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Editorial Comment

Editorial Comment from Dr Saito and Dr Shimizu to Propiverine increases urethral wall catecholamine levels and bladder leak point pressure in rats

Many reports have shown that muscarinic receptor antagonists have been used and are thought to be effective against overactive bladder, but not for stress urinary incontinence (SUI).[1] In Japan, only clenbuterol hydrochloride, a selective β2-adrenergic agonist, is available to prescribe for SUI patinents.[2,3] In addition, tricyclic antidepressants, such as imipramine hydrochloride, are also used for off-label use.[4] Interestingly, previous manuscripts have reported the efficacy of propiverine, an anticholinergic drug with calcium antagonistic action, against pure SUI patients in Japan.[5] In the present study, Nishijima *et al.* tried to investigate the mechanism through which propiverine is effective for treating SUI.[6] The authors found that intravenous injection of propiverine increased the leak point pressure in rats with vaginal distention. The mechanism of this effect could be that propiverine acted like a noradrenaline re-uptake inhibitor, and subsequently increased noradrenaline and/or dopamine levels in the plasma, cerebrospinal fluid, and urethral wall perfusion fluid. The authors concluded that the inhibition of noradrenaline re-uptake by propiverine mainly occurs at the urethral level, and partially at the central nervous system; furthermore, it might stimulate the smooth muscles of the bladder neck and proximal urethra through α1-adrenergic receptors, as well as it might stimulate the striated muscles of the urethra and pelvic floor by an activation of the spinal motoneurons. These data clearly suggest a new mechanism for the protective effect of propiverine in the lower urinary tract in the rat. A limitation of this study was whether their new finding; that is, propiverine's action as a noradrenaline re-uptake inhibitor, can be applied to humans in clinically used-doses, considering that it is quite difficult to confirm the new finding in humans.

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Conflict of interest

None declared.

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Editorial Comment

Editorial Comment from Dr Negoro to Propiverine increases urethral wall catecholamine levels and bladder leak point pressure in rats

The article by Nishijima *et al.* showed that propiverine, known as an antimuscarinic and Ca-antagonistic agent, increased leak point pressure in rats by acting as a noradrenaline re-uptake inhibitor like imipramine and nisoxetine, which mainly occurred in the urethra through α1-adrenoceptor.[1] Elucidating the pharmacological action of propiverine on stress urinary incontinence is appreciated, as treating stress urinary incontinence pharmacologically is not straightforward, especially in patients suffering after radical prostatectomy, and progress in this field has been awaited.

This basic research is important to support the clinical effect of propiverine on stress urinary incontinence in a human study, though there are some points to be carefully considered, because differences in the pharmacological effect

were observed in rats and humans.[2] First, relatively high doses of propiverine as 3 mg/kg i.v. and 5 mg/kg p.o. were required to induce a noradrenaline re-uptake effect in rats, and almost no effect was observed at 1 mg/kg i.v. The maximum human dose of propiverine is 40 mg/day, which is much less than that of rats used here. The high dose required in rats is compatible with table 1 of this report showing the much weaker effect of propiverine than that of nisoxetine. Second, an increase of plasma catecholamine levels by propiverine was observed in the present study. The authors speculated that it was from leakage of catecholamines from the peripheral organs, including the urethra, in addition to from the adrenal glands, though it was not observed in the human study.[2] On this point, the authors guessed that propiverine administration can also increase the catecholamine level in the urethral wall elderly people, but its level seems not to influence the plasma catecholamine level. It would be expected that differences between young and old subjects in addition to those of different species would be evaluated, as various effects of propiverine have been reported in different conditions.[3–5] Further research will help to answer whether the administration of a physiological dose of propiverine in elderly patients actually has an inhibitory effect of noradrenalin re-uptake and increases catecholamine in the urethral wall.

The authors did not discuss the structure of propiverine that can work as a noradrenalin re-uptake inhibitor, but it might be interesting to focus on this, and to evaluate its metabolites or create new drugs that are expected to have a higher affinity in the urethral wall to increase the effect on stress urinary incontinence and reduce the side-effects.

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None declared.

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Editorial Comment

Editorial Comment from Dr Aizawa to Propiverine increases urethral wall catecholamine levels and bladder leak point pressure in rats

The prevalence of stress urinary incontinence (SUI) increases with age as well as with several factors including living habits, surgery and vaginal delivery, especially in women.[1] For the pharmacotherapy of SUI, there has been little success in the development of agents, whereas duloxetine, a serotonin-noradrenaline reuptake inhibitor, has shown clinical efficacy and has been approved in Europe, but there are concerns regarding liver toxicity and suicidal events.[2] Regarding the mechanism and site of action, duloxetine inhibits serotonin–noradrenaline re-uptake in the central nervous system ("Onuf's nucleus" in the sacral spinal cord), and thereby it has been proposed that this mechanism increases the rhabdosphincter tone and contractility through the central stimulation of pudendal motor neuron α1-adrenergic and 5-HT_2 receptors.[3]

The current study by Nishijima *et al.* has explored the possible treatment option of propiverine, an anticholinergic agent, for SUI.[4] They showed that: (i) intravenous propiverine and duloxetine increased the leak point pressure (LPP) in rats with vaginal distention; (ii) intrathecal naftopidil, an $\alpha 1_{A/D}$-adrenergic antagonist, decreased the LPP, whereas subsequent intravenous propiverine restored the LPP; (iii) propiverine showed an inhibition of the noradrenaline re-uptake; and (iv) noradrenaline and dopamine levels in the plasma and urethral wall were increased by oral propiverine supplementation (5 mg/mL/day for 10 days). These findings were consistent with their previous report that propiverine supplementation (5 mg/mL/day for 2 weeks) increased the urethral baseline pressure, whereas imidafenacin (an anticholinergic agent, 0.01 mg/mL/day) did not show such an increased response.[5] Regarding the mechanism and site of action of propiverine based on the current and previous results, it is conceivable that an increase of noradrenaline induced by propiverine can activate both sympathetic pathways and Onuf's nucleus through α1-adrenergic receptors to increase the urethral baseline pressure and LPP. These mechanisms might be reasonable to ameliorate SUI, and propiverine could be a promising tool for the treatment of SUI.

As harmonized with these basic findings, propiverine has been proven to clinically improve SUI without serious adverse events, which was also shown by the same group.[6] However, this previous clinical study showed no elevation of blood catecholamine at 8 weeks after propiverine treatment. Therefore, evidence of propiverine as an inhibitor of nora-