PHARMACEUTICALS, BINDING SITES, AND PHARMACOLOGICAL EFFECT

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ABSTRACT

Cardiovascular pharmaceuticals have been classified in many different ways. Each class has specific desired pharmacological actions and pharmaceuticals within each class may have similar structures. In addition, pharmaceuticals with similar structures might have different pharmacological actions. Algorithms, such as those developed by the American Heart Association (AHA) for its Advanced Cardiac Life Support (ACLS) courses, recommend certain pharmaceuticals and certain classes of pharmaceuticals as primary selections. In the AHA’s 2000 revision of its ACLS Algorithms, amiodarone was added as a pharmaceutical of choice for treatment of Ventricular Fibrillation/Pulseless Ventricular Tachycardia. (ACLS.net 2002) This pharmaceutical replaced lidocaine as the first choice pharmaceutical following epinephrine. (Bledsoe 1997) Through molecular modeling, an attempt was made to understand how amiodarone acts as a stronger pharmaceutical in treatment of Ventricular Fibrillation/Pulseless Ventricular Tachycardia than lidocaine does. Amiodarone has become known for its competitive inhibition of thyroid hormone to the thyroid hormone receptor subtype beta 1. (Drvota 1995) Protein Databases were searched for the structure of thyroid hormone receptors containing a binding site for amiodarone or the thyroid hormones that it inhibits. The Protein Data Bank (Protein Data Bank 2002) yielded two proteins that might provide a binding site; however, it was not clear whether either of these proteins were the ones mentioned by Drvota as being the most prevalent in the human heart which might yield cardiovascular results. (Rastinejad 1995) The first avenue, therefore, was to examine the suggestion that amiodarone’s antiarrhythmic properties are due to its interaction with the thyroid hormone. (Drvota 1995) Two thyroid hormones, Levothyroxine Sodium and Liothyronine Sodium, were chosen for structural comparison with amiodarone and lidocaine. After examining the chemical structure of the four pharmaceuticals, molecular calculations were conducted through the use of HyperChem. From these calculations, a graphic representation of the HOMO and LUMO states of the pharmaceuticals was obtained. The comparison of chemical structure and HOMO and LUMO states indicated that amiodarone is similar to the thyroid hormones, while lidocaine differs significantly from the other three pharmaceuticals. Based upon these findings, it was concluded that the chemical structure and HOMO and LUMO states of pharmaceuticals is not enough to determine the effects that binding would have on pharmacological effect. However, if cardio-
vascular function is enhanced by interaction with thyroid hormones (Drvota 1995), these calculations indicate a possible way in which amiodarone is more likely to interact with these hormones than lidocaine is.

LITERATURE CITED


Drvota, V., B. Carlsson, J.Hagglad, and C. Sylven. 1995. Amiodarone is a dose-dependent noncompetitive and competitive inhibitor of T3 binding to thyroid hormone receptor subtype beta 1, whereas disopyramide, lignocaine, propafenone, metoprolol, dl-sotalol and verapamil have no inhibitory effect. Journal of Cardiovascular Pharmacology. 26: 222-226.
