

Differential Effects of the Betablockers Carvedilol, Metoprolol and Bisoprolol on Cardiac K_v4.3 (I_{to}) Channel Isoforms

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Table S1 – plasma concentrations of cardioselective betablockers in clinical use

Carvedilol			
Maximum dosage: 25mg single dose, 50mg daily maximum dose			
Molecular weight: 406.474g/mol			
Used dose	C _{max}	Studied group	Reference
25mg IR (immediate release):	R -> 149.1nM S -> 63.7nM R + S -> 212.8nM	Patients with stable, mild, moderate, or severe HF as well as survivors of a recent acute myocardial infarction (n = 188)	[36]
80mg CR (controlled release):	R -> 132.4nM S -> 55.8nM R + S -> 188.2nM		
25mg	-> 108 (68.7) ng/ml -> 265.7nM	Male patients with chronic HF (n = 22)	[37]
12.5mg on Day 1: 25mg on Day 9:	46.7 (23.3)ng/ml -> 114.9nM 104 (58.9)ng/ml -> 255.9nM	Patients with mild to moderate essential hypertension (n = 12)	[38]
25mg	-> 53.84 (45.10)ng/ml -> 132,5nM	Volunteers (n = 36)	[39]
12.5mg Carvedilol	-> 17.8 ± 11.3ng/ml R -> 8.5 ± 6.4ng/ml S	Healthy subjects (n = 12)	[40]
128 mg SR (slow release) carvedilol	-> 77.04 (66.99)ng/ml -> 189.5nM	Healthy male subjects (n = 30)	[41]
Metoprolol			
Maximum dosage: 200mg metoprolol tartrate/190mg metoprolol succinate			
Molecular weight: 684.81g/mol (metoprolol tartrate)			
Used dose	C _{max}	Studied group	Reference
200mg	-> Day 1: 17 (82)ng/ml -> 261.4nM	Healthy male volunteers (n = 6)	[42]

	-> Day 8: 247 (167)ng/ml -> 360nM		
2 x 100mg	-> Day 1, Young: 115 ± 24ng/ml -> 167.9nM -> Day 8, Young: 190 ± 20ng/ml -> 277.4nM -> Day 1, Elderly: 106 ± 24ng/ml -> 154.8nM -> Day 8, Elderly: 169 ± 28ng/ml -> 246.8nM	Healthy female volunteers (n = 15)	[43]
100mg	-> Control group: 103 (66)ng/ml -> 150.4nM -> Oral contraceptive group: 140 (57)ng/ml -> 204.4nM	Young female volunteers (n = 11 for control group, n = 12 for oral contraceptive group)	[44]
100mg	-> 210.72 (100.23)ng/ml -> 307.7nM	Healthy volunteers (n = 32)	[45]
50mg	-> 52.7 ± 22.0ng/ml -> 77.0nM	Healthy male volunteers (n = 12)	[46]
100mg	-> 77.67ng/ml -> 113.4nM	Healthy male volunteers (n = 6)	[47]
100mg	-> 101 (54.2)ng/ml -> 147.5nM	Healthy men (n = 31)	[48]
100mg	-> 132 ± 40.7ng/ml -> 192.8 nM	Healthy men (n = 12)	[49]
50mg	-> 65.1ng/ml -> 95.1nM	Healthy volunteers (n = 20)	[50]

Bisoprolol

Maximum dosage: 10mg, maximum daily dosage of 20mg

Molecular weight: 325.443g/mol

Used dose	C _{max}	Studied group	Reference
10mg	-> 54.3 ± 2.1ng/ml -> 166.8nM	Hyperthyroid patients (n = 9)	[51]
10mg	-> 51 (43-63)ng/ml -> 156.7nM	Healthy controls (n = 11)	[52]
10mg	-> 32.0 (13.6)ng/ml -> 98.3nM	Healthy male volunteers (n = 8)	[53]
5mg	Test product -> 20.71 (4.14)ng/ml -> 63.6nM Reference -> 20.67 (4.03)ng/ml -> 63.5nM	Healthy volunteers (n = 18)	[54]
10mg	Test -> 44.2 ± 9.6ng/ml -> 135.6nM Reference -> 43.9 ± 8.3ng/ml -> 134.9 nM	Healthy volunteers (n = 26)	[55]
10mg	-> 55.5 ± 6.4ng/ml -> 170.5 nM	Healthy volunteers (n = 6)	[56]
10mg	-> 52 ng/ml -> 159.8nM	Healthy subjects (n = 8)	[57]