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PHARMACOKINETIC AND PHARMACODYNAMIC ANALYSIS OF DISTIGMINE BROMIDE FOR THE TREATMENT OF UNDERACTIVE BLADDER

Hypothesis / aims of study

Impaired bladder emptying can be caused by chronic conditions such as bladder outlet obstruction in men with benign prostatic hyperplasia and impaired detrusor contractility in patients of either sex [1]. Pharmacotherapy using cholinomimetic drugs, such as muscarinic agonists and acetylcholinesterase (AChE) inhibitors, has been used as effective way for impaired bladder emptying [2] since the drugs may improve detrusor contractility by activating the parasympathetic cholinergic system. However, despite *in vitro* experimental evidences indicating that AChE inhibitors increase detrusor contractility, the mechanism underlying pharmacological effects of these agents under *in vivo* conditions remains to be still clarified. Distigmine bromide (distigmine), a reversible and long-acting carbamate cholinesterase inhibitor, is commonly used for the treatment of voiding dysfunction with impaired detrusor contractility [3]. However, its use is often limited by the serious side effects such as cholinergic crisis. In order to overcome these problems, it is important to clarify the relationship between pharmacokinetics and pharmacodynamics of distigmine. Thus, we analyzed simultaneously the plasma concentration and blood AChE inhibition of distigmine in rats after the oral administration.

Study design, materials and methods

Distigmine (0.3, 1.0, 3.0 mg/kg) was orally administered to male SD rats, and blood samples were collected at 0, 3, 10, 30 min and 1, 1.5, 2.5, 4, 6, 12 h after the administration. The plasma concentrations of distigmine were determined by liquid chromatography/tandem mass spectrometry. The blood AChE activity was measured by dithiobisnitrobenzoic acid (DTNB) method. A semiparametric approach was used in the pharmacokinetic and pharmacodynamic analysis.

Results

The plasma concentration of distigmine in rats peaked 0.5 h after oral administration at doses of 0.3, 1.0 and 3.0 mg/kg and decreased gradually. On the other hand, the maximum inhibition of blood AChE activity was observed 3 h after the distigmine administration and lasted until 12 h. The plasma concentration and AChE inhibition by these doses of distigmine were dose-related. A profound counter-clockwise hysteresis loop was observed for the relationship between the plasma concentration and blood AChE inhibition of distigmine at each oral dose. Such delay between the plasma concentration and pharmacological effect of this drug was significantly minimized by the pharmacokinetic and pharmacodynamic analysis by using “effect compartment” modelling. As shown in Fig. 1, there was a good agreement between observed and predicted AChE activity in rats after oral administration of distigmine.

Interpretation of results

It has been shown that the concentration-effect relationship of distigmine could be described satisfactorily by the “effect compartment” approach linked to the plasma concentration by a first-order process. Accordingly, the proposed “effect compartment” approach may be useful as a guide for predicting clinical effects of distigmine on the basis of its dose and thereby effective therapy with less side effect.

Concluding message

The plasma concentration-effect relationship of distigmine for the treatment of underactive bladder could be described satisfactorily by the pharmacokinetic and pharmacodynamic analysis of “effect compartment” approach.

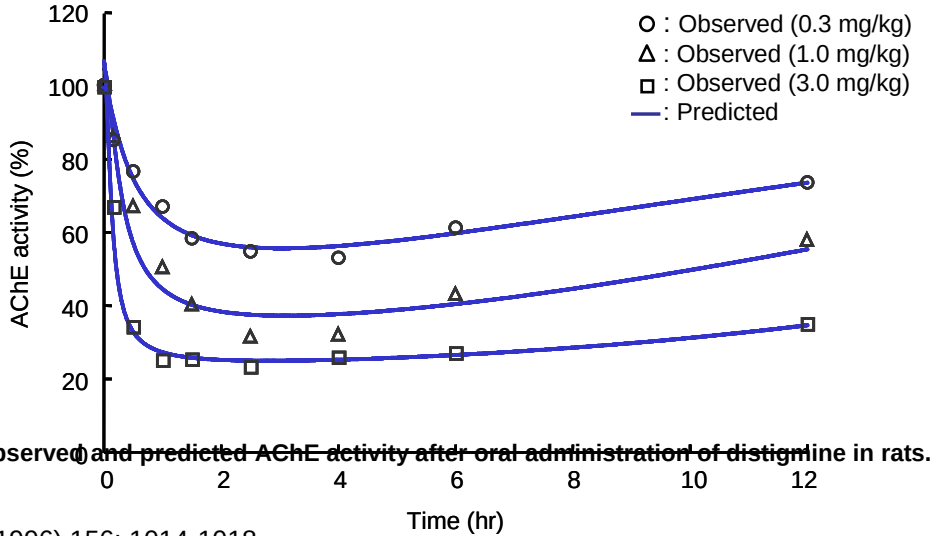

Fig. 1 **The observed and predicted AChE activity after oral administration of distigmine in rats.**

References

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3. Urol (1977) 10; 83-89

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Is this a clinical trial?	**No**
What were the subjects in the study?	**ANIMAL**
Were guidelines for care and use of laboratory animals followed or ethical committee approval obtained?	**Yes**
Name of ethics committee	**This study was done in accordance with recommendations of the US National Institutes of Health and also the guidelines of Central Research Laboratory, and the Experimental Animal Ethical Committe of the University of Shizuoka.**