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# NONINVASIVE EVALUATION OF BRAIN MUSCARINIC RECEPTOR OCCUPANCY OF IMIDAFENACIN, DARIFENACIN AND OXYBUTYNIN IN RATS BY POSITRON EMISSION TOMOGRAPHY

Hypothesis / aims of study

While antimuscarinic agents have proven effective in patients with overactive bladder, they are also associated with anticholinergic side effects. Notably, agents that can cross the blood brain barrier (BBB) and bind to muscarinic receptors in the brain presented a risk of causing central nervous system (CNS) dysfunction including cognitive impairment. Such side effects are of great concern in elderly patients due to the increase in the BBB permeability with age. Imidafenacin, a recently developed antimuscarinic agent, has been shown to act in the bladder without influencing the CNS [1-3]. The current study was conducted to evaluate the binding of antimuscarinic agents (imidafenacin, darifenacin, oxybutynin) used to treat overactive bladder to muscarinic receptors in rat brain, by the noninvasive positron emission tomography (PET).

Study design, materials and methods

Muscarinic receptor occupancy in the rat brain after the intravenous injection of imidafenacin, darifenacin and oxybutynin was evaluated by using a small animal PET system, and compared with the results by *in vivo* autoradiographic and *ex vivo* radioligand binding experiments. As selective radioligands to label muscarinic receptors, we used (+)*N*-[$^{11}$C]methyl-3-piperidyl benzilate ([$^{11}$C](+)3-MPB) for PET and autoradiographic study, and [N-methyl-$^{3}$H]scopolamine methyl chloride ([$^{3}$H]NMS) for *ex vivo* radioligand binding study.

Results

In PET study, the intravenous injection of oxybutynin but not imidafenacin or darifenacin at pharmacological doses decreased significantly binding potential (BP) of (+)*N*-[$^{11}$C]methyl-3-piperidyl benzilate ([$^{11}$C](+)3-MPB) in the rat cerebral cortex and corpus striatum in a dose-dependent manner (Fig. 1). Similarly, in the *in vivo* autoradiographic experiment, oxybutynin dose-dependently reduced binding of [$^{11}$C](+)3-MPB in the brain, whereas darifenacin and imidafenacin did not. Following the intravenous injection of imidafenacin, darifenacin and oxybutynin, there was a similar degree of binding to muscarinic receptors in the bladder as demonstrated by a significant increase in apparent dissociation constant ($K_d$) values for specific [N-methyl-$^{3}$H]scopolamine methyl chloride ([$^{3}$H]NMS) binding. Significant binding of muscarinic receptors in the brain was observed after the injection of oxybutynin but not darifenacin or imidafenacin.

Interpretation of results

Oxybutynin but not imidafenacin or darifenacin has potential side effects on the central nervous system (CNS) in patients with overactive bladder. The results reveal the noninvasive characterization of brain receptor occupancy by PET to be a powerful tool for precise evaluation of adverse CNS effects of antimuscarinic agents in pre-clinical and clinical evaluations.

Concluding message

Imidafenacin and darifenacin compared with oxybutynin are relatively safe in the elderly population in terms of less CNS side effects.

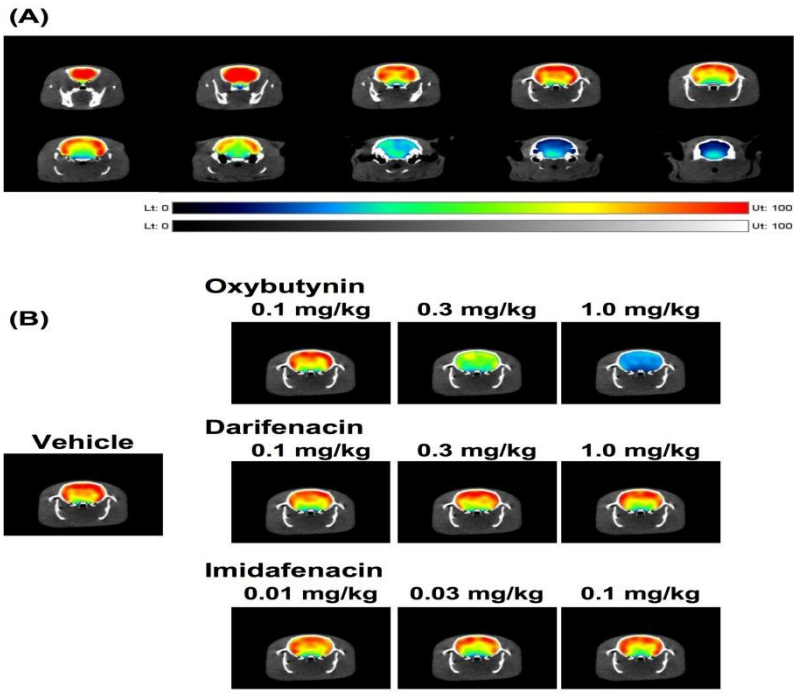


Fig. 1. (A) Typical PET images fused with CT images in the brain of rats injected i.v. with [$^{11}$C](+)3-MPB. The images were generated by summing the data 40-60 min after the [$^{11}$C](+)3-MPB injection. Each coronal section was different at 2.1 mm intervals. Upper left section: frontal lobe region, lower right section: cerebellum region. Third section in the upper panel was Bregma. (B) Effects of different doses of oxybutynin (0.1-1.0 mg/kg), darifenacin (0.1-1.0 mg/kg) and imidafenacin (0.01-0.1 mg/kg) on PET images of [$^{11}$C](+)3-MPB in the rat brain. Rats received an i.v. injection of each agent 10 min prior to the [$^{11}$C](+)3-MPB injection. Each section represents the typical one for Bregma - 2.1 mm region (fourth section in the upper panel (A)).

References

1. Arzneimittel-Forschung, 57: 147-154 (2007)
2. Int J Urol, 16: 499-506 (2009)
3. J Pharmacol Exp Ther, 336: 365-371 (2011)

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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*** | **Helsinki** |