Full Paper

Effects of NSAIDs on Bladder Function in Normal and Cystitis Rats: a Comparison Study of Aspirin, Indomethacin, and Ketoprofen

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Abstract. To clarify the potential usefulness of non-steroidal anti-inflammatory drugs, NSAIDs, for patients with overactive bladder, we examined the effect of NSAIDs on urodynamic parameters in normal and cystitis rats and compared their ulcerogenic activity in the gastrointestinal mucosa. Cystometry was performed after administration of the conventional NSAIDs, aspirin, indomethacin, or ketoprofen. Prostaglandin levels were measured in the bladder of cystitis rats pretreated with NSAIDs. Furthermore, the ulcerogenic responses were examined. NSAIDs increased bladder capacity without any effect on micturition pressure in normal rats in the following rank order of potency: ketoprofen > indomethacin > aspirin. In cystitis rats, bladder capacity was increased and micturition frequency was decreased. The levels of prostaglandin were significantly increased in cystitis rats. All NSAIDs inhibited the increment of prostaglandin levels at doses equal to that effective in the improvement of bladder functions. When administered intraduodenally, both ketoprofen and indomethacin induced lesions in the gastrointestinal mucosa. However, aspirin had no significant effect. We demonstrate that NSAIDs are effective in animal models of disease, most likely by suppressing by prostaglandin synthesis. Since aspirin, in contrast to ketoprofen or indomethacin, did not cause any gastrointestinal lesions, aspirin might be the NSAIDs treatment of choice for overactive bladder.

Keywords: aspirin, non-steroidal anti-inflammatory drug, overactive bladder, urodynamic parameter, gastrointestinal lesion

Introduction

Prostanoids, generated by cyclooxygenase (COX) following bladder stretch, are thought to play a physiological role in the function of the lower urinary tract (1–5) and their inhibition may decrease bladder contractility. It has been demonstrated that various non-steroidal anti-inflammatory drugs (NSAIDs) improved the urodynamic dysfunction in experimental animal models of cystitis (1). Furthermore, several clinical trials have been carried out to demonstrate effectiveness of NSAIDs on detrusor instability (2, 3) and primary enuresis (4, 5). The levels of prostaglandin were increased in the urine of patients with several kinds of cystitis. Thus, it is considered that prostaglandins (PGs) play an important role in the pathogenesis of lower urinary dysfunction and NSAIDs could therefore be expected to be a useful treatment of overactive bladder. However, NSAIDs have seldom been used for this purpose, probably due to their gastrointestinal side effect (6–8). It is well known that conventional NSAIDs produce gastric damage, irrespective of whether they are administered orally or parenterally.

The most famous NSAIDs is aspirin that widely used as an analgesic and anti-thrombosis drug. Velasco et al. (9) recently reported that aspirin increased bladder capacity in a model of overactive bladder in rats. Aspirin’s efficacy in this model is most likely mediated by the inhibition of C-fiber activation as a consequence of PG synthesis blockade (10). In contrast to conventional NSAIDs, aspirin causes gastric damage only when given orally in rats (11). Furthermore, it has been shown

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in clinical trials that enteric-coated aspirin causes significantly less gastrointestinal damage than the same dose of non-coated aspirin in healthy male volunteers (12).

From these findings, we hypothesized that aspirin could be a useful drug with few side effects for the treatment of overactive bladder. The present study was designed to compare the efficacy and gastrointestinal side effect profile of aspirin and conventional NSAIDs.

**Materials and Methods**

**Animals**

Female Sprague-Dawley (SD) rats (Charles River Japan, Tokyo; 8-week-old) were used in all experiments. They were housed with free access to food and water and maintained on a light-dark cycle at 22–24°C except during experiments. During experiments in the anesthetized condition, animals were kept under a heating lamp to prevent a fall of body temperature. Animals were handled according to the guidelines set by The Animal Welfare Committee at Research Center Kyoto of Bayer Yakuhin, Ltd., which are based on the principles by JALAS (Japanese Association of Laboratory Animal Science).

**Rhythmic bladder contraction**

Animals were anesthetized by an intraperitoneal (i.p.) injection of urethane (1.0 g/kg). Following a midline incision of the abdomen and exposure of the urinary bladder, both ureters were ligated and cut to prevent influx of extra urine into the bladder. A balloon (Suzuran gold; Suzuken, Nagoya)-tipped catheter (PE50; Becton Dickinson, Tokyo) was implanted into the bladder through the bladder dome and secured in place by a silk ligature, and the abdomen was closed. The catheter was connected to a transducer (MLT0698; BioResearch Center, Nagoya) to monitor intravesical pressure by the PowerLab system (BioResearch Center). Saline was infused into the balloon until spontaneous bladder contraction was observed. When the rhythmic contractions had become stable, usually 10 min after vehicle loading, aspirin (0.1 – 10 mg/kg), indomethacin (0.01 – 0.3 mg/kg), or ketoprofen (0.001 – 0.1 mg/kg) was administered in cumulative doses through a polyethylene cannula inserted into the femoral vein. The contraction interval that is defined as maximum time for the disappearance of the contraction and the lowest contraction amplitude after administration assessed the effects of compounds.

**Cystometry in normal rats**

In a separate set of experiments, we revealed that continuous cystometry under anesthesia is not as appropriate condition to estimate bladder capacity. For example, i.v. injection of oxybutynin or atropine prolonged micturition intervals only for a few micturition cycles after administration. Under these conditions, it was found that the residual urine volume was increased due to the failure of complete contraction in anesthetized rats. Thus compounds that induce residual urine volume as well as prolongation of micturition intervals are difficult to be evaluated on bladder capacity using continuous cystometry under anesthesia. For this reason, we removed the residual urine from the bladder after each micturition to be able to determine bladder capacity precisely (intermittent cystometry, details below).

Animals were anesthetized and both ureters were cut as previously described. A polyethylene catheter (PE50) was inserted into and secured to the proximal bladder via an opening at the tip of the bladder dome. The bladder catheter was attached using a three-way cork to connect a pressure transducer for the measurement of intravesical pressure and an infusion pump (TE-3310N; TERUMO, Tokyo) for the infusion of saline.

Cystometry under anesthesia was performed after a 1-h recovery period from the surgical procedure. Saline was infused at a rate of 3.6 ml/h until micturition was observed. Just after onset of micturition, saline infusion was stopped and the residual saline was removed from the bladder. These procedures were repeated with 15-min infusion intervals. Vehicle and test compound were injected at different doses every subsequent micturition via the femoral vein 5 min prior to the start of saline infusion; and micturition interval, micturition pressure, and residual volume were determined. Bladder capacity was calculated using the following equation: bladder capacity (ml) = micturition interval (min) × 3.6 ml / 60 min.

**Cystometry in cyclophosphamide (CYP)-induced cystitis rats**

Cystometry in cystitis rats were performed according to the method described by Lecci et al. (13) with slight modification. Briefly, cyclophosphamide (CYP) (150 mg/kg) was injected i.p. into animals 18 h before cystometry. Animals were anesthetized with urethane (1.25 g/kg, i.p.). After laparotomy, the bladder was exposed and both ureters were tied and cut. The polyethylene catheter (PE50) was implanted into the bladder dome and the abdomen was closed. The bladder was emptied by gently pushing the hypogastrium. Compound or vehicle was injected i.v. 5 min prior to saline infusion. Treatment effects were expressed as bladder capacity and micturition frequency, which were calculated from
the 30-min data after the beginning of cystometry. Bladder capacity was calculated using the following equation: Bladder capacity (ml) = time required for first micturition (min) × 3.6 ml / 60 min. In case of intraduodenal (i.d.) administration of aspirin, it was administered i.d. 1 h prior cystometry.

Measurement of bladder PG levels

PGE\(_2\) and PGF\(_{1\alpha}\) levels in the bladder tissue were measured 18 h after administration of CYP (150 mg /kg, i.p.) or saline. PGF\(_{1\alpha}\) was determined indirectly by measuring 6-keto-PGF\(_{1\alpha}\), a stable metabolite of PGI\(_2\). Vehicle or compound (aspirin: 10 and 30 mg/kg, indomethacin: 3 mg/kg, ketoprofen: 1 mg/kg) were administered via the femoral vein 5 min before bladder isolation under ether anesthesia. The bladder was isolated, weighed, frozen in liquid nitrogen, and stored at –80°C until further use.

Frozen bladder samples were crushed in a small amount of liquid nitrogen and put in a tube containing pure ethanol and 5 mM indomethacin. Indomethacin was used to prevent further PG synthesis during the homogenization process. Samples were homogenized for 40 s at 10-s intervals and centrifuged for 10 min at 4°C at 7200 × g (14). The supernatant was dried using nitrogen gas in a 37°C water bath. Dried samples were dissolved in assay buffer and centrifuged for 10 min at 4°C at 7200 × g. PGE\(_2\) and 6-keto-PGF\(_{1\alpha}\) levels in the supernatant were determined by an EIA kit (Amersham Biosciences, Piscataway, NJ, USA). Protein content in the supernatant was also determined by the BCA Protein Reagent (Pierce, Rockford, IL, USA).

Induction of gastrointestinal lesions

The animals received either vehicle, aspirin (200 mg /kg), indomethacin (10 mg/kg), or ketoprofen (10 mg/kg) intraduodenally (i.d.) 24 h before sacrificing. Thirty minutes prior to sample collection, 1% Evan’s blue solution (1 ml/animal, i.v.) was injected to delineate the gastrointestinal damage. Under deep ether anesthesia, stomach and small intestine were removed and treated with 2% formalin for tissue fixation. Stomach and intestine were opened along the greater curvature and examined for lesions under a microscope using a micrometer. The length of hemorrhagic erosions was measured, summed per stomach or intestine, and used as a lesion score.

Drugs

Drugs used were indomethacin, ketoprofen, and urethane (Sigma Chemicals, St. Louis, MO, USA); aspirin (Nacalai Tesque, Kyoto); ethanol, Tween80, CYP, and diethyl ether (Wako Chemicals, Osaka). Indomethacin and aspirin were dissolved in 1% Na\(_2\)CO\(_3\) (Wako) and ketoprofen was dissolved in 0.1 N NaOH for i.v. administration. For i.d. administration, all compounds were suspended in saline with a few drops of Tween80. Urethane and CYP were dissolved in saline. Drugs were prepared immediately before use, at volumes of 0.5 ml/kg body weight for i.v. administration and 5 ml/kg body weight for i.p. or i.d. administration, respectively.

Statistical analyses

Data were presented as the mean ± S.E.M. from 4 to 14 animals per group as indicated. Statistical analyses were performed using Student’s t-test if appropriate or by one-way ANOVA and Dunnett’s test. P values of <0.05 were considered as significant.

Results

Rhythmic bladder contraction

Intravenous administration of aspirin (0.1 – 10 mg /kg), indomethacin (0.01 – 0.3 mg/kg), and ketoprofen (0.001 – 0.1 mg/kg) resulted in dose-dependent suppression of rhythmic bladder contraction induced by distension (Fig. 1). At the highest dose of aspirin and ketoprofen, rhythmic contractions disappeared for about 10 – 20 min, and the effects on the contraction interval reached statistical significance. Indomethacin at 1 mg/kg was injected and suppressed bladder contractions. Because the rhythmic bladder contraction did not recover completely probably due to the potent efficacy, the data could not be demonstrated. No effect on the contraction amplitude was observed.

Cystometry in normal rats

In our preparation, bladder capacity, micturition pressure and residual urine volume in the vehicle group were 0.4 – 0.5 ml, 26 – 28 cmH\(_2\)O and 0.13 – 0.15 ml, respectively (Table 1). Bladder capacity was increased in a dose-dependent manner following i.v. administration of aspirin, indomethacin, or ketoprofen. Significant effects of aspirin, indomethacin, and ketoprofen on the bladder capacity were observed at a dose of 10, 3, and 0.1 mg/kg, respectively. All compounds failed to affect micturition pressure. Ketoprofen but none of the other NSAIDs tested induced a significant increase in residual urine volume (0.14 ± 0.02 ml: vehicle, vs 0.33 ± 0.06 ml: ketoprofen) at the dose of 0.1 mg/kg.

Cystometry in cystitis rats

Injection of 150 mg/kg CYP (i.p.) caused a decrease in bladder capacity as well as an increase in micturition frequency compared to normal controls (Fig. 2). In
addition, the bladder wet weight of rats with CYP-induced cystitis was significantly increased (normal: 70.4 ± 5.3 mg, cystitis: 120.1 ± 5.4 mg, P<0.05, data not shown). Intravenous administration of aspirin (3, 10, and 30 mg/kg), indomethacin (0.3, 1, and 3 mg/kg), or ketoprofen (0.01, 0.1, and 1 mg/kg) increased the bladder capacity (Fig. 2A) and decreased the micturition frequency (Fig. 2B) in cystitis rats. Significant effects on bladder capacity were observed at doses of 10 mg/kg (aspirin), 3 mg/kg (indomethacin), and 1 mg/kg (ketoprofen), respectively. In addition, significant effects on the micturition frequency were observed at doses of 30 mg/kg for aspirin, ≥3 mg/kg for indomethacin, and ≥0.1 mg/kg for ketoprofen. While micturition pressure and bladder weight were not changed by NSAIDs, the residual urine volume was increased by 1 mg/kg ketoprofen (data not shown). In addition, 10, 30, and 100 mg/kg aspirin was administered intraduodenally. Aspirin was dose-dependently increased bladder capacity and decreased micturition frequency. Signifi-

Table 1. Effects of various NSAIDs on cystometric parameters in normal rats. Under urethane anesthesia, cystometry was performed intermittently.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose (mg/kg, i.v.)</th>
<th>Bladder capacity (ml)</th>
<th>Micturition pressure (cmH2O)</th>
<th>Residual volume (ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>Vehicle</td>
<td>0.40 ± 0.04</td>
<td>25.8 ± 2.05</td>
<td>0.15 ± 0.04</td>
</tr>
<tr>
<td></td>
<td>0.1</td>
<td>0.39 ± 0.06</td>
<td>28.3 ± 3.46</td>
<td>0.12 ± 0.02</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>0.47 ± 0.04</td>
<td>26.3 ± 2.07</td>
<td>0.13 ± 0.03</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>0.58 ± 0.06*</td>
<td>26.4 ± 1.77</td>
<td>0.22 ± 0.06</td>
</tr>
<tr>
<td>Indomethacin</td>
<td>Vehicle</td>
<td>0.44 ± 0.04</td>
<td>28.1 ± 1.70</td>
<td>0.13 ± 0.02</td>
</tr>
<tr>
<td></td>
<td>0.03</td>
<td>0.36 ± 0.02</td>
<td>27.9 ± 1.58</td>
<td>0.12 ± 0.02</td>
</tr>
<tr>
<td></td>
<td>0.3</td>
<td>0.48 ± 0.05</td>
<td>26.8 ± 1.64</td>
<td>0.18 ± 0.03</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>0.71 ± 0.10*</td>
<td>31.4 ± 2.58</td>
<td>0.18 ± 0.03</td>
</tr>
<tr>
<td>Ketoprofen</td>
<td>Vehicle</td>
<td>0.53 ± 0.07</td>
<td>26.8 ± 2.73</td>
<td>0.14 ± 0.02</td>
</tr>
<tr>
<td></td>
<td>0.1</td>
<td>0.77 ± 0.12*</td>
<td>31.0 ± 4.6</td>
<td>0.33 ± 0.06*</td>
</tr>
</tbody>
</table>

Vehicle or test compound was administered 5 min before starting saline infusion in a cumulative manner. Data are expressed as the mean ± S.E.M. from 7 or 8 animals. *Significantly different from the vehicle, at P<0.05.
significant effects on bladder capacity (vehicle: 0.12 ± 0.01 ml, and 100 mg/kg: 0.17 ± 0.01 ml, P<0.05) and micturition frequency (vehicle: 58.7 ± 7.5 times/h, and 100 mg/kg: 30.2 ± 3.9 times/h, P<0.05) were observed at 100 mg/kg. Residual urine volume was not increased (data not shown).

*Fig. 2. Effects of various NSAIDs on cystometric parameters in cyclophosphamide (CYP)-induced cystitis rats. CYP (150 mg/kg, i.p.) was injected 18 h prior to the experiment. Under urethane anesthesia, cystometry was performed. Vehicle or test compound was administered 5 min before starting saline infusion. Data are expressed as the mean ± S.E.M. from 5 to 14 animals. **Significantly different from the normal and vehicle treatment group, at P<0.05, respectively.

*Fig. 3. Effects of various NSAIDs on PGE_2 and PGF_1α levels in the bladder of CYP-induced cystitis rats

Eighteen-hours after CYP administration, both PGE_2 and PGF_1α contents in the bladder were markedly increased as compared to normal bladders. When animals were pretreated with aspirin, indomethacin, or ketoprofen.
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ketoprofen, the CYP-induced increase of PGE$_2$ and PGF$_{1\alpha}$ contents in the bladder were significantly inhibited (Fig. 3).

Ulcerogenic responses by NSAIDs

Finally, the ulcerogenic potential of the NSAIDs was aroused by intraduodenal administration of the test compounds. Twenty-four hours after indomethacin (10 mg/kg) or ketoprofen (10 mg/kg) administration, severe hemorrhagic lesions were observed both in the stomach and the lower part of the small intestine. The lesion scores were 16.3 ± 4.0 and 4.6 ± 1.0 mm$^2$ for indomethacin and 113.5 ± 47.4 and 21.4 ± 9.1 mm$^2$ for ketoprofen (Fig. 4), respectively. In contrast aspirin at 200 mg/kg induced few gastric lesions of comparatively minor size (0.8 ± 0.6 mm$^2$).

Discussion

Currently, anticholinergic drugs are widely used for treatment of urinary incontinence (UI), but they cause a decrease of micturition pressure so that they have a risk to increase urine residual volumes, an undesirable side effect for the patients. In addition, they also have some other side effects such as dry mouth, blurred vision, and increased heart rate. It is desirable that the drug for UI prolongs the storage phase without any effect on micturition pressure, resulting in no increment of residual urine volume. Expectedly, NSAIDs prolonged micturition interval without any effect on micturition pressure because some NSAIDs such as ketoprofen used clinically for the treatment of detrusor instability caused a prolongation of micturition interval.

NSAIDs are widely used as analgesic drugs in clinical practice. The inhibition of PG synthesis via the inhibition of COX enzymes is the principle mechanism of action of NSAIDs. It has been reported that PGs play an important role in bladder function in humans and in experimental animals (1 – 5). However, there are few reports describing the usefulness of aspirin in bladder disorders. Recently, we confirmed that aspirin was effective in overactive bladder in animal models (10). Therefore, in the present study, we examined the characteristics and the potential differences between aspirin and other NSAIDs such as indomethacin and ketoprofen.

First, we examined the effects of NSAIDs on distension-induced rhythmic bladder contraction. The amplitude of contraction pressure and the contraction interval were considered. The contraction interval means the time period in which rhythmic bladder contraction was completely inhibited. The frequency of the rhythmic bladder contractions is related to the sensory afferent arms of the micturition reflex and is regulated by the micturition center in the central nervous system (15). The amplitude of contraction pressure can be regarded as almost equivalent to the network of the detrusor muscle. Therefore, the rhythmic bladder contraction model is known to be useful for investigating the mode of action of drugs (15). In the present study, NSAIDs prolonged the contraction interval without any effect on the contraction amplitude. These results suggest that NSAIDs can modulate afferent pathways in the bladder and/or micturition center in the central nerve system. While both aspirin and ketoprofen significantly prolonged the interval, ketoprofen showed effects already at doses 10 times lower than aspirin. On the other hand, indomethacin also showed a tendency of interval prolongation from 0.1 mg/kg onwards. Indomethacin at 1 mg/kg was also administered after 0.1 mg/kg application, but its effect was so strong that rhythmic bladder contraction did not recover completely. Furthermore, Maggi et al. (16) demonstrated that 0.5 mg/kg indomethacin suppressed the contractions for more than 15 min. Therefore, these findings indicate that indomethacin has also significant efficacy on rhythmic bladder contraction with an efficacy weaker than ketoprofen, but stronger than aspirin.

Secondly, we compared the effects of NSAIDs on normal cystometry in anesthetized rats. Aspirin, indomethacin, and ketoprofen significantly increased bladder capacity as measured by the micturition interval at doses of 10, 3, and 0.1 mg/kg, respectively. It has been recently demonstrated that the micturition reflex is regulated by the sensory neuron (17) in rats and that the C-fiber in the sensory neuron is activated by prostanoids released during urinary bladder stretch.
Therefore, the results obtained in the normal cystometry model suggest that NSAIDs increase the threshold of firing of the sensory neuron, resulting in an increment of bladder capacity. While aspirin, indomethacin, and ketoprofen had effects on urodynamic parameters under normal conditions such as rhythmic bladder contraction and normal cystometry (see Table 1 and Fig. 1), NS-398, a selective COX-2 inhibitor, had no effect on these parameters (1). Thus, prostanoids derived from COX-1 activity may play a major role in controlling the micturition reflex under normal conditions. Interestingly, only ketoprofen but not aspirin and indomethacin increased the residual urine volume after micturition (see Table 1). This action of ketoprofen is possibly a consequence of disturbing the functional coordination between bladder and urethra, yet the exact mechanism remains to be explored.

In the next step, NSAIDs were evaluated in the model of the CYP-induced cystitis. Since the CYP-induced cystitis model in rats mimics symptoms such as pollakiuria, a very common and severe complication of CYP therapy in humans, it is considered that this model is useful for drug evaluation on the overactive bladder. CYP has been demonstrated to induce cystitis that is caused by the urinary excretion of acrolein, a metabolite of CYP (18). CYP administration results in several modifications of urinary bladder physiology and severely affects the micturition reflex. The main urodynamic changes observed after CYP administration are to decrease bladder capacity and increase micturition frequency (see Fig. 2). It is known that NK1 antagonists (13) and B1 bradykinin antagonists (19) increase bladder capacity and decrease micturition frequency by acting on the spinal cord in this model. Moreover, CYP-induced detrusor hyperreflexia is abolished when the sensory nerve is functionally impaired by pretreatment of rats with high dose capsaicin (20). Thus, CYP-induced detrusor hyperreflexia is thought to be mediated through stimulation of capsaicin-sensitive afferent neurons. In the present study, all NSAIDs were able to significantly revert these urodynamic changes induced by CYP. While the degree of decreasing the micturition frequency was identical for all NSAIDs at their effective dose, the amount of increased bladder capacity by 1 mg/kg ketoprofen was significantly bigger than that for aspirin and indomethacin. However, 1 mg/kg ketoprofen significantly increased the residual urine volume and 3 mg/kg indomethacin also showed a similar tendency. Such an effect on the residual urine volume was not observed for aspirin at any dose (data not shown). In addition, it has been reported that NS-398, a COX-2 selective inhibitor, can reduce the micturition frequency in rats with CYP-induced cystitis (1). Since conventional NSAIDs used in the present study are also known to inhibit COX-2 enzyme activity, COX-2 derived PGs might be involved in CYP-induced overactive bladder. This hypothesis is supported by the evidence that COX-2 protein as well as mRNA expression were up-regulated in the bladder following treatment with CYP (21).

In this study we confirmed that not only PGE2 but also PGF1α levels were increased in the cystitis bladder. Since both receptors for PGE2 and PGF1α are expressed on sensory C-fibers (22) and since PGs have been demonstrated to stimulate the micturition reflex, possibly through the activation of capsaicin-sensitive bladder afferent, it is likely that the activation of these receptors might be involved in cystitis-induced overactive bladder. All NSAIDs we used completely inhibited the synthesis of PGE2 and PGF1α at doses at which pharmacological actions on urodynamics could be observed, suggesting that the pharmacological action of NSAIDs is based on the inhibition of the sensory capsaicin-sensitive bladder afferent activation by the inhibition of PGs synthesis. As mentioned above, different efficacy of NSAIDs was observed in the cystometry study, with regard to change in the residual urine volume or bladder capacity. This might be due to other pharmacological actions apart from COX inhibition. To clarify this issue, further investigations are required.

The therapeutic potential of NSAIDs for detrusor instability and enuresis has been already discussed in the clinical state (2 – 5). However, due to their side effects in the gastrointestinal tract, they have not been using widely for urinary incontinence therapy. In the present study, we examined ulcerogenic effects of NSAIDs on gastrointestinal mucosa and found that indomethacin and ketoprofen induced hemorrhagic gastrointestinal mucosal damage when administered i.d. or s.c. However, aspirin did not provoke any damage in the gastrointestinal mucosa. A clinical study also demonstrated that enteric coated aspirin could reduce the risk of gastrointestinal side effects (12). The reason why parenteral aspirin does not induce gastrointestinal lesion remains unexplored. Conventional NSAIDs are known to increase gastric and intestinal motility, a phenomenon important in the gastrointestinal ulcerogenic response to these agents. However, aspirin does not increase the basal gastric motility, but even suppressed the enhanced gastric and intestine motility caused by indomethacin (14, 23). It is known that gastric hypermotility may cause mucosal hypoxia and microvascular injury due to smooth muscle contraction, leading to neutrophil infiltration and release of various cytokines (24). Furthermore Takeuchi et al. (14) reported that salicylic acid, the metabolite of aspirin, has a cytoprotective
action against NSAID-induced gastric erosion. Thus, the failure of aspirin to induce gastrointestinal damage may be explained, at least partly, by a lack of hypermotility and a protective action of salicylic acid. In the present study, we examined gastrointestinal side effects of NSAIDs by i.d. administration. Although we could make a direct comparison between the gastrointestinal side effect and pharmacological action of aspirin, we confirmed that i.d. administration of aspirin could increase bladder capacity and decrease micturition frequency in the rat with cystitis (data not shown) at the dose of 100 mg/kg. Therefore, we could conclude that aspirin did not cause any gastrointestinal lesions even when it was used at a dose higher than the pharmacological one.

In conclusion, we demonstrated that conventional NSAIDs including aspirin are functionally effective to improve urodynamic functions both under normal and cystitis conditions in rats. The rank order of potency was ketoprofen > indomethacin > aspirin. However, only ketoprofen increased the residual urine volume. Importantly and in contrast to ketoprofen and indomethacin, intraduodenal administration of aspirin did not provoke gastrointestinal lesions which are a common and familiar side effect of NSAIDs. This might open a novel aspirin treatment avenue for urinary incontinence.

References
8 Whittle BJ. Temporal relationship between cyclooxygenase inhibition, as measured by prostacyclin biosynthesis, and the gastrointestinal damage induced by indomethacin in the rat.