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Ejaculatory dysfunction caused by the new α_1-blocker silodosin: A preliminary study to analyze human ejaculation using color Doppler ultrasonography

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Objectives: In order to clinically investigate the mechanism of ejaculatory dysfunction attributable to the α_1-blocker silodosin, a real-time observation of ejaculation by healthy males was performed.

Methods: Following intake of silodosin, a newly developed selective α_1-blocker for benign prostatic hypertrophy, ejaculation was dynamically observed using color Doppler ultrasound in three healthy males. Normal ejaculation was also investigated in the same manner.

Results: With silodosin intake, no antegrade ejaculation was observed in cases 1 or 2. In case 1, seminal fluid slowly but continuously flowed out from the seminal vesicles into the bladder. In case 2, only a small amount of seminal fluid flowed into the bladder during the ejaculatory sensation. In case 3, ejection of a small amount of semen from the external urethral orifice was observed and inflow of a small amount of seminal fluid into the bladder was also captured. Without silodosin intake, all three subjects exhibited antegrade ejaculation.

Conclusions: The mechanism of ejaculatory dysfunction is intricately related to retrograde ejaculation (retrograde inflow of seminal fluid), insufficient contraction of the seminal vesicles, and insufficient rhythmic contraction of the muscles of the pelvic floor.

Key words: α_1-blocker, ejaculation, color Doppler ultrasonography, silodosin.

Introduction

The use of ultrasonic diagnostic devices has enabled analysis and clarification of the male ejaculatory process.[1–3] In particular, dynamic analysis of ejaculation has become possible using color Doppler ultrasonography. The process of the ejaculation of semen, beginning at the seminal vesicles, passing through the ejaculatory duct, and spurting into the bulbous urethra, has been clearly confirmed.[3]

Recently, reports have been made regarding ejaculatory dysfunction due to α_1-blockers, especially the selective blocker tamsulosin, used in the treatment of benign prostatic hyperplasia (BPH). Attempts have been made to understand the mechanism of deleterious effects on ejaculation of tamsulosin.[4–9] In this regard, we focused on the ejaculatory dysfunction caused by silodosin, a newly developed prostate selective α_1-blocker.[10] This drug is already on the market in Japan, while phase 2 and 3 studies are underway in other countries including the USA. Compared with tamsulosin, silodosin exhibits 40-fold greater α_{1A} selectivity,[11] and its usefulness in the treatment of BPH has been demonstrated.[12] Concerning adverse events observed in the clinical studies conducted during development of this drug, ejaculatory abnormality was observed at a high incidence of 22.3%, compared with 1.6% in those treated with tamsulosin.[12]

Since the ejaculatory disorder attributable to α_1-blockers has attracted considerable clinical attention, we clinically examined the mechanism of ejaculatory dysfunction induced by α_1-blockers by real-time observation using color Doppler ultrasonography of ejaculation in healthy men who were taking oral silodosin. We also observed normal ejaculation, and obtained new insights into the process of ejaculation.

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Methods

This study was performed under approval by the Ethics Committee of Kawasaki Medical School. Three healthy males capable of normal ejaculation and without urinary dysfunction were used as subjects. Informed consent was obtained from each (cases 1, 2, and 3; 30, 24, and 29 years of age, respectively). A 4 mg dose of silodosin both in the morning and evening (total 8 mg per day) for was administered 3 days and ejaculation was induced 2 h after the final intake of silodosin under audio-visual sexual stimulation and by manual stimulation of the penis. A 7.5 MHz ultrasonic probe (UST-669) with SSD-2000 (Aloka Ltd.) was introduced into the rectum in the left lateral decubitus position to visualize the bladder neck, prostate, and posterior urethra. In this fashion, dynamic observation of ejaculation was performed. After a 10-day period for washout of silodosin, normal ejaculation was also investigated, and results were compared with those of ejaculation observed during silodosin administration.

Results

All ejaculations with and without oral silodosin were clearly observed (Figs 1–3). In case 1 with oral silodosin, the bladder neck opened before stimulation (Fig. 1a-I). Close to ejaculation, contraction of the prostate was observed, but the bladder neck did not completely close. Seminal fluid was observed to flow slowly out of the seminal vesicle into the bladder (Fig. 1a-II). No ejection of semen from the external urethral orifice was observed. In case 2 with oral silodosin, the bladder neck was clearly open (Fig. 2a-I) and did not completely close during the ejaculatory sensation. Only a small amount of seminal fluid flowed into the bladder (Fig. 2a-II), and no ejection of semen from the external urethral orifice was observed. In case 3 with oral silodosin, ejection of a small amount of semen from the external urethral orifice was observed, with a slight flow of seminal fluid into the bladder (Fig. 3a). Urinalysis after the experiment revealed sperm in each sample, with a pH of 6.26–6.61.

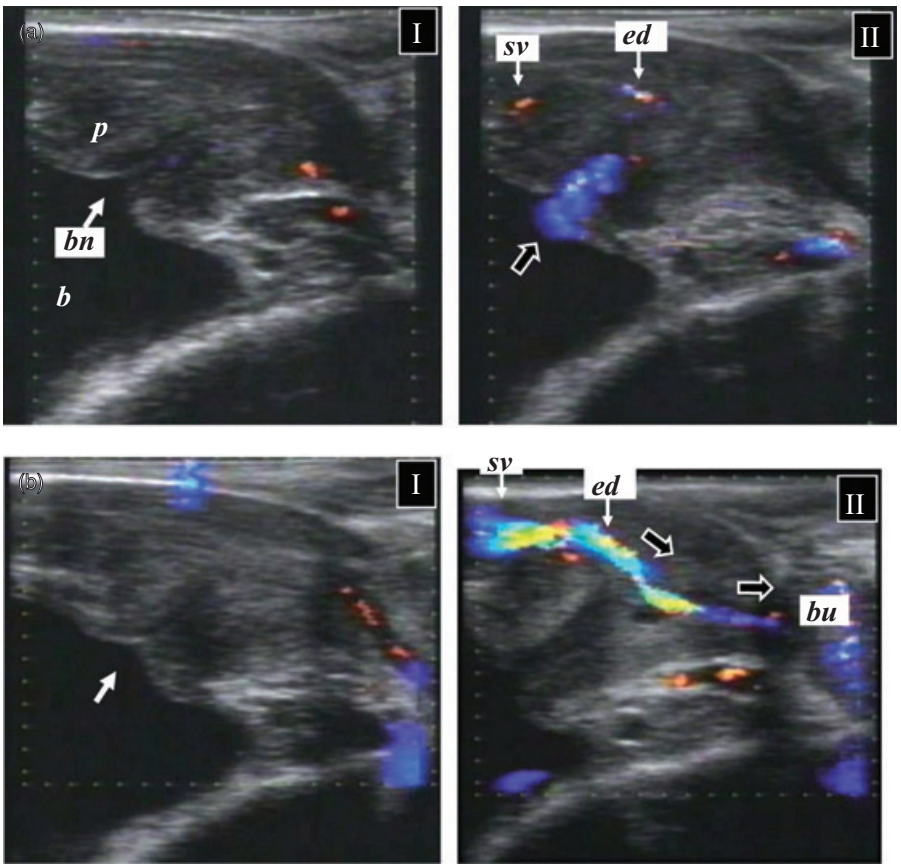

Fig. 1 Color Doppler ultrasonographic images of ejaculation in case 1. (a) With oral silodosin. (I) Prostate (*p*), bladder (*b*), and opening of bladder neck (*bn*). (II) Seminal fluid stream (black arrow) flows slowly out of the seminal vesicle (*sv*) through the ejaculatory duct (*ed*) into the bladder. (b) Without oral silodosin. (I) Bladder neck (white arrow) does not open. (II) Ejaculatory stream (black arrow) from the seminal vesicles (*sv*) spurting towards the bulbous urethra (*bu*) through the ejaculatory duct (*ed*).

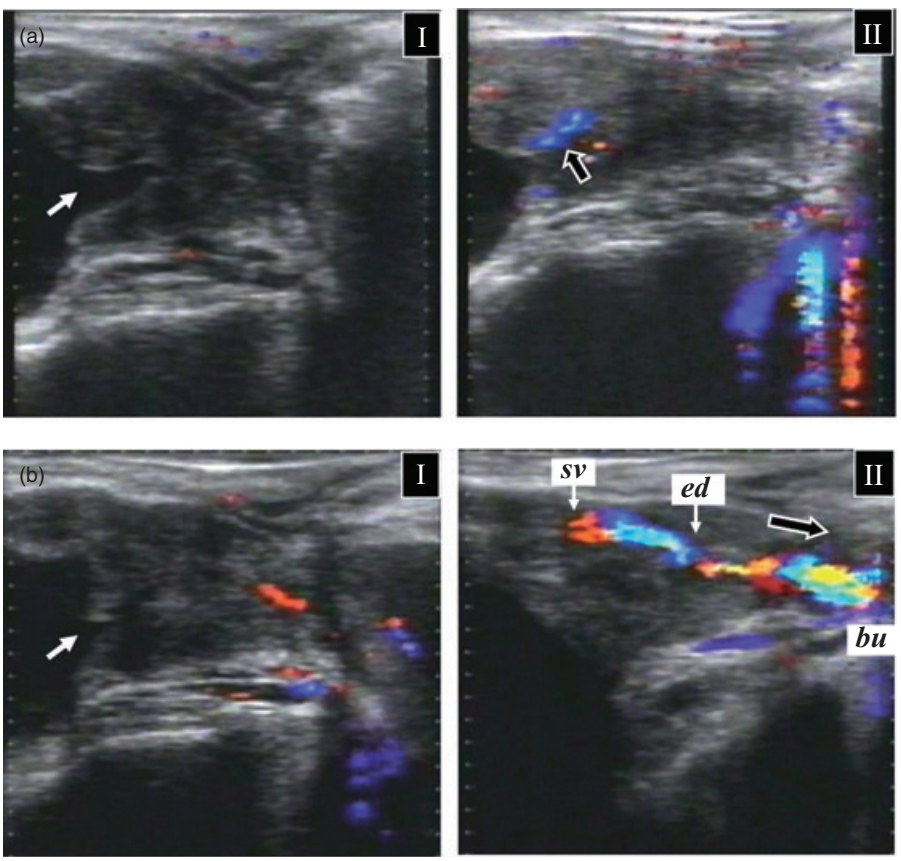

Fig. 2 Color Doppler ultrasonographic images of ejaculation in case 2. (a) With oral silodosin. (I) Significant opening of bladder neck (white arrow). (II) A small amount of seminal fluid flows into the bladder (black arrow). (b) Without oral silodosin. (I) Bladder neck (white arrow) does not open. (II) Spurting stream (black arrow) from the seminal vesicles (*sv*) towards the bulbous urethra (*bu*) through the ejaculatory duct (*ed*).

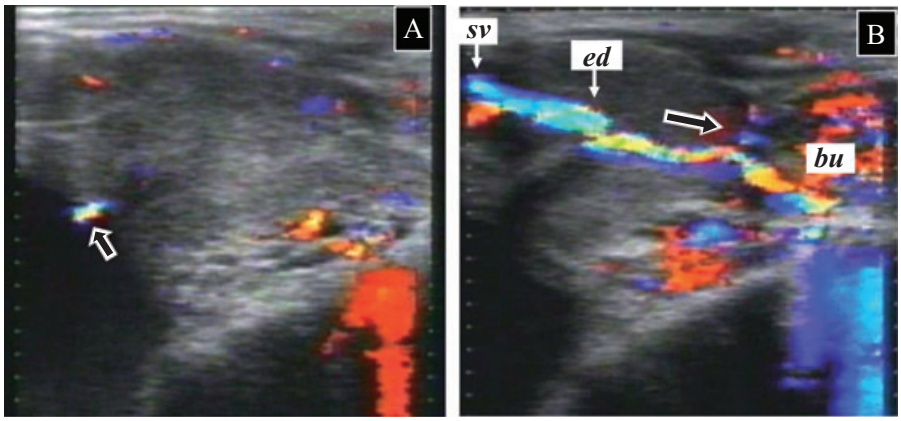

Fig. 3 Color Doppler ultrasonographic images of ejaculation in case 3. (A) With oral silodosin. A small amount of semen flows into the bladder (black arrow). (B) Without oral silodosin. Normal ejaculatory stream from seminal vesicles (*sv*) towards the bulbous urethra (*bu*) through the ejaculatory duct (*ed*).

Without silodosin, all three subjects exhibited antegrade ejaculation. The opening of the bladder neck observed in cases 1 and 2 under silodosin administration did not occur after the washout of silodosin (Figs 1b-I,2b-I). The bladder neck flattened and closed in association with the contraction of the prostate before ejaculation. Immediately afterwards, rhythmical ejection of seminal fluid from the seminal vesicles through the ejaculatory duct and into the bulbous urethra was observed. The findings were identical to those obtained in our previous study[2,3] (Figs 1b-II,2b-II,3b).

Discussion

Because of their high degree of α_1 selectivity, α_1-blockers, which are used to treat BPH, demonstrate superior efficacy against this condition when it is accompanied by lower urinary tract symptoms (LUTS). However, ejaculatory dysfunction has attracted clinical attention as an adverse reaction to these drugs. The incidence of ejaculatory dysfunction attributable to α_1-blockers for patients with prostatic hypertrophy is reported to be 0.3–18.1%.[4,5] A study of ejaculatory dysfunction in healthy adult men revealed a 35.4% rate of complete lack of ejaculation with administration of 0.8 mg tamsulosin daily.[7] As noted above, many reports have been made on the ejaculatory dysfunction caused by tamsulosin. There are also a large number of reports on the mechanism of ejaculatory dysfunction attributable to this drug. Hisasue *et al*. examined the seminal fluid of healthy male volunteers who demonstrated an 80% decrease in ejaculatory volume after taking oral tamsulosin at 0.4 mg for 3 days, and reported that no semen was observed, and that the ejaculatory dysfunction induced by tamsulosin is not a form of retrograde ejaculation but instead a loss of seminal emission.[6] Hellstrom investigated healthy volunteers who were orally administered tamsulosin at 0.8 mg for 5 days, and reported that ejaculate volume was reduced in 90% of the subjects, and that an ejaculation was observed in 35%.[7] There was relatively little difference in semen concentration after ejaculation in comparison with the placebo group and the alfuzosin group, so it was concluded that ejaculatory dysfunction with tamsulosin was not attributable to retrograde ejaculation.[7]

Compared with tamsulosin, silodosin exhibits 40-fold greater α_{1A} selectivity.[11] According to the results obtained in the clinical studies conducted during development, ejaculatory dysfunction was observed at an incidence of 22.3% of those treated with silodosin against 1.6% of those treated with tamsulosin.[12] Accordingly, we focused on this drug and investigated ejaculatory status in healthy volunteers by conventional methods using a color Doppler device.

Under silodosin administration, the flow of seminal fluid into the bladder was observed in all three subjects despite individual differences in the manner of ejaculation. In case 2, only a small amount of seminal fluid flow into the bladder was noted, and although rhythmic contraction of the prostate was noted, ejection of the usual amount of seminal fluid was not observed. In case 3, the prostate contracted rhythmically but only a small amount of antegrade ejaculation was observed, and only a small amount of ejaculatory fluid flowed into the bladder. Continuous flow of seminal fluid from the seminal vesicles through the ejaculatory duct into the bladder was imaged in case 1. Unlike cases 2 and 3, however, in case 1 rhythmic contraction of the prostate and seminal vesicles did not occur during the ejaculatory sensation. In all cases, seminal fluid flow into the bladder was confirmed. Although these findings could be considered those of 'retrograde ejaculation', the term 'retrograde inflow of seminal fluid' seems more appropriate. In addition to the retrograde inflow attributable to insufficient closure of the bladder neck, insufficient contraction of the seminal vesicles may also occur under silodosin administration. It has already been reported that α_{1A} receptors are present in the spermatic ducts and seminal vesicles.[13–15] The findings of the present study are consistent with the report that contraction of the seminal vesicles is involved in ejaculation.

After a 10-day washout of silodosin, all three subjects exhibited antegrade ejaculation. Frank ejection of seminal fluid from the seminal vesicles through the ejaculatory duct and toward the bulbous urethra was observed in each. This finding was the same as obtained previously, and endorsed our previous observations.[3] In the phase I study of silodosin,[16] the half-life was 4.5 h and the plasma drug concentration at 48 h was beneath the limit of determination after a single administration at 8 mg, indicating the validity of use of a 10-day washout period. The usual dose of silodosin in the treatment of patients with prostatic hypertrophy is 8 mg/day, and equivalent to the oral dose given in this study.

Levin[17] noted in his review on ejaculation that relaxation of the distal sphincter and striated pelvic musculature, especially that associated with the bulbocavernous rhythmical spurts, is required for ejaculation. In this regard, we also found in a previous study that rhythmical contraction of the muscles of the pelvic floor is required for ejaculation.[3] It appears that this muscle contraction is weakened by α_1-blockers.

In the present study, it was possible to capture ejaculatory status and ejaculatory dysfunction by color Doppler ultrasound after administration of a new prostate selective α_1-blocker. Though this study was conducted as a pilot study, ejaculatory dysfunction is known to be intricately related to retrograde inflow of seminal fluid into the bladder, insufficient contraction of the seminal vesicles, and insufficient rhythmic contraction of the muscles of the pelvic floor. The findings of this study revealed individual differences in the manifestation of this condition.

In the future, it will be necessary not only to observe ejaculation in relation to silodosin administration but also its effects on orgasm. Recently, the relationship between erectile dysfunction and LUTS has attracted attention.[18] In this regard, further investigation of the relationships between use of α_1-blockers and disorder of micturition and sexual dysfunction will be important. The incidence of ejaculatory dysfunction attributable to oral α_1-blockers is high. If orgasm is attained, however, this symptom cannot be considered a serious adverse reaction but instead a mild disorder related to quality of life which is probably tolerable. It has been reported that ejaculatory dysfunction was significantly improved by changing the frequency of administration of tamsulosin from daily to every other day.[19] This finding is of significance to future strategies for the clinical use of α_1-blockers. With the advent of new α_1-blockers, research on LUTS and male sexual function can be expected to make further progress.

Conclusions

The mechanism of the ejaculatory dysfunction caused by the new α_1-blocker silodosin was examined using ultrasonic color Doppler. This type of ejaculatory dysfunction is intricately related to retrograde inflow of seminal fluid into the bladder, insufficient contraction of the seminal vesicles, and insufficient rhythmic contraction of the muscles of the pelvic floor, and there appear to be individual differences in the manifestation of it.

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