

ASSESSMENT OF THE USEFULNESS AND OPTIMAL METHOD OF ADMINISTRATION OF DISTIGMINE BROMIDE FOR THE TREATMENT OF VOIDING DYSFUNCTION DUE TO UNDERACTIVE DETRUSOR

Hypothesis / aims of study

No effective treatment for voiding dysfunction due to underactive detrusor is available anywhere in the world. Distigmine bromide is an anticholinesterase that inhibits acetylcholine breakdown by acetylcholinesterase (AChE) and cholinesterase (ChE) at neuromuscular junctions. The inhibition of Ach breakdown prolongs its action at nerve endings and its ability to act on Ach receptors. Since using distigmine bromide involves the risk of causing a cholinergic crisis, patients should be monitored for diarrhea, sweating, bradycardia, fatigue, etc., as early symptoms of a cholinergic crisis.

Distigmine bromide is commonly used to temporarily treat early dysuria in other countries, but in Japan it is often used to treat patients as many as several years after surgery, or to treat diabetic neurogenic bladder. We evaluated the usefulness of distigmine bromide for the treatment of voiding dysfunction due to underactive detrusor and optimal method of administration of it.

Study design, materials and methods

The study was a prospective study approved by the institutional ethics committee in which 11 women with detrusor underactivity and without bladder outlet obstruction diagnosed on the basis of a urodynamic study were divided into two groups by the envelope method, a group that took distigmine bromide (Ubretid[®] 5 mg) orally 30 min before the morning meal (preprandial administration group; n=6) and a group that took Ubretid[®] 5 mg orally 30 min after the morning meal (postprandial administration group; n=5), and we measured the plasma distigmine concentration, serum AChE level, and serum ChE level before and 4 weeks after the start of administration.

In addition, before and after the 4-week period of administration we administered quality of life (QOL) questionnaires (King's Health Questionnaire [KHQ], Urogenital Distress Inventory [UDI-6], International Prostate Symptom Score [IPSS]) regarding lower urinary tract symptoms (LUTS) and an adverse effect questionnaire, and we performed uroflowmetry and measured post void residual (PVR).

Results

The plasma distigmine bromide concentration was 2.4 times higher in the preprandial administration group than in the postprandial administration group (Fig. 1.).

After 4 weeks of administration the serum AChE level in the preprandial administration group had decreased to 41.3% of the level before the start of administration, whereas in the postprandial administration group it had decreased to only 58.8%, and the serum ChE level had decreased to approximately 61.8% and 78.5%, respectively (Fig. 2.). There were positive correlations between both the serum Ach reduction rates and serum ChE reduction rates and the plasma distigmine bromide concentrations. And the serum Ach reduction rates were strongly correlated with the rates serum ChE reduction rates, with a numerical coefficient of determination in which $r^2 = 0.96$ (Fig. 3.).

Uroflowmetry showed a tendency for Q_{max}, Q_{ave}, and the rate of PVR to improve in both the preprandial group and the postprandial group, but there were no significant differences in values between before and 4 weeks after the start of administration. In the IPSS significant improvements in total score and QOL were seen between before and after the 4-week period of Ubretid[®] administration, but there were no significant differences according to whether administration was preprandial or postprandial. When the IPSS was evaluated according to the individual questions, a significant improvement in dysuria was seen between before and after the 4-week period of administration. The results of the UDI-6 showed a significant improvement in difficulty of emptying bladder in the preprandial administration group. With the exception of the development of loose stools, no serious adverse effects that were clearly caused by Ubretid were seen, and it was unnecessary to discontinue administration in any of the cases because of adverse effects.

Interpretation of results

Distigmine bromide decreased the serum AChE level more when administered preprandially.

The tendencies of the serum AChE levels to change can be inferred from the serum ChE levels, which usually can be measured.

A significant improvement in dysuria of the IPSS was seen between before and after the 4-week period of administration, and in difficulty of emptying bladder of the UDI-6 showed a significant improvement in the preprandial administration group.

Concluding message

In conclusion, we demonstrated that plasma distigmine bromide concentrations are affected by meals, and that as a result meals also have an impact on its effects, which reduce the serum AChE level. The results of this study suggested that Ubretid[®] 5 mg/day is useful as a treatment for female voiding dysfunction due to underactive detrusor and that after careful attention to cholinergic symptoms administration 30 min before a meal may be more effective than the traditional administration after meals.

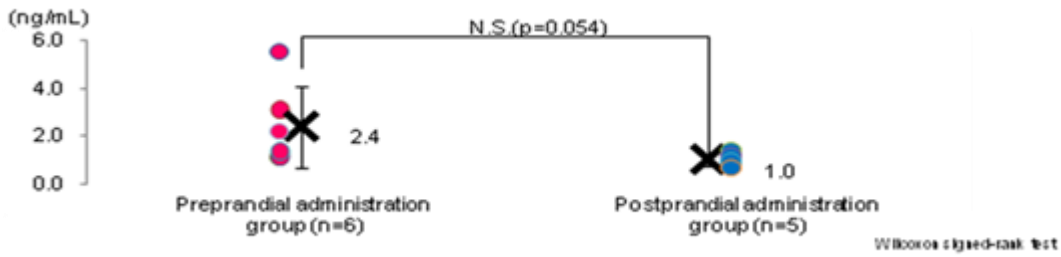


Fig. 1.: The plasma distigmine bromide concentration in the pre and postprandial administration group

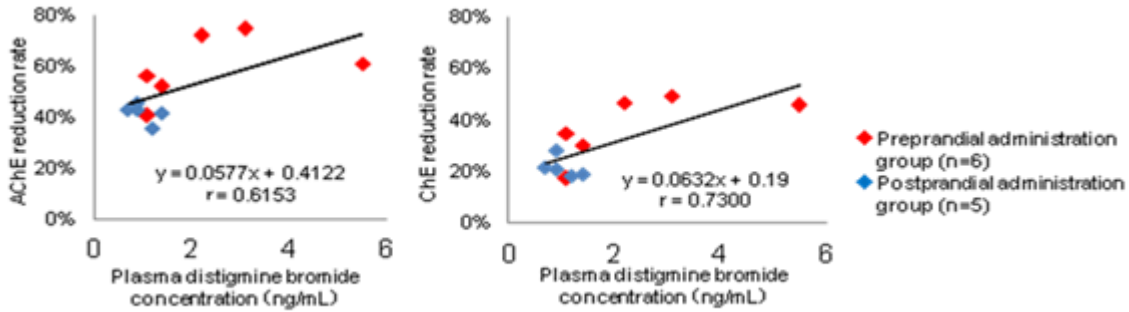


Fig. 2.: Correlation with the serum AChE or ChE level and the plasma distigmine concentration

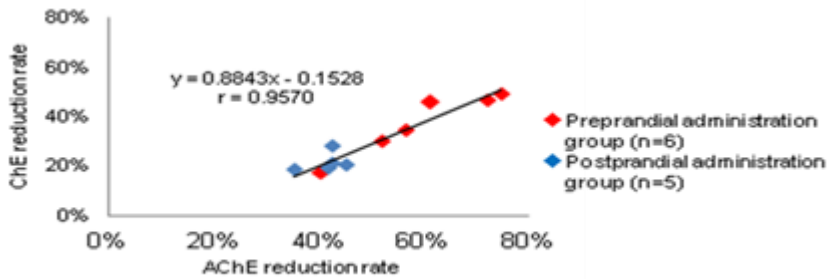


Fig. 3.; Correlation with the serum ChE reduction rate and the serum AChE reduction rate

Disclosures

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