Quantifying endothelial function using dose equivalence theory

Neil S. Lamarre[1] and Ronald J. Tallarida[1]

***Abstract* — The endothelium is a single cell layer lining the lumen of every blood and lymph vessel in the body. It has a powerful influence on the regulation of vessel diameter, which is a primary determinant of blood flow. The endothelium often works to offset vasoconstriction, and loss of this endothelium-dependent vasodilatory contribution can result in exaggerated vasoconstriction to a given dose. Here we will present a novel use of dose equivalence methodology to quantitate endothelial function in a model of vascular contractility.**

***Keywords* — dose equivalence, endothelial function.**

I. Purpose

The endothelium is a single cell layer lining the lumen of blood vessels throughout the body. It has a powerful influence on the regulation of vessel diameter, which is a primary determinant of blood flow. The endothelium often works to offset vasoconstriction, by releasing vasodilatory substances such as nitric oxide [1]. Loss of this endothelium-dependent vasodilatory contribution can result in exaggerated vasoconstriction to normal plasma levels of catecholamines and vasoactive peptides (i.e., angiotensin II). This is one consequence of endothelial dysfunction that is may contribute to the high incidence of idiopathic hypertension [2].

Dose equivalence theory is a methodology that was originally developed to evaluate combinations of two drugs working together towards the same effect [3]. The predicted additive effect is a function of the individual dose response curves of the two constituent drugs. Departures from the predicted additive response include a greater effect than expected (i.e., synergistic effect) or less than expected (sub-additive). Dose equivalence theory predicts the additive effect of a combination of two drugs, thereby allowing us to make statistical comparisons to observed (experimental) results. Our lab has recently expended the application of this theory to quantify the endothelium-dependent component of action of overt vasoconstrictors [4].

Experimental Paradigm

Vascular contractility (isometric tension) of isolated rat aortic rings was recorded, and allowed us to generate dose response curves to agonists of interest. Physical removal of the endothelium (denuding) was accomplished by gently rubbing the lumen with a wooden dowel. An intact endothelium resulted in a dose response curve that was shifted to the right, sometimes with a reduction of the maximum effect.

Using these two (endothelium denuded and intact) dose response curves as bounding parameters, we can use nonlinear regression to provide a coefficient of endothelial function ranging between 0 and 1 for an experimentally derived dose response curve that lies between these two curves. (As would be expected after some treatment that resulted in endothelial dysfunction). Therefore, we can use this technique to quantitate the degree to which this endothelium-dependent component of action (of overt vasoconstrictors) is disrupted.

II. Conclusion

Endothelial dysfunction results in a loss of endothelium-dependent vasodilation (to agonists like acetylcholine and bradykinin) and a dramatic potentiation of vasoconstriction (to norepinephrine, endothelin-1, etc). Here we present a technique (based on dose equivalence theory) for quantifying the endothelial-dependent component of action of overt vasoconstrictors, resulting in a coefficient of endothelial function that can be used to measure endothelial dysfunction in animal models. In modeling applications, this single variable could be used to modify the dose response relationships to a number of agonists at once, reflecting the effects of endothelial dysfunction on contractility across the entire dose range.

References

[1] Feletou M (2011) *The Endothelium: Part 1: Multiple Functions of the Endothelial Cells-Focus on Endothelium-Derived Vasoactive Mediators*. Morgan & Claypool Life Sciences, San Rafael CA.

[2] Puddu P, Puddu GM, Zaca F and Muscari A (2000) Endothelial dysfunction in hypertension. *Acta cardiologica* 55:221-232.

[3] Tallarida RJ (2000) *Drug Synergism and Dose-Effect Data Analysis*. Chapman & Hall/CRC, Boca Raton FL.

[4] Lamarre NS, Parry T and Tallarida RJ (2011) On the quantitation of an agonist with dual but opposing components of action: application to vascular endothelial relaxation. *Eur J Pharmacol* 670:204-207

[1]Center for Substance Abuse Research and Department of Pharmacology, Temple University School of Medicine, Philadelphia, PA.
E-mail: neil.lamarre@temple.edu