^{19}F NMR Study Of Trifluoperazine Crossing Blood-Brain-Barrier Due To P-glycoprotein Modulation

P. Wang[1], A. Aszalos[2], and J. A. Vick[2]
1 Department of Radiology, Howard University, Washington, DC
2 Center for Drug Evaluation and Research, FDA, Laurel, MD

Introduction

Cancer chemotherapy often fails due to efflux of anti-cancer drugs from resistant cancer cells by plasma membrane bound pumps, such as P-glycoprotein (Pgp) (1) and the multidrug resistance associated protein (MRP) (2). To enhance the effectiveness of cancer chemotherapy, blockers which stop the function of these pumps are being developed and tested in the clinic. However, early clinical experiences indicate that the use of most blockers is associated with toxicity at the concentrations necessary to block pump action (3). To reduce this toxicity, multiple blockers at suboptimal concentrations could be administered concomitantly to synergistically block Pgp function (4).

Some of the anti-psychotic drugs have also been shown to block the function of P-glycoprotein at the blood-brain-barrier (5). It is not uncommon that anti-psychotic drugs be used in cancer patients undergoing chemotherapy. Concomitant administration of anti-psychotic drugs with anti-cancer drugs may alter the pharmacokinetics of both drugs. Pharmacological studies monitoring Pgp modulation mostly use radioactive molecules, tissue extraction, positron emission tomography or neurotoxicity assessments methods. In this study, *in vivo* ^{19}F NMR spectroscopy technique is used to detect the anti-psychotic drug trifluoperazine crossing the blood-brain-barrier when co-administered with a clinically useful Pgp blocker PSC833.

Method

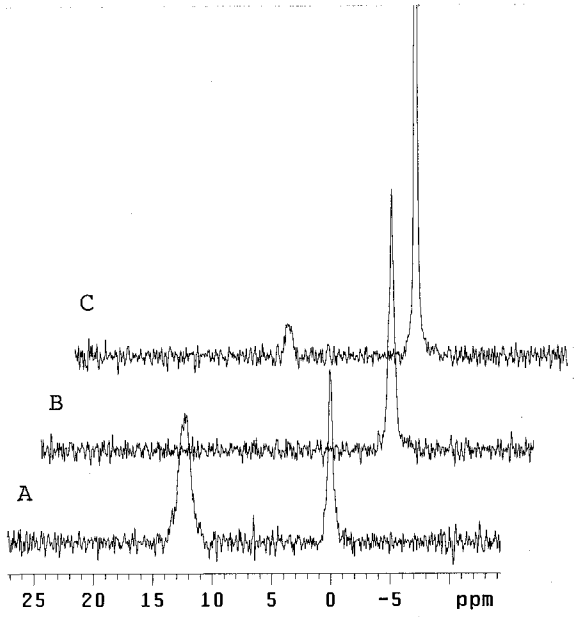
A 4.7 T, 33 cm horizontal bore Varian NMR machine was used. The RF coil was a curved rectangular-shaped copper coil, 22 mm x 17 mm. The RF coil was positioned immediately adjacent to the rat skull. A small bulb containing trifluoroacetic acid placed against the skull at the center of the RF coil served as a reference marker. Another volume coil was used for detection of fluorine signal from the abdomen to confirm the success of administration of trifluoperazine in the animal.

Sprague-Dawley rats, weight 300-350 g, were used. The rats were anesthetized by sodium pentobarbital (40 mg/kg, i.p.). After anesthesia, a clinically useful Pgp blocker, PSC833 (1.2 mg/kg) was administered through the tail vein. PSC833 was dissolved in 0.3 ml DMSO. The target anti-psychotic drug, trifluoperazine was administered intravenously (30 mg/kg) 15 minutes after PSC833 injection. Trifluoperazine was in phosphate buffered saline (PBS). In the control study, no PSC833 was administered, only trifluoperazine was injected.

Fifteen minutes after injection of trifluoperazine, a series of either 10 minutes or 20 minutes ^{19}F spectra were obtained. A simple one pulse sequence was used. The RF pulse was a 7 msec sech 90° pulse centered at the fluorine resonance frequency of trifluoperazine. The repetition time was one second.

Results

Spectra A and B were from the control study, in which only trifluoperazine was administered. Spectrum A was from the abdominal region. A single peak was found at 12.3 ppm relative to an external reference trifluoroacetic acid. The spectrum was an accumulation of 3600 scans and baseline corrected. This confirmed the success of the trifluoperazine injection. Spectrum B was also a control from the rat brain. There was no detectable fluorine signal over two hours. However, if a Pgp modulator PSC833 was concomitantly administered with trifluoperazine, a clear fluorine signal was detected in spectrum C. This demonstrated that by modulating P-glycoprotein the trifluoperazine was able to cross the blood-brain-barrier.



Conclusion

Fluorine signal from the anti-psychotic drug trifluoperazine can only be detected in the brain after administration of P-glycoprotein modulator PSC833 but not without it. In both cases, fluorine signals can be detected from the liver. These results suggest that pharmacokinetic interactions of drugs that modulate P-glycoprotein must be carefully studied prior to concomitant clinical use. Concomitantly administering Pgp modulators may increase influx of anti-cancer or anti-psychotic drugs into the brain.

References

1. Pastan, I., Gottesman, M.M., Ueda, K., Lovelace, E., Rutherford, A.V., Willingham, M.C., *Proc.Nat.Acad.Sci.*, 85, 4486, 1988.
2. Cole, S.P.C., Bhardwaj, G., Gerlach, J.H., Mackie, J.H., Grant, C.E., Almquist, K.C., Stewart, A.J., Kurtz, E.U., Duncan, A.M., Deeley, R.G., *Science*, 258, 1650, 1992.
3. Salmon, S.A., Dalton, W.S., Grogan, T.M., Pleiza, P., Lehnert, M., Toe, D.J., Miller, T.P., *Blood*, 78, 44, 1991.
4. Hwang, M., Ahn, C.H., Pine, P.S., Yin, J.J., Hrycyna, C.A., Licht, T., Aszalos, A., *Int.J.Cancer*, 65, 389, 1996.
5. Szabo, D., Szabo Jr., G, Ocsovski, I., Aszalos, A., Molnar, J., *Cancer Lett.*, 139, 115, 1999.