M, nonselective P2X antagonist), n = 6					
Base pressure (cmH_2O)	2.99 ± 0.53	2.43 ± 0.62	3.09 ± 0.81	2.58 ± 0.69	2.70 ± 0.46
Micturition threshold (cmH_2O)	9.17 ± 1.89	9.48 ± 2.02	10.09 ± 2.16	7.83 ± 2.23	9.39 ± 1.12
Peak pressure (cmH_2O)	50.63 ± 5.30	39.77 ± 3.76	40.80 ± 3.67	46.01 ± 6.56	48.28 ± 2.49
Bladder capacity (ml)	1.20 ± 0.23	0.99 ± 0.28	1.48 ± 0.22	1.07 ± 0.27	1.14 ± 0.18
Voided volume (ml)	1.26 ± 0.25	1.07 ± 0.31	1.55 ± 0.22	1.13 ± 0.29	1.19 ± 0.18

Values are indicated as mean ± SEM.
*$P < 0.05$: significant difference from base (two-way ANOVA followed by Tukey's test).

A total of 29 single-unit afferent fibers were isolated in 24 rats (maximum 2 fibers per 1 rat); 7 units corresponded to criteria for myelinated Aδ-fibers (CV: 3.80 ± 0.66 m/sec), and 22 for unmyelinated C-fibers (CV: 1.80 ± 0.09 m/sec). After GSK instillation, bladder compliance did not change significantly (baseline: 0.0223 ± 0.0011 ml/cmH_2O, GSK-1st instillation: 0.0247 ± 0.0011 ml/cmH_2O, GSK-2nd instillation: 0.0217 ± 0.0012 ml/cmH_2O, GSK-3rd instillation: 0.0220 ± 0.0015 ml/cmH_2O). The afferent activity of the Aδ-fibers did not change after either GSK or Cap instillation (Figs. 3A and 4). The afferent activities of C-fibers were divided into two groups by the Cap-sensitivity; Cap-insensitive (Fig. 3B) and Cap-sensitive (Fig. 3C). Among 22 discriminated C-fiber single units, 14 units were classified as the Cap-insensitive fibers, and the remaining 8 units as the Cap-sensitive fibers. Upon GSK instillation activities of the Cap-insensitive fibers in response to the bladder filling increased significantly at the first instillation, but the effect of GSK gradually attenuated at the second and third instillations (Fig. 4). The activities of Cap-sensitive C-fibers showed no significant change by GSK instillation (Fig. 4).

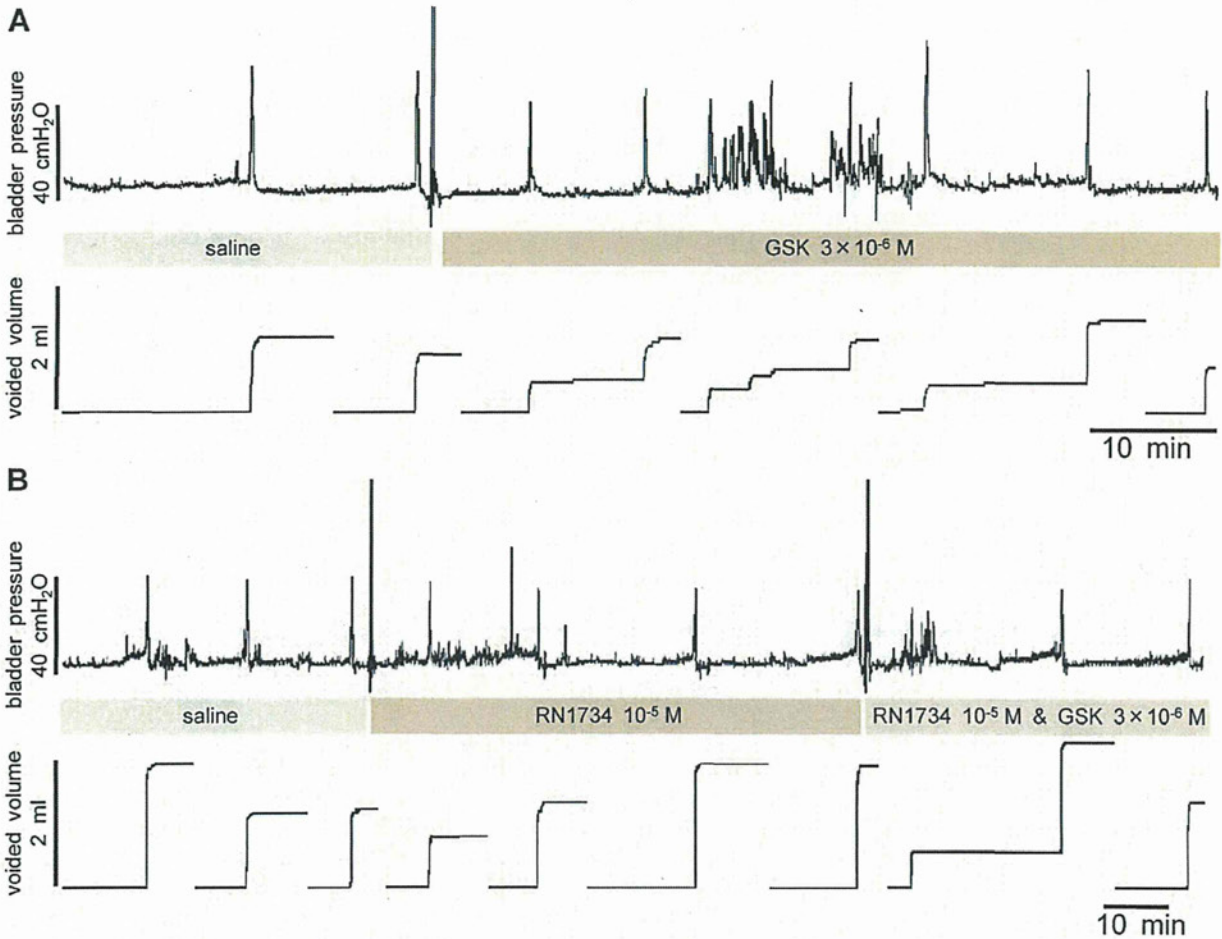

Fig. 1. Representative cystometric recordings (bladder pressure and voided volume) in a conscious free-moving rat before and during intravesical instillation of GSK **(A)** and RN1734/GSK **(B)**. GSK: GSK1016790A, TRPV4 agonist; RN1734: TRPV4 antagonist.

DISCUSSION

In the present study, we investigated the effects of a TRPV4 agonist, GSK, on CMG and mechanosensitive primary bladder afferent activities by directly instilling this and other compounds into the bladder, hereby yielding direct exposure of the bladder urothelium. Intravesical instillation of GSK significantly decreased BC and VV at first, and then these effects were attenuated with time and disappeared, suggesting desensitization of the receptor. Such desensitization of TRPV4 was reported in a previous study with HeLa cells transiently transfected with TRPV4.[16] The effects of GSK on BC and VV were counteracted by RN1734, a TRPV4 antagonist, although instillation of RN1734 alone caused no significant changes in these cystometric parameters. This implies that the effects of GSK were indeed TRPV4-mediated and that in the absence of exogenous agonist there was little endogenous tone on the TRPV4 receptors under our experimental conditions. In previous reports,[8,21] TRPV4$^{-/-}$ mice had increased BC, suggesting a physiological role of TRPV4 for MT volume. This discrepancy between the previous findings in TRPV4$^{-/-}$ mice and the present findings with RN1734 may occur by differences in experimental condition and species of animal, or occur by the influence of systemic or local TRPV4 channel reaction. Nevertheless, Thorneloe et al.[21] demonstrated that intravesical instillation of 10^{-5} M GSK induced bladder overactivity in TRPV4$^{+/+}$ mice with no effect in TRPV4$^{-/-}$ mice, further confirming that this compound indeed selectively acts via TRPV4. The dose used in that study was higher than that (3×10^{-6} M) used in rats in the present study. These results suggest that the transient activation of the micturition reflex by GSK was mediated through TRPV4, and also suggest that under these specific conditions TRPV4 does not play a role physiologically in control of the MT.

Recently, it has been reported that activation of TRPV4 in rat and mouse bladder urothelial cells induces Ca^{2+} influx-evoked ATP release, and the released ATP modulates bladder sensory transduction.[7,8,18] To test involvement of an ATP-mediated mechanism, we further conducted cystometric investigation with P2X-purinoceptor antagonists. Although neither TNP-ATP, a $P2X_3$-purinoceptor antagonist,[27–29] nor PPADS, a nonselective P2X-purinoceptor antagonist,[30] significantly affected any of cystometric parameters, both antagonists blocked the effects of GSK when instilled in combination