29D10-4

THE ACTIVE METABOLITE (DPr-P-4(N→O)) MAY CONTRIBUTE TO THE BLADDER SELECTIVITY OF PROPIVERINE HYDROCHLORIDE USED TO TREAT PATIENTS WITH OVERACTIVE BLADDER

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Propiverine (Prop) is commonly used for the therapy of overactive bladder. Orally administered Prop is metabolized in the gut and liver, forming an active metabolite, 1-methyl-4-piperidyl benzilate N-oxide (DPr-P-4(N→O)). DPr-P-4(N→O) is assumed to contribute to the muscarinic receptor blockade of the parent compound, but the pharmacological relevance of this metabolite is not fully understood. To clarify this issue, we characterized muscarinic receptor binding in the bladder and submaxillary gland of rats treated orally with Prop, and the tissue concentrations of Prop and DPr-P-4(N→O) of these rats were simultaneously measured. Oral administration of Prop displayed relatively longer-lasting muscarinic receptor binding in the bladder than in the submaxillary gland of rats. Interestingly, the measurement of tissue concentration revealed markedly higher concentration of DPr-P-4(N→O) in the bladder than in the submaxillary gland of rats received oral Prop, while there was similar concentration of Prop in these tissues. These data suggest that DPr-P-4(N→O) formed in the blood of rats after oral administration of Prop distributes at higher concentration in the bladder than in the salivary gland and binds continuously to muscarinic receptors in the bladder. The present study has provided the first pharmacological evidence to support the idea that DPr-P-4(N→O) may contribute largely to the bladder selectivity in overactive bladder patients treated with Prop.

29D10-5

INTERACTION OF PRAZOSIN AND METOPROLOL IN SPONTANEOUSLY HYPERTENSIVE RATS - PK-PD ASSESSMENT BASED ON BLOOD PRESSURE REGULATORY SYSTEM -

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Blood pressure is regulated by coordinated factors such as norepinephrine (NE). We previously reported that coadministration of prazosin (PRZ; α1-blocker) and metoprolol (MET; β1-blocker) have an advanced hypotensive effect compared with the treatment without MET in normal rats. A pharmacokinetic-pharmacodynamic approach based on the blood pressure regulatory system, revealed that the advanced drug action results in both a suppressed NE response and a delayed pharmacokinetics of PRZ by MET. This study was to explain the interaction in hypertensive rats, quantitatively. Drugs were infused through the jugular vein for 30 min in spontaneously hypertensive rats (SHRs). Blood pressure was measured via a transducer connected with the femoral artery catheter. Plasma concentrations of drugs are determined by the HPLC methods. Pharmacokinetics of PRZ and MET were described by 2-compartment models. PRZ treatment showed a significant decrease in blood pressure and an increase in plasma NE. MET showed a continuous hypotensive effect, although did not change in plasma NE. After concomitant infusion of PRZ and MET, an enhanced and prolonged hypotensive effect was observed compared with the PRZ treatment alone. After concomitant use, elimination of plasma PRZ was delayed, however there is not a significant change in the pharmacokinetics of MET. Coadministered MET suppressed PRZ-induced response in plasma NE. These results indicate that the interaction can be related to the depression of blood pressure regulatory activity induced by MET in SHRs as well as normal rats.