Vural, E. M. et al. (2014). "Optimal dosages for melatonin supplementation therapy in older adults: A systematic review of current literature." *Drugs Aging* 31(6):441–451.

BACKGROUND: Melatonin is a hormone that regulates circadian rhythm, and its levels decline with age. As melatonin levels decrease, older adults are prone to develop disorders related to an altered circadian rhythm. The effective dose of melatonin supplementation in these disorders remains unclear. OBJECTIVES: Our objective was to define the optimal dosage of exogenous melatonin administration in disorders related to altered melatonin levels in older adults aged 55 years and above by determining the dose–response effect of exogenous administered melatonin on endogenous levels. METHODS: We conducted a systematic review through PubMed/MEDLINE and Embase, both from 1980 until November 2013. Included articles studied the effect of exogenous melatonin administration on endogenous melatonin levels in either serum, urine, or saliva in humans aged 55 years and above. RESULTS: We included 16 articles, nine of which were randomized controlled trials (RCTs). The mean age varied from 55.3 to 77.6 years. Melatonin dosage varied from 0.1 mg to 50 mg/kg and was administered orally in all studies. Pre- and postintervention levels revealed a significant elevation of the postintervention melatonin levels in a dose-dependent fashion. The maximum concentrations measured in serum and urine were all elevated compared with placebo, and a higher elevation in older adults than in younger adults was demonstrated. Even though there were no differences between times to reach maximum concentration in serum and urine, melatonin levels with higher doses were maintained longer above a certain threshold than were lower doses. CONCLUSION: In older adults, we advise the use of the lowest possible dose of immediate-release formulation melatonin to best mimic the normal physiological circadian rhythm of melatonin and to avoid prolonged, supraphysiological blood levels.

Permeation

Aguirre, T. A. et al. (2015). "In vitro and in vivo preclinical evaluation of a minisphere emulsion-based formulation (SmPill(R)) of salmon calcitonin." *Eur J Pharm Sci* 79:102–111.

Salmon calcitonin (sCT, MW 3432Da) is a benchmark molecule for an oral peptide delivery system because it is degraded and has low intestinal epithelial permeability. Four dry emulsion minisphere prototypes (SmPill(R)) containing sCT were coformulated with permeation enhancers (PEs): sodium taurodeoxycholate (NaTDC), sodium caprate (C10) or coco-glucoside (CG), or with a pH acidifier, citric acid (CA). Minispheres protected sCT from thermal degradation and the released sCT retained high bioactivity, as determined by cyclic AMP generation in T47D cells. Preminisphere emulsions of PEs combined with sCT increased absolute bioavailability (F) compared to native sCT following rat intrajejunal (i.j.) and intracolonic (i.c.) loop instillations, an effect that was more pronounced in colon. Minispheres corresponding to ~2000 I.U. (~390 μg) sCT/kg were instilled by i.j. or i.c. instillations and hypocalcaemia resulted from all prototypes. The absolute F (i.j.) of sCT was 11.0, 4.8, and 1.4% for minispheres containing NaTDC (10 μmol/kg), CG (12 μmol/kg) or CA (32 μmol/kg) respectively. For i.c. instillations, the largest absolute F (22% in each case) was achieved for minispheres containing either C10 (284 μmol/kg) or