INTERNATIONAL JOURNAL OF UROLOGY
International Journal of Urology (2014) 21, 1162–1166 doi: 10.1111/iju.12533

Original Article: Clinical Investigation

Effect of carbazochrome sodium sulfonate on refractory chronic prostatitis

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Abbreviations & Acronyms
CP/CPPS = chronic non-bacterial prostatitis/chronic pelvic pain syndrome
IPSS = International Prostate Symptom Score
IPSS-QOL = International Prostate Symptom Score Quality of Life
VAS = visual analog scale

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Received 22 January 2014; accepted 18 May 2014.
Online publication 25 June 2014

Objectives: To study the effect of carbazochrome sodium sulfonate, an agent that reduces capillary permeability, on refractory chronic prostatitis.

Methods: Patients with prostatitis refractory to at least 8 weeks of routine therapy and with urinalysis positive for microhematuria were considered for the present study. In addition to their prior therapy, the patients received carbazochrome at a dose of 30 mg three times a day. The severity of pain (score 0–10), daytime and night-time frequency, international prostate symptom score, global self-assessment, urine occult blood positivity, and adverse events were assessed after 4 and 8 weeks of treatment, and compared with baseline findings.

Results: A total of 50 patients (mean age 68.6 ± 8.5 years) were evaluable. The pain score decreased significantly from 3.2 ± 2.1 at baseline to 1.7 ± 1.4 after 4 weeks of treatment and to 1.1 ± 1.8 after 8 weeks. Daytime and night-time frequency, storage symptoms, post-micturition symptoms, and urine occult blood positivity also significantly improved. More than 36% of the patients gave a global self-assessment rating of "improved" or "better" after both 4 and 8 weeks of treatment. Mild adverse events occurred in three patients; one had nausea and two developed drug rash.

Conclusions: Carbazochrome seems to effectively improve pain as well as storage and post-micturition symptoms in patients with refractory chronic prostatitis.

Key words: capillary permeability, carbazochrome, chronic prostatitis, urine occult blood.

Introduction

The cause of "CP/CPPS" is still unknown, but involvement of systemic factors, including an autoimmune mechanism, has been suggested considering that patients often have inflammatory features without apparent bacterial infection.[1,2] Accordingly, the efficacy of various treatments that target the prostate itself (α-blockers, antimicrobial agents, anti-inflammatory agents, herbal preparations and physical therapy) is uncertain, and better therapies are now being investigated in clinical studies.[3–5]

CP/CPPS accounts for 90–95% of all prostatitis, and category III of CP/CPPS (various storage/voiding symptoms lasting more than 3 months or pelvic discomfort and pain associated with sexual-related symptoms are present, but overt infection is not proven) in the "prostatitis classification" proposed by the National Institutes of Health in 1999 largely covers this disease.[6] Category III is divided into category IIIa (inflammatory CP/CPPS) in which white blood cells are identified in the semen/prostatic secretions after prostate massage or in the urine, and category IIIb (non-inflammatory CP/CPPS) in which white blood cells are not detected.[6] In addition to discomfort in the pelvic, perineal and suprapubic regions, CP/CPPS is often complicated by storage/voiding symptoms and sexual dysfunction, and thus has an unfavorable effect on the quality of life and work.[7] Involvement of pelvic congestion (venous congestion) in the pathogenesis of prostatitis and chronic inflammation is suspected.[8,9]

In female rats, urinary frequency and reduction of locomotor activity (a marker of pain) occur when pelvic congestion is induced by ligation of the bilateral common iliac veins,[10] whereas bilateral common iliac vein ligation plus bilateral orchiectomy can evoke urinary frequency and chronic prostatitis in male rats.[11] However, these female rats with pelvic congestion and male rats with chronic prostatitis do not develop urinary frequency or impairment of locomotor

activity if they are treated with carbazochrome sodium sulfonate (carbazochrome), a drug that reduces capillary permeability.[10,12,13] Carbazochrome is a stable oxyepinephrine derivative that is classified as a capillary stabilizer hemostatic drug.[14] It is used clinically for the treatment of hemorrhage as a result of capillary fragility. Although its mechanism of action is unknown, recent studies suggest that it reverses the thrombin-, tryptase-, and bradykinin-induced increase of endothelial cell permeability by reducing intracellular actin stress fiber formation and restoring intercellular tight junctions.[13,15] Therefore, it is possible that carbazochrome has the potential to improve extravascular leakage of blood. In fact, we sometimes experience favorable symptom relief of refractory prostatitis by oral administration of normal dose carbazochrome in clinical practice. Therefore, we investigated whether symptoms of refractory chronic prostatitis were improved by administration of carbazochrome, which would be expected to correct increased capillary permeability associated with pelvic congestion.

Methods

The participants were patients diagnosed with refractory chronic prostatitis (CP/CPPS) between 1 December 2011 and 31 March 2013 who were positive for urinary occult blood and satisfied the following selection/exclusion criteria. Patients with a positive test for urinary occult blood were enrolled because a "bleeding tendency due to decreased capillary resistance and increased permeability" is the indication for treatment with carbazochrome.

Selection criteria included: (i) men aged 20 years or older; (ii) no overt bacterial urinary tract infection, but with symptoms such as bladder pain, perineal pain, frequency and urgency; and (iii) pain in the prostate gland and positive white blood cells (over 5 cells/high power field) in expressed prostatic secretions or the initial 5–10 mL of urine voided after prostate massage. Among patients with chronic prostatitis who satisfied the aforementioned criteria, those with refractory chronic prostatitis (defined as inadequate improvement of symptoms after more than 8 weeks of treatment with antibiotics, anti-inflammatory agents, α1-blockers and/or herbal preparations) were included in the present study. If white blood cells were not detected in expressed prostatic secretions (1–5 cells/high power field) probably as a result of inadequate expression of the prostate, prostatitis was still diagnosed if the patient complained of severe tenderness derived from prostatitis.

Exclusion criteria were as follows: (i) untreated organic disease of the lower urinary tract (prostate cancer, prostate hypertrophy, bladder neck contracture, urethral stenosis, bladder cancer or bladder calculus); (ii) bacterial urinary tract infection (bacterial cystitis or bacterial prostatitis); (iii) lack of a desire to urinate; (iv) cognitive dysfunction that would affect understanding the purpose of the study and the medical interview sheet; and (v) other patients whom the physician considered inappropriate for the present study.

In addition to the prior treatment, carbazochrome (30 mg) was given orally three times a day to patients who satisfied the aforementioned criteria. At baseline, and after 4 and 8 weeks of treatment, the following items were evaluated: (i) prostate size (baseline only); (ii) frequency of urination during the daytime and night-time (from retiring to bed until awakening); (iii) IPSS, IPSS-QOL score and Overactive Bladder Symptom Score; (iv) bladder pain including lower abdominal and perineal pain on a VAS from 0 (no pain) to 10 (very severe pain); (v) urinalysis/urine sediment, and urine occult blood reaction (a surrogate marker of capillary extravascular leakage of blood) was classified into the following five grades: occult blood – (score 0), occult blood +/− (score 0.5), occult blood 1+ (score 1), occult blood 2+ (score 2) and occult blood 3+ (score 3); (vi) Global Self-Assessment of symptoms (a 5-grade scale of markedly improved, improved, slightly improved, unchanged or worse); and (vii) adverse events that had developed during the relevant period.

This was a multicenter clinical study. Approval was obtained from the ethics committee of Okinawa Kyodo Hospital, as a representative of all participating institutions. Approval of the local ethics committee of an institution was also obtained before commencement of the clinical study if required. Before enrolment, the patients were given a detailed explanation of the objectives and methods of the study, and gave their consent in writing. Results are expressed as the mean ± SD, and the paired *t*-test was used for statistical analysis, with $P < 0.05$ showing significance.

Results

A total of 50 patients were enrolled and evaluable in the present study. Their mean age was 68.6 ± 8.5 years, mean prostate volume was 19.8 ± 9.5 mL and average duration of illness was 4.8 ± 3.4 years. There were many complications including hypertension (17 cases), diabetes (seven cases), hyperlipidemia (six cases), hyperuricemia (four cases), ischemic heart disease (three cases) and others (18 cases). After 4 weeks of carbazochrome treatment, 47 patients could be evaluated, two patients dropped out because of adverse events and one patient was not evaluated. After 8 weeks of treatment, 39 patients could be evaluated, and the remaining nine patients dropped out.

The daytime frequency of urination was 9.6 ± 3.3 at baseline, and it decreased significantly to 8.7 ± 2.9 after 8 weeks of carbazochrome treatment ($P = 0.030$). The nocturnal frequency of urination was 2.1 ± 1.3 at baseline, and it also decreased significantly to 1.8 ± 1.2 ($P = 0.001$) after 4 weeks of treatment and showed further improvement to 1.4 ± 1.1 ($P = 0.002$ *vs* 4 weeks) after 8 weeks of treatment.

The total IPSS was 13.5 ± 7.0 at baseline, and it improved significantly to 12.6 ± 6.4 ($P < 0.001$) after 4 weeks of treatment and to 10.5 ± 6.7 ($P < 0.001$ *vs* baseline and 4 weeks) after 8 weeks (Fig. 1). There were no changes of "slow stream" and "straining" among the voiding symptoms. However, storage symptoms (urgency, from 1.9 ± 1.8 at baseline to 1.3 ± 1.3 at 8 weeks, $P < 0.001$) and post-micturition symptoms (incomplete emptying, from 1.9 ± 1.6 at baseline to 1.3 ± 1.4 at 8 weeks, $P = 0.008$) showed slight, but significant, improvement.

The total Overactive Bladder Symptom Score improved significantly from 6.4 ± 3.7 at baseline to 5.6 ± 3.7 after 4 weeks of treatment ($P < 0.001$) and to 4.6 ± 3.4 ($P < 0.001$ *vs* baseline and 4 weeks) after 8 weeks (Fig. 2). Individual variables also showed significant improvement after 8 weeks of treatment.

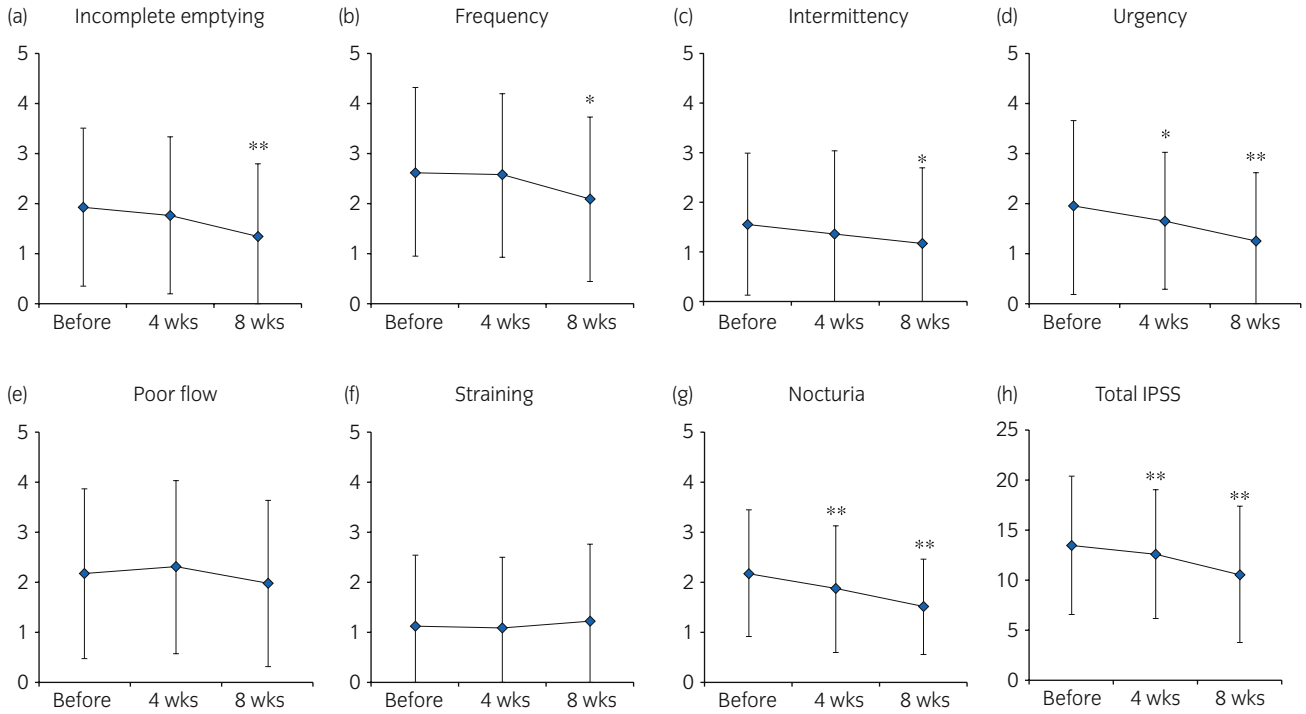

Fig. 1 IPSS before and after 4 and 8 weeks of carbazochrome treatment. *$P < 0.05$, **$P < 0.01$.

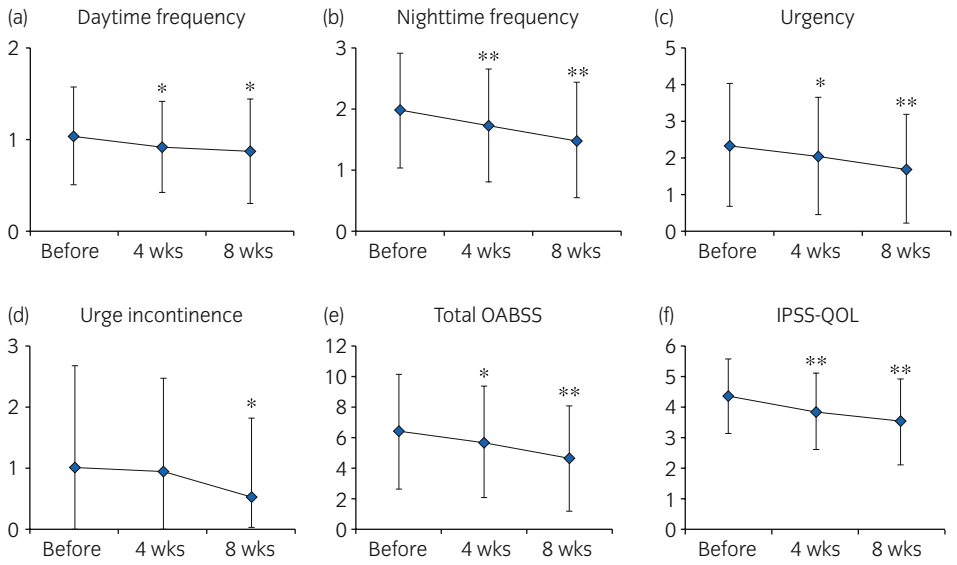

Fig. 2 Overactive Bladder Symptom Score and IPSS-QOL index before and after 4 and 8 weeks of carbazochrome treatment. *$P < 0.05$, **$P < 0.01$.

IPSS-QOL decreased significantly from 4.3 ± 1.2 at baseline to 3.8 ± 1.3 ($P = 0.001$) after 4 weeks of treatment and to 3.5 ± 1.4 ($P = 0.009$ *vs* baseline) after 8 weeks. None of the patients showed worsening of IPSS-QOL.

Bladder pain and urine occult blood positivity improved rapidly after the start of carbazochrome treatment (Fig. 3). Improvement of bladder pain was particularly marked, with the VAS score declining from 3.2 ± 2.1 at baseline to 1.7 ± 1.4 ($P < 0.001$) after 4 weeks of treatment and to 1.1 ± 1.8 ($P < 0.001$ *vs* baseline and 4 weeks) after 8 weeks of treatment. In the patients ($n = 28$) with a bladder pain score of 3 or more at baseline, there was also significant improvement from 4.6 ± 1.7 at baseline to 2.4 ± 1.4 ($P < 0.001$) after 4 weeks of treatment and to 1.6 ± 2.1 ($P < 0.001$ *vs* baseline and 4 weeks) after 8 weeks. Remaining bladder pain (pain score of 3 or more) after 8 weeks of treatment was observed in four patients (VAS score 3.8–9.0, median 4), for whom the efficacy of carbazochrome was very poor on examined items, including

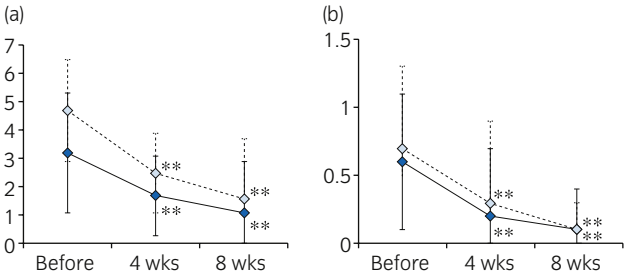

Fig. 3 (a) Bladder pain (VAS from 0: no pain to 10: very severe pain) and (b) the urine occult blood reaction (no occult blood: score 0, occult blood +/–: score 0.5, occult blood 1+: score 1, occult blood 2+: score 2, and occult blood 3+: score 3) before and after 4 and 8 weeks of carbazochrome treatment. Solid line: all cases, dashed line: cases with VAS ≥3. $^{**}P < 0.01$. —◆—, All cases; ··◇··, Cases with VAS ≥3.

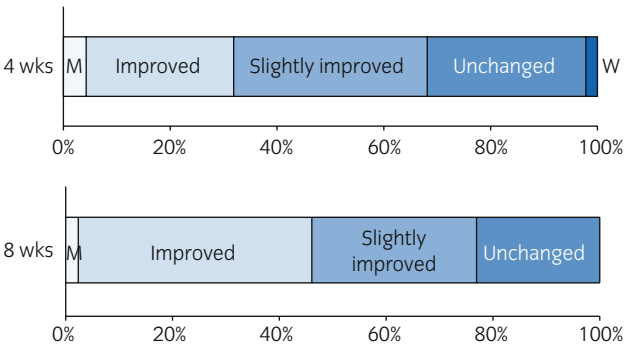

Fig. 4 Global Self-Assessment of symptoms after 4 and 8 weeks of carbazochrome treatment. After 4 weeks, the Global Self-Assessment rating was "markedly improved" (M) in 4%, "improved" in 28%, "slightly improved" in 36%, "no change" in 30%, and "worse" (W) in 2% of 47 patients. After 8 weeks, the Global Self-Assessment rating was "markedly improved" in 3%, "improved" in 44%, "slightly improved" in 31%, "no change" in 23% and "worse" in 0% of 39 patients.

IPSS-QOL. The urine occult blood reaction improved significantly from 0.6 ± 0.5 at baseline to 0.2 ± 0.5 after 4 weeks of treatment ($P < 0.001$) and to 0.1 ± 0.3 ($P < 0.001$ *vs* baseline) after 8 weeks. There was no difference of the effect on urine occult blood between all patients and the patients with a bladder pain score of 3 or more. In Figure 3, the pattern of improvement of the urine occult blood reaction after administration of carbazochrome was very similar to the pattern of change of bladder pain.

The Global Self-Assessment rating was "markedly improved" or "improved" in 32% of 47 patients after 4 weeks of carbazochrome treatment, and in 46% of 39 patients after 8 weeks of treatment (Fig. 4). In nine patients who dropped out at 8 weeks, 33% of the patients were "improved" at 4 weeks of treatment. Adverse events occurred in three patients. One patient complained of nausea, two patients developed drug rash and all of them withdrew from the study in week 4. Each event was mild, and all of the events improved rapidly after discontinuation of treatment.

Discussion

In patients with refractory chronic prostatitis, the addition of carbazochrome led to a marked improvement of pain, and also improved storage symptoms and post-micturition symptoms. Accordingly, treatment with carbazochrome might be worthwhile in patients who have refractory chronic prostatitis showing a poor response to standard therapy.

Pelvic congestion could be responsible for the pathological condition of CP/CPPS.[8,9] With respect to the association between regurgitation into the inferior vena cava as a result of tricuspid incompetence and urological diseases, it has been reported that there is a significant increase of inferior vena cava regurgitation in men with chronic prostatitis.[9] Pelvic congestion secondary to inferior vena cava regurgitation might be one of the factors contributing to refractory prostatitis with or without clinical symptoms. It has also been reported that many patients with prostatitis have hemorrhoids too, which might be attributable to pelvic congestion.[8] Prolonged walking and sitting worsen the symptoms of CP/CPPS, whereas lying down improves symptoms, also suggesting the involvement of pelvic congestion.[9] The pathogenesis of CP/CPPS should probably be considered to be multifactorial, so the main condition causing a particular patient's symptoms is likely to differ, and it is important to consider pelvic circulatory disturbance as one of the factors.

It was particularly noteworthy in the present study that carbazochrome had a marked effect on storage symptoms and bladder pain after a short period in patients in whom prior treatment with α-blockers and/or anti-inflammatory agents had been ineffective. In the patients with a bladder pain score of 3 or more at baseline, carbazochrome had a marked effect on bladder pain after a short period, showing a significant effect of carbazochrome in patients who had a certain level of pain at baseline. In contrast, improvement of voiding symptoms by carbazochrome was poor compared with storage and post-micturition symptoms. It is believed that improvement of storage and post-mictrition symptoms was obtained through the relief of bladder pain. Diuretic or anti-inflammatory effects have not been reported for carbazochrome,[13] so it is possible that the mechanism of action is related to improvement of conditions related to capillary permeability. In a rat model of tranilast-induced interstitial cystitis with increased vascular permeability in the bladder, locomotor activity (an indicator of pain) was reduced, but administration of carbazochrome decreased vascular permeability in the bladder and improved locomotor activity, suggesting that pain was suppressed by carbazochrome.[16]

Improvement of the urine occult blood reaction in the present study might have mainly resulted from suppression of increased glomerular capillary permeability in the kidneys. However, the two patterns of improvements of bladder pain and the urine occult blood reaction after administration of carbazochrome were very similar, also suggesting that carbazochrome inhibits extravascular leakage of a bladder-stimulating substance.

Assessment of the pathological mechanism is difficult from results of the present study, and more detailed investigations will be required, including a study on the mechanism of action of carbazochrome in CP/CPPS. Various empirical therapies have been ineffective for CP/CPPS and there are not many options available, so the results of the present study should be worth considering by doctors who deal with this condition. Carbazochrome can be easily prescribed and has several advan-

tages, as it is inexpensive, does not often cause serious adverse reactions, can be added without changing previous medications (few interactions) and is well known by urologists. Further clarification of the pathology underlying CP/CPPS is expected. As a next step, investigations of the relationship among pelvic congestion, lower urinary tract symptoms/findings, and the more detailed pharmacological effect and mechanism of action of carbazochrome will be required in the future.

In patients with refractory chronic prostatitis, carbazochrome was mainly effective for pain as well as storage and post-micturition symptoms. Carbazochrome also decreased urine occult blood reaction. Carbazochrome might improve the symptoms of chronic prostatitis by improvement of conditions related to capillary permeability. Carbazochrome could be a potential treatment for chronic prostatitis.

Conflict of interest

None declared.

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