

# A NMR Study of TRifluoperazine Crossing Blood-Brain-Barrier Due to P-Glycoprotein Modulation

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## INTRODUCTION

Elderly patients and patients with cancer are often treated with a combination of therapies for secondary illnesses such as depression, and cardiopulmonary diseases in addition to their primary illnesses. The potential for drug-drug interaction under these conditions is high. Such interactions may cause changes in the pharmacokinetics, especially for drugs with narrow therapeutic indices (1, 2). These changes can alter efficacy and toxicity of the administered drugs. Drug-drug interactions may occur due to interaction of common metabolic pathways, but can also be caused by interference at the P-glycoprotein (Pgp) level. Pgp, which is a nonspecific transport protein, is expressed constitutively at the blood-brain-barrier (BBB), intestine, kidney, and liver (3). Interaction at the blood-brain barrier may occur if Pgp is blocked by a drug, allowing a concomitantly administered second drug, which would not penetrate brain if administered singly, to be able to penetrate the brain freely (4,5). The potential for drug-drug interactions is not routinely studied at the Pgp level during drug development. Its presence is assumed only after unexpected clinical symptoms arise. In this study, we used a dynamic NMR method based on detection of a fluorinated drug, trifluoperazine (TFP), in combination with an immune suppressor, cyclosporin A (CsA), to monitor the drug penetration through the blood-brain-barrier due to Pgp modulation (6).

## METHODS

Sprague-Dawley rats, weight 100-400 g, were used. The rats were first anesthetized by i.p. injection of sodium pentobarbital (40 mg/kg). A catheter (0.26 mm i.d.) was then inserted into the tail vein for later drug infusions. A Pgp modulator, cyclosporin A (15 mg/kg) was administered 15 min before trifluoperazine (25 mg/kg) was injected. <sup>19</sup>F NMR using a Varian 4.7 T machine was utilized to detect trifluoperazine in the brain. A 22 x 17 mm RF coil was positioned immediately adjacent to the rat skull. A small bulb containing trifluoroacetic acid was used as an extern reference. After shimming and tuning, a series of 10 minutes spectra were obtained. The repetition time was one second. The same animal was used as control without cyclosporin A. The test results of five different rats were averaged for each data point.

## RESULTS

Figure 1 shows TFP crossing BBB as function of TFP dosages ranging from 5 to 35 mg/kg. This demonstrates that <sup>19</sup>F signal can be used as a reliable probe to monitor TFP accumulation in the brain. In Figure 2, the spectrum A shows a control, in which only TFP was administered. The spectrum B shows a 22% increase of TFP crossing BBB in a 200 gm rat after co-administering a Pgp modulator, cyclosporin A. Figure 3 shows the increased amount of TFP crossing BBB as function of age (or body weight). Younger rats weighing below 100 gm showed no increase of TFP penetration. However, for older adult rats weighing more than 200 gm, a 20-25% increase of TFP crossing BBB was evident.

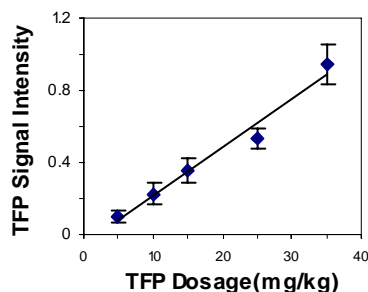


Figure 1

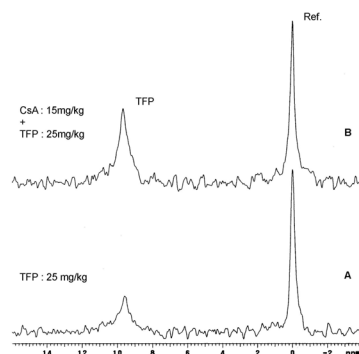


Figure 2

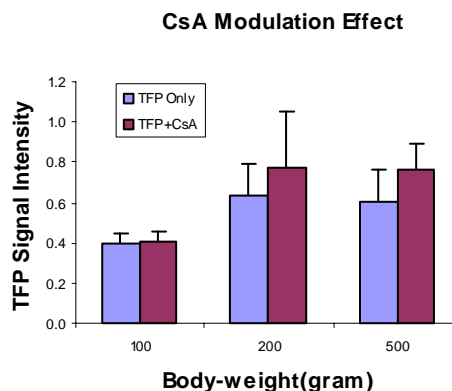


Figure 3

## DISCUSSION

This experiment has demonstrated that a concomitantly administered Pgp modulator enhanced the amount of TFP, an antipsychotic drug, to cross blood-brain-barrier in vivo. The pharmacology of this noninvasive model for increasing the crossing of drugs over the BBB due to drug-drug interactions was based on previously attained knowledge about how to modulate Pgp, and also because the drug was able to be detected by in vivo <sup>19</sup>F NMR spectroscopy. It also demonstrated that Pgp modulation is more problematic for older rats. In the case of polypharmacy, particularly for elderly or cancer patients, drug-drug interaction is not always understood. The noninvasive dynamic NMR technique can be a very useful tool to study multidrug interactions in drug development.

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