

EFFECT OF TAK-802, A NOVEL ACETYLCHOLINESTERASE INHIBITOR, AND VARIOUS CHOLINOMIMETICS ON THE URODYNAMIC CHARACTERISTICS IN ANAESTHETIZED GUINEA PIGS

Hypothesis / aims of study

Detrusor underactivity is one of the causes of voiding dysfunction. Although it has been proposed that cholinomimetic drugs, such as muscarinic agonists and acetylcholinesterase (AChE) inhibitors, may be useful in the pharmacologic treatment of voiding dysfunction associated with detrusor underactivity, clean intermittent catheterization remains the first choice of treatment. We previously reported that TAK-802, a novel AChE inhibitor, potentiates isovolumetric bladder contraction in vivo, and that this drug has a higher selectivity for muscarinic over nicotinic actions than distigmine, a carbamate AChE inhibitor (1). In this study, we investigated the effects of TAK-802 on the urodynamic characteristics in anaesthetized guinea pigs, and compared these effects with those of various other cholinomimetics.

Study design, materials and methods

Pressure flow studies: Male Hartley guinea pigs (250–380 g) were anaesthetized with urethane (1.5 g/kg, i.p.). Two catheters (PE-100) were inserted into the bladder dome, one for recording the intravesical pressure and the other for intravesical infusion of saline (0.3 ml/min). The intravesical pressure and voided volume were measured using a pressure transducer and electronic balance, respectively. Each signal was concomitantly recorded using an MP100A apparatus (Biopac systems). The signal of the voided volume was differentiated to obtain the flow rate. After confirming three successive micturition reflexes induced by intravesical infusion of saline, the bladder was completely drained off, and the infusion was restarted. Bladder filling was continued until micturition was observed. The following urodynamic parameters were measured, as in the previous report (2): maximum flow rate (Q_{max}), bladder capacity (B_c), voided volume (V_v), intravesical pressure at Q_{max} (P_{ves}(Q_{max})), and bladder compliance (B_{com}). Each of the urodynamic parameters was measured before and after intravenous administration of the drugs.

Urethral pressure measurement: Female guinea pigs (300–350 g) were anaesthetized with urethane. A Mikro-tip® pressure transducer was positioned so as to record the highest urethral pressure in the distal part of the external urethral sphincter. After measuring the pre-drug urethral pressure, the post-drug pressures were measured 30 minutes after the intravenous administration of the respective drugs.

Results

Effects on urodynamic parameters: TAK-802 (0.003–0.03 mg/kg, i.v.) significantly increased the Q_{max} and V_v without affecting either the P_{ves}(Q_{max}) or B_{com}. Distigmine (0.03–0.3 mg/kg, i.v.) and neostigmine (0.01–0.1 mg/kg, i.v.), both carbamate AChE inhibitors, significantly increased the P_{ves}(Q_{max}) but not the Q_{max}, and decreased the B_{com}. Bethanechol (0.1–1 mg/kg, i.v.), a muscarinic agonist, significantly decreased the V_v, B_c and B_{com}, but did not affect either the Q_{max} or the P_{ves}(Q_{max}).

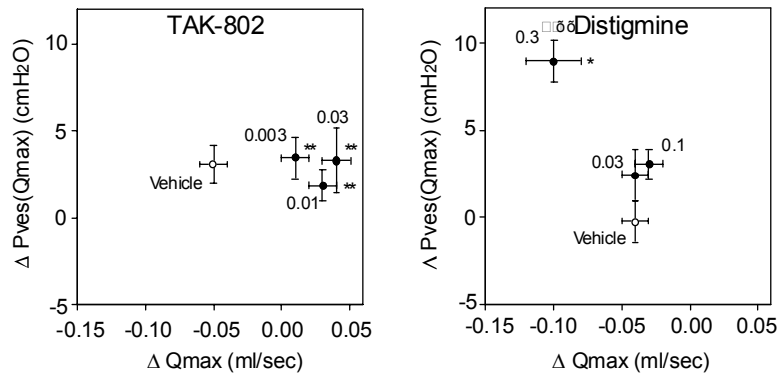


Figure. Effects of TAK-802 and distigmine on the pressure/flow characteristics. Values are represented as the differences between the pre-drug and post-drug values and the mean \pm S.E.M. The numbers besides the filled circles indicate the dosage (mg/kg, i.v.). *P<0.05, **P<0.01, vs.

ΔQ_{max} in the vehicle-treated group, $^{\dagger}P<0.05$, $^{\dagger\dagger}P<0.01$, vs. $\Delta P_{ves}(Q_{max})$ in the vehicle-treated group (Dunnett's test). N=9-10.

Effects on urethral pressure: TAK-802 did not affect the intraurethral pressure at doses of up to 0.03 mg/kg. Distigmine significantly increased the intraurethral pressure when administered at the dose of 0.3 mg/kg, and the effect was completely abolished by pretreatment with α -tubocurarine, a neuromuscular blocking agent.

Interpretation of results

TAK-802 reinforced the bladder-voiding function by enhancing the detrusor contractility without increasing the urethral resistance or decreasing the bladder storage function in anaesthetized guinea pigs. Carbamate AChE inhibitors not only caused deterioration of the bladder voiding function by increasing the urethral resistance, but also caused deterioration of the bladder storage function when administered at higher doses. The increase in urethral resistance induced by a carbamate AChE inhibitor might be attributed to contraction of the external urethral sphincter muscle induced by this drug. Bethanechol clearly decreased the bladder capacity, possibly due to a tonic contractile effect on the detrusor smooth muscle.

Concluding message

TAK-802 may be a more useful drug than either carbamate AChE inhibitors or muscarinic agonists for the treatment of voiding dysfunction associated with detrusor underactivity.

References

1. Effects of TAK-802, a novel acetylcholinesterase inhibitor, on distension-induced rhythmic bladder contractions in rats and guinea pigs, *Eur J Pharmacol*, 485: 299-305, 2004
2. Analysis of pressure/flow characteristics in the female rat and their pharmacologic modulation, *Neurourol Urodyn*, 15: 513-527, 1996