The Brain and Propranolol Pharmacokinetics in the Elderly

Andy R. Eugene
Division of Clinical Pharmacology, Department of Molecular Pharmacology and Experimental Therapeutics, Gonda 19, Mayo Clinic, 200 First Street SW, Rochester, Minnesota 55905, USA
Tel.: +1-507-284-2790; Fax: +1-507-284-4455
E-mail: eugene.andy@mayo.edu

Wayne T. Nicholson
Department of Anesthesiology, Mayo Clinic, 200 First St SW, Rochester, MN 55905.
E-mail nicholson.wayne@mayo.edu

Abstract

Propranolol, a non-selective β-blocker, has been found to have a tremendous array of indications. Recent evidence has suggested that propranolol may be effective in patients suffering from post-traumatic stress disorder by suppressing activity in the amygdala and thereby inhibiting emotional memory formation. Dosage requirements have been well established in the pediatric and adult population, however, there has been no definitive geriatric dose recommended in the package inserts made available to the public. The aim of this paper is to use pharmacokinetic simulations in order to establish a pharmacokinetic profile dosage equivalent for the elderly as has been found in young patients. After completing the Monte-Carlo simulations for the elderly and young patients, a single 10mg dose in the elderly has shown comparable pharmacokinetic profiles as found in young patients administered a 40mg single dose.

Keywords: propranolol; elderly; pharmacokinetics; brain

1. Introduction

Propranolol, a sympatholytic nonselective beta blocker, β1 and β2 receptors,has been successfully used in patients with a variety of clinical indications ranging from pediatrics cases of hemangioma, to thyrotoxicosis, and familial tremor (essential tremor), angina, and in patients who suffered from a previous myocardial infarction(Lawley *et al.*, 2009; Olakowska and Olakowski, 2006). Neurological actions of propranolol, due to its lipophilic properties have been effective in treating patients with social anxiety(Tyrer and Lader, 1974; Wohleb *et al.*, 2011).In a study with fifty-two healthy right-handed participants (18 to 30 years old; 26 men, 26 women), propranolol was found to inhibit memory consolidation in the amygdala and the hippocampus(Schwabe *et al.*, 2012). The mechanism for propranolol's influence on enhancing emotional memories is due to noradrenenaline and the drug's effect on blocking noradrenergic receptors(Cahill *et al.*, 1994; Strange and Dolan, 2004).

When considering the neurological effects of propranolol in the elderly, tremendous caution is warranted due to the wide array of physiological changes that occur in aging (Lichtman, 2007; Zoller, 1987). Elderly dosage requirements play a critical role in minimizing both adverse drug reactions and drug-to-drug interactions. Thus, in an attempt to provide insight into the differences of plasma drug levels between young versus elderly patients, this paper attempts to provide insight for selecting an appropriate dose for Propranolol.This is will accomplished using Monte-Carlo-based pharmacokinetic simulations of Propranolol in young populations and elderly populations. Remembering that, Propranolol was the pioneer beta-blocker whose discovery led the winning of the Nobel Prize, in 1988, by Dr. James Black, a Pharmacologist, from Lanarkshire, Britain(Black, 1989; Black *et al.*, 1997; Nobelprize.org, 1989).

In this simulation-based investigation, one may hypothesize that due to the physiological changes relative to aging, elderly patients will have higher plasma levels of propranolol as compared to young patients at the same dose and that β-receptor blockade. Moreover, plasma concentration will be achieved quicker in elderly patients as well as similar plasma concentration of

propranolol will be achieved in elderly patients at approximately half of the dose of younger patients.

2. Methods

2.1. Patient Data

The pharmacokinetic plasma levels for Propranolol have been primarily referenced from the Castleden et al article published in the *British Journal of Clinical Pharmacology* in 1975(Castleden *et al.*, 1975). Models parameters were derived for both the young and elderly simulations from the 1975 publications. The resultant simulations where later validated with a different dataset based from the digitized values from Castleden et al 1979 publication(Castleden and George, 1979), for the elderly patients, and the Taegtmeyeret al 2014(Taegtmeyer *et al.*, 2014) publication for the younger patients. The young patient, Castleden et al 1975, cohort included 9-participants (5-male and 4-females) with an average age of 27 ± 2; while, the elderly patient cohort included 9-participants (3-males and 6-females) with a mean age of 77 ± 2. Both groups were administered a single-oral dose of 40mg of Propranolol. A secondary reference for plasma Propranolol levels was from an article by Taegtmeyer et al in 2014, where five healthy participants with three males and two females had average age was 37 ± 17. The later publication would serve to further corroborate the calculated pharmacokinetic simulation drug levels.

2.2. Pharmacokinetic Analysis

Study samples were modeled using PKSolver, a Microsoft Excel add-in programmed in Microsoft's Visual Basic that computes pharmacokinetic and pharmacodynamic model parameters(Zhang *et al.*, 2010). The pharmacokinetic (PK) simulations were accomplished using a classical one-compartmental model with first order absorption and linear elimination using the Accelera for Sandwich Simulator, which was developed using MatLab version 6.5.1.199709, Release 13 (The MathWorks Inc., Natick, MA, USA)(Shampine and Reichelt, 1997; Shampine *et al.*, 1999). The PK/PD simulator, Accelera for Sandwich Simulator (A4S), was developed by Pfizer's Global Clinical Pharmacology in Sandwich, United Kingdom(Germani *et al.*, 2013). Similarly, the pharmacodynamic (PD) portion with the linked PK data was realized using the A4S simulator. Lastly, Microsoft Excel 2010 was used to visualize the results.

The Pfizer A4S Simulator has been cross-validated with the commercially available software WinNonlin (WNL), version 3.1 and is used by Pfizer's internal scientist for PKPD simulations(Germani *et al.*, 2013). Pharmacokinetic Models follow the same nomenclature and parameterization as the NONMEM software (Bauer, 2011) where used in A4S to simulate the results. Simulation parameters for Propranolol were based on the ADVAN2 and TRANS1 subroutines describing a one-compartment linear model with first-order absorption for the elderly patients and the ADVAN4 and TRANS1 subroutine, which describe a two-compartment linear model with first-order absorption, for the young patients.

3. Results

Based on the Castleden et al 1975 Propranolol plasma values in the young and elderly participants, PKSolver, provided the following modeling results outlined in Table1 and Table2. Based on these values, the simulation parameters were ready for the pharmacokinetic simulations using the Pfizer Accelera for Sandwich software package. To properly fit the experimental blood samples, coefficients of variations, covariates, of 20% for the volume in the central compartment (V_c) and 10% for the absorption rate constant (Ka) for both young and elderly patients.

Table 1.The ADVAN4 TRANS1 subroutine of a two-compartment linear model with first-order absorption to describe the propranolol kinetics in young patients.

Parameter	Estimate		CV %
V_c	0.667445	L	20
V2	8.60988	L	0
Ka	0.965986	1/hr	10
K10	1.40E-05	1/hr	0
K12	0.602943	1/hr	0
K21	0.046273	1/hr	0
CL/F	9.27E-06	L/hr	0
Q	0.398408	L/hr	0
alpha	1.00E-06	1/hr	0
beta	0.64923	1/hr	0

Table 2.The ADVAN2 TRANS1 subroutine of a one-compartment linear model with first-order absorption to describe propranolol kinetics in elderly patients.

Parameter	Estimate		CV %
V_c/F	0.1782	L	20
CL/F	0.0597	L/hr	0
K10	0.331667	1/hr	0
Ka	0.556	hr	10

Table 2.Calculated pharmacokinetic parameters in a single-dose of 40mg of propranolol in young versus elderly participants.

	Young	Elderly
AUC (mg/L*hr)	154.739	633.35
Cmax (mg/L)	27.8303	102.911
Tmax (hr)	1.36918	2.29915
$T_{1/2}$ (hr)	--	2.16535

Propranolol has been found to be therapeutically effective, to obtain a clinical response by beta-adrenoceptor blockade, at plasma levels of greater than 20 ng/mL(Coltart *et al.*, 1971; Frishman, 1988; Johnsson and Regàrdh, 1976). Thus, to display the data, we used highlighted plasma concentration where the pharmacokinetic curve falls below 20ng/mL threshold for therapeutic efficacy in the patient's plasma.

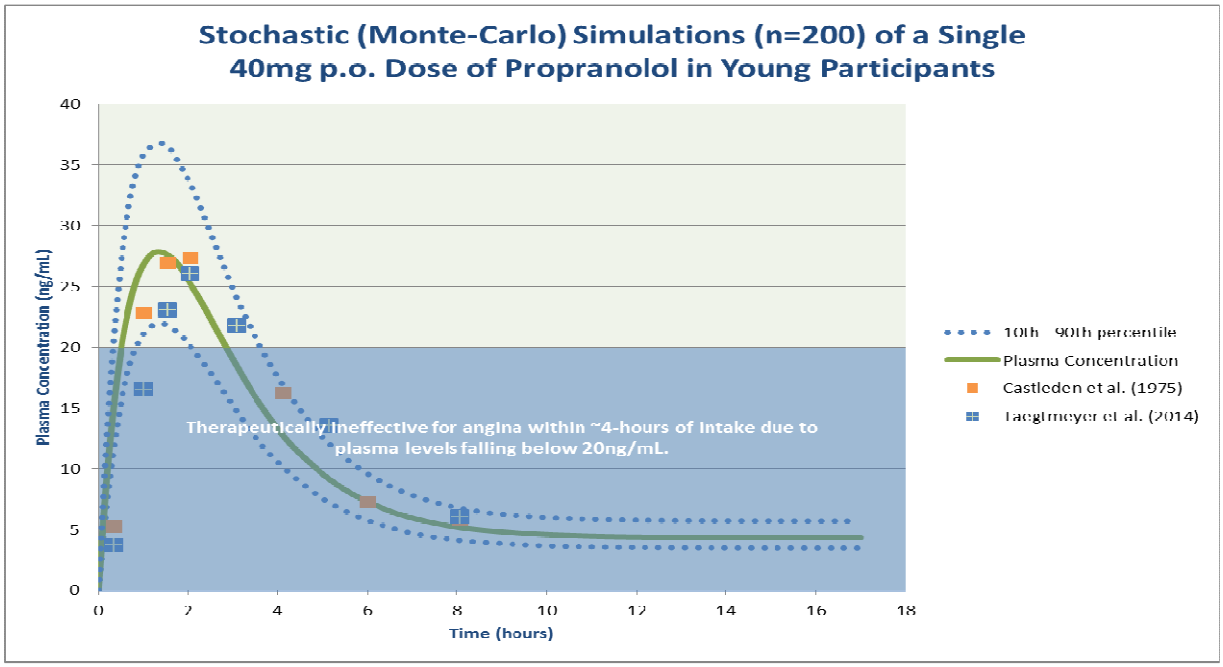

Figure 1.(a)Results of the Monte-Carlo simulations to describe pharmacokinetics of young patients with validation from the Taegtmeyer 2014 publication(Taegtmeyer et al., 2014). The dotted lines illustrate the 10th and 90th percentiles of plasma levels of the young population.

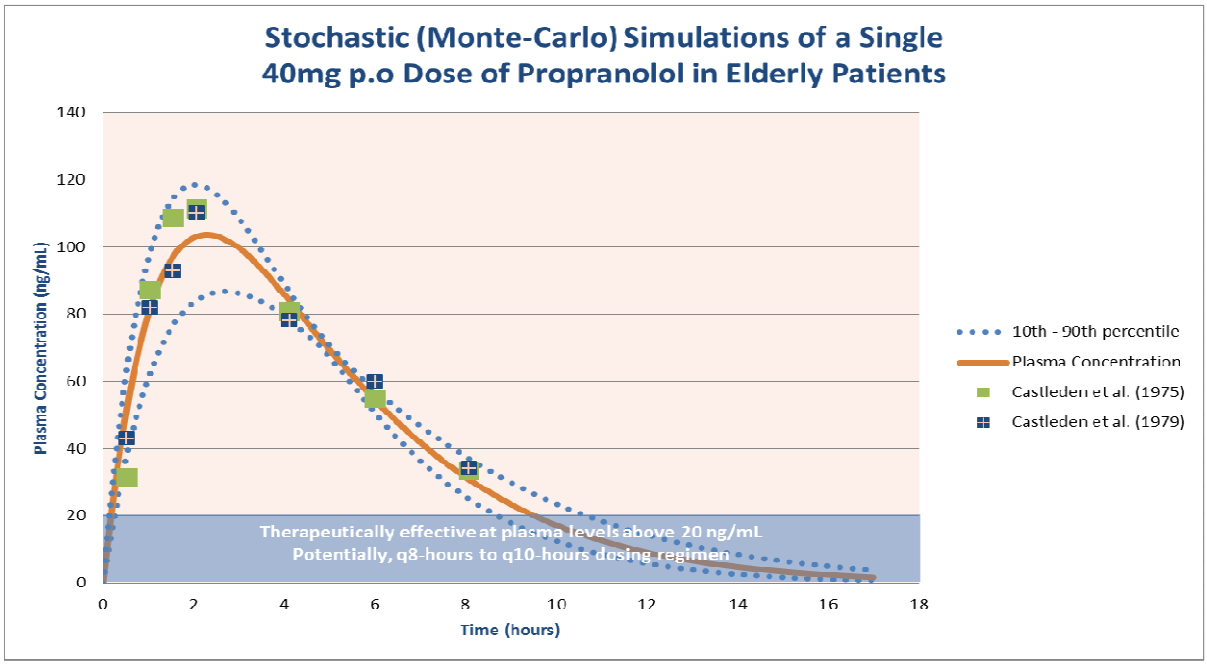

Figure 2.(a)Results of the Monte-Carlo simulations describing a population of elderly patients after a single oral dose of propranolol. The population has been validated with the Castleden et al 1979 publication(Castleden and George, 1979). The dotted lines illustrate the 10th and 90th percentiles of plasma levels of the elderly population.

Table 3. Propranolol single oral dose pharmacokinetics in young participants compared to elderly patients at 40mg.

	Young	Elderly
Dose	**40mg**	**40mg**
AUC (mg/L*hr)	154.739	633.35
Cmax (mg/L)	27.8303	102.911
Tmax (hr)	1.36918	2.29915
$T_{1/2}$ (hr)	--	2.16535

In effort to identify the recommended Propranolol dosage for elderly patients, we identified the patient package inserts from the Food and Drug Administration (FDA) Inderal label, who manufacture propranolol. Based from FDA Wyeth Propranolol label, for dosing in the geriatric population,the label states that there were not sufficient numbers of clinical study participants who were 65-years and older to properly determine the difference in response young and elderly patients.

Thus, the package insert (see [1]) recommends clinicians start at the lower end of the dosing range, without further details.

Similarly, Pfizer manufactures Inderal® LA (Propranolol HCI), which is the long-acting form of propranolol and their package insert (see [2]) states, "There is no information available for elderly patients." Though the kinetics for the long-acting formdiffers from the standard form, manufactured by Wyeth, we would suspect a 10mg dose for the elderly would achieve a similar maximum plasma concentration (Cmax) to that of the younger patient cohort.This 10mg, which is 25% of the original 40mg, dosing schedule is based on our simulations at 10mg in the geriatric population.

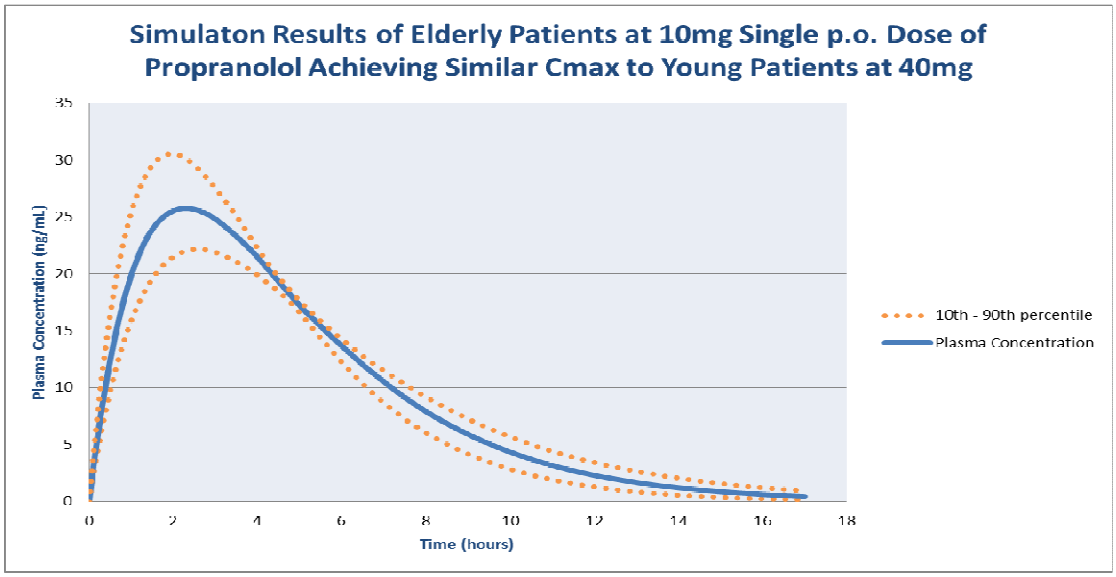

Figure 4. Simulation (Monte-Carlo, n=200) results elderly patients taking a 10mg oral dose resulting in similar Cmax, maximum plasma concentration, to the young patients taking a 40mg oral dose. The dotted lines illustrate the 10th and 90th percentiles of plasma levels of the elderly population with a 10mg oral administration of propranolol.

[1] http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/016418s080,016762s017,017683s008lbl.pdf

[2] http://www.pfizer.ca/en/our_products/products/monograph/265

Table 4.Summary table of propranolol single oral dosing pharmacokinetics in young, 40mg, versus elderly patients at 40mg and 10mg.

	Young	Elderly	$Elderly_{new}$
Dose	**40mg**	**40mg**	**10mg**
AUC (mg/L*hr)	154.739	633.35	164.28
Cmax (mg/L)	27.8303	102.911	25.4874
Tmax (hr)	1.36918	2.29915	2.28764
$T_{1/2}$ (hr)	--	2.16535	2.25417

It is important to note that plasma propranolol levels above 100ng/mL would completely saturate the beta-adrenergic receptors and thus provide no therapeutic benefit to elderly patients, especially patients with angina pectoris (Pine *et al.*, 1975). For many indications, an initial propranolol dose recommendation for the adult patient is 40mg and it is clear based on this model 10mg would be yield comparable pharmacokinetics in the older population relative to the younger population.

4. Discussion

Considering the differences single-dose pharmacokinetics between young and elderly patients, starting a regimen of 40mg t.i.d. in the elderly population would further complicate therapy. We are able to reject the null hypothesis, and accept our original hypotheses, but slightly modify the elderly dosing from one-half that of the younger patient's dose to, actually, one-fourth of the propranolol dose (i.e. from 40mg to 10mg) in the elderly to achieve similar peak plasma concentrationsas in younger patients.

4.1. Patients with Angina

Apharmacodynamic model,with parameters in the table below, may be used to visualize the propranolol concentration-effect (β-blockade) relationship in patients suffering from angina pectoris. These results have been adapted from the Pine et al article published in *Circulation* in 1975 which identified a linear relationship plasma Propranolol (ng/mL) to an effect of % β-Adrenergic Blockade in a single-oral dose of 40mg Propranolol in exercising individuals (Pine *et al.*, 1975).

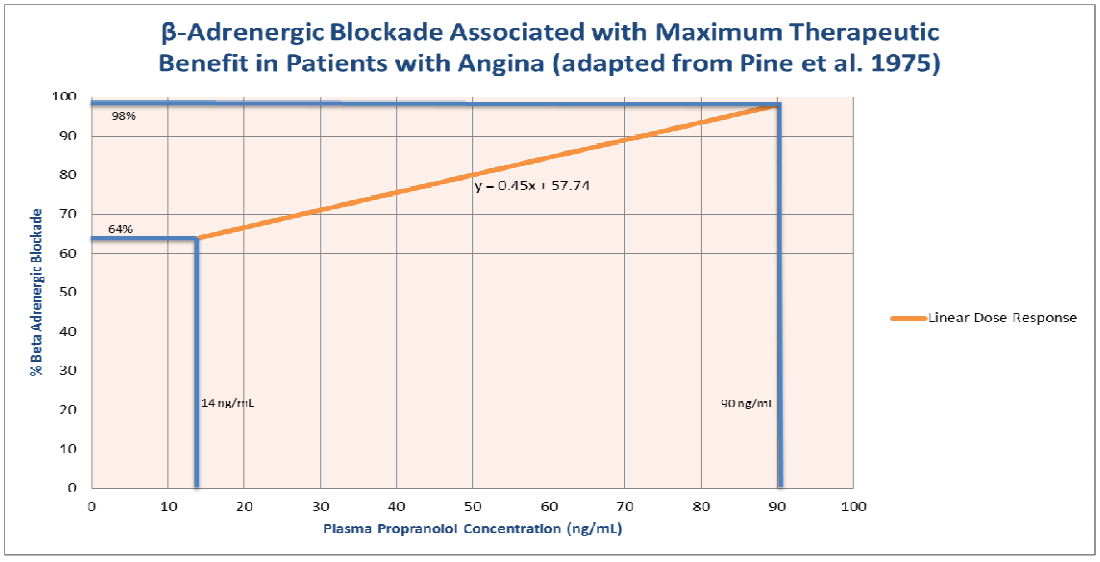

Figure 5.(a)Linear (y=0.45x + 57.74) dose-response relationship between plasma propranolol to % β-adrenergeric blockade derived from healthy study participants and translate into patients with angina pectoris. This image has been adapted from(Pine et al., 1975).

The relationship may be expressed in the form of a Hill Stimulation Linear Model as shown below and is valid for a minimum concentration of 14ng/mL, which corresponds to 64% beta-adrenergic receptor blockade.

Table 5. The pharmacodynamics plasma propranolol concentration and effect (% β-adrenergeric blockade) values from the Pine et al publication for therapeutic benefit in patients with angina pectoris (Pine *et al.*, 1975).

(Plasma Concentration, % Effect)	Values Referenced from Pine et al
(C_1, E_1)	C_2 = 14 ng/mL, E_2 = 64 (% Effect)
(C_2, E_2)	C_2 = 90 ng/mL, E_2 = 98 (% Effect)

$$E = E_0 + G \cdot C$$

Table 5.Description of the pharmacodynamics variables describing the Hill Stimulation Linear Model for propranolol.

Variables	Description
E	Intensity of the effect (% of β-receptor pharmacologic blockade)
E_0	Baseline effect in the absence of the drug (Propranolol); E_0=57.74
G	Slope of linear concentration-effect relationship; G=0.45
C	Propranolol Concentration at the effect (β-Adrenergic Receptor) sites

4.2. Propranolol and the Amygdala

In the past decade, there has been much interest in identifying treatment in adding to the current treatment options for war veterans suffering from Post-Traumatic Stress Disorder (PTSD). The studies investigating secondary-preventative measures for PTSD using Propranolol due to the drug's ability to inhibit the actions of the neurotransmitter norepinephrine,which has been implicated to enhance the consolidation(McGhee *et al.*, 2009; Pitman *et al.*, 2002; Stein *et al.*, 2007).Further, in a double-blind, placebo-controlled,functional Magnetic Resonance Imaging (fMRI) study, in healthy volunteers, Hurlemann et al. found that a single oral 40mg dose of propranolol attenuatedthe leftbasolateral amygdala responses to the face perception paradigm(Hurlemann *et al.*, 2010). The study participants were eighteen healthy (9 females, 9 males; mean age 23 years; age range 19–31 years) who had their fMRI acquisition 1.5-hours after the oral administration of propranolol. An adapted image of the study findings are shown in Figure 6.

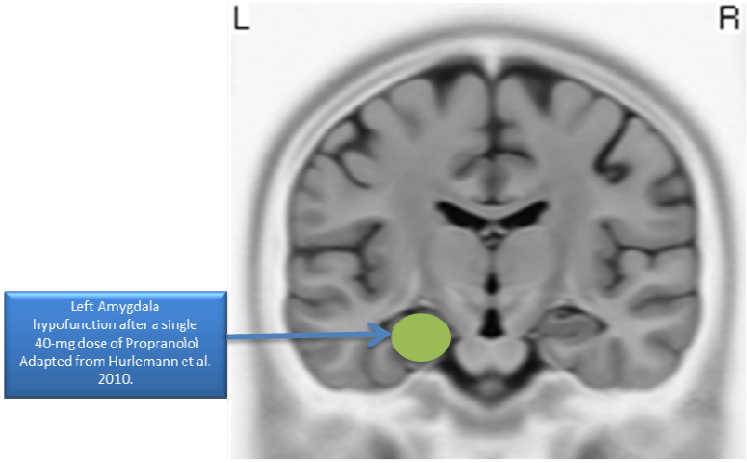

Figure 6.Amygdala hypofunction after a single oral 40-mg dose, 1.5-hours post-dose, in young study participants.The image has been adapted from (Hurlemann et al., 2010).

Based on our Propranolol dosing findings for matching the peak propranolol concentration in both the young and in elderly, these results may help pave the way for starting dosages for clinical trials looking to co-administer Risperidone with Propranolol in elderly patients who may be at an increased risk for fractures(Liperoti *et al.*, 2007). A recent study identified that, in rats, Propranolol protected against trabecular bone-loss in female mice treated with the atypical antipsychotic Risperidone(Motyl *et al.*, 2012). These findings are based on the implications that maintenance of sympathetic tone is important in understanding the osteoporotic process of coupling and uncouplingduring bone remodeling (Farr *et al.*, 2012). Overall, propranolol has proven to have a myriad of indications and proper dosage in the elderly yielding similar pharmacokinetics as in the adult has been identified here in this paper, however, investigations as to the neurological pharmacodynamics would need to be investigated.

5. Acknowledgements

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6. Conflicts of Interest

The author declares no conflict of interest.

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