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CURRENT OPINION

Pharmacokinetics of Melatonin: The Missing Link in Clinical Efficacy?

Lars Peter Holst Andersen[1] · Ismail Gögenur[2] · Jacob Rosenberg[1] ·
Russel J. Reiter[3]

Abstract Despite widespread clinical application of melatonin, several unanswered questions remain regarding the pharmacokinetics of this drug. This lack of knowledge may contribute to the inconsistency of results in previous clinical studies. Currently, a t_{max} value of 30–45 min and a $t_{\frac{1}{2}elimination}$ of 45 min are well established. Several questions relate to what constitutes a clinically effective plasma concentration, the choice of ideal administration route, and the optimal method of analysis. Furthermore, investigations of melatonin metabolites in humans are urgently needed in order to characterize their biological functions and the metabolic fates of these derivatives. Finally, pharmacokinetics in patients should be investigated further in order to reduce the risk of potential adverse effects, such as daytime sleepiness or unintended sedation.

Key Points

A t_{max} of 30–45 min of oral melatonin is well established.

The $t_{\frac{1}{2}elimination}$ of melatonin is 45 min.

The pharmacokinetics of melatonin in patients needs to be investigated further.

✉ Lars Peter Holst Andersen
  lphandersen@gmail.com

1 Department of Surgery, Herlev Hospital, University of Copenhagen, Herlev Ringvej 75, 2730 Herlev, Denmark

2 Department of Surgery, Roskilde and Køge Hospital, University of Copenhagen, Roskilde, Denmark

3 Department of Cellular and Structural Biology, The University of Texas Health Science Center, San Antonio, TX, USA

1 Introduction

Exogenous melatonin has been administered for various diseases, such as insomnia [1], hypertension [2], metabolic syndrome [3], chronic obstructive pulmonary disease [4], and inflammatory bowel disease [5]. Its use in surgical patients has also demonstrated anxiolytic, analgesic and antioxidative properties of the drug [6–9]. In addition, a number of studies indicate possible regulation of sleep and delirium in critically ill patients [10].

Unexpectedly, the findings in clinical studies have been conflicting [6], despite an abundance of evidence from experimental research implying that it could be an effective treatment [11, 12]. Interestingly, recent studies indicate that genetic variants coding melatonin receptors may, in part, cause these differences [13]. Currently, exogenous melatonin is therefore only recommended routinely as a sleeping aid in primary and secondary sleep disorders [14]. Clearly, a number of unanswered questions concerning possible future indications of melatonin and its mechanisms of action remain [15]. A fundamental step towards clinical efficacy of any drug is a thorough understanding of its pharmacokinetic properties.

2 Could Variable Pharmacokinetics Explain The Discrepancy In Clinical Effect?

Only a limited number of studies have been performed investigating the pharmacokinetic properties in humans [16]. These studies primarily included young healthy subjects who were administered various doses and formulations, employed different pharmacokinetic analyses, and reported a variety of pharmacokinetic variables [16].

Harpsøe and colleagues have previously reviewed their findings in detail [16], although a number of imperative questions relating to pharmacokinetic properties and clinical efficacy still remain. This paper aims to address these scientific questions in order to augment future clinical melatonin research.

Despite the major differences in study designs, time to reach maximal plasma concentrations (t_{max}) and elimination half-life ($t_{½elimination}$) of melatonin in humans are well established [16]. Oral melatonin is rapidly absorbed from the small intestine by first-order kinetics, and t_{max} is achieved after approximately 30–45 min [16]. An oral administration 45 min before intended effects may therefore still be advocated if maximal plasma concentrations (C_{max}) coincide with maximal clinical effects; however, this correlation needs to be established in future studies.

Similarly, a $t_{½elimination}$ of approximately 45 min has been documented in several studies in a wide range of doses, up to 100 mg intravenously [16]. This parameter may also be described by first-order elimination kinetics, and is independent of dose and route of administration [16]. Interestingly, an experimental study in prepubertal subjects suggested an accelerated elimination in children compared with adults [17]. Another clinical study in critically ill patients documented an impeded elimination, probably owing to altered liver and kidney function in this patient group [18]. The clinical impact of these findings in different subject/patient groups remains to be established.

A generally low bioavailability (f) of oral melatonin has been documented in a number of studies, although displaying variable mean values ranging from 3 to 33 % [16]. Similarly, studies demonstrated a substantial intrastudy variation between subjects [19]. A recent experimental report recorded values ranging between 0.7 and 12.7 % [20]. It is generally agreed that the low f is caused by a considerable first-pass metabolism in the liver [19]. Di and colleagues addressed this issue by measuring the production of the main metabolite 6-hydroxymelatonin sulphate following oral and intravenous administration [19]. Compared with intravenous injection, oral administration provided an increased metabolite/melatonin plasma level ratio, indicating liver metabolism as the main determinant of the low oral f [19]. However, the exact values and applied methods were not reported in this small study. The significance of liver metabolism was also emphasized by other reports in which coadministration of cytochrome P450 (CYP) 1A2 enzyme drug substrates, such as fluvoxamine [21], caffeine [22], or oral contraceptives [23], along with exogenous melatonin, had a substantial impact on subsequent plasma melatonin levels. Finally, studies in liver cirrhosis patients also demonstrated reduced elimination rates and increased plasma melatonin levels [24].

In general, the reported C_{max} and area under the curve from time zero to infinity (AUC_{∞}) values also varied extensively between studies as a result of differences in experimental designs [16]. Also of note, these values were highly variable between subjects following identical dosing regimens. For example, following 10 mg of oral melatonin, maximal plasma levels ranged between 1105 and 58,900 pg/ml [20]. The exact cause of this extreme variability is unknown but may obviously relate to interindividual differences in absorption, distribution, metabolism, and elimination of the drug. Correspondingly, clearance (CL) and volume of distribution (V_d) following intravenous administrations fluctuated extensively but may, at this moment, be estimated to be approximately 0.025 L min^{-1} kg^{-1} and 2.0 L kg^{-1}, respectively [16, 20].

3 Unanswered Questions

Several unanswered questions remain with respect to analytical methods, clinically relevant plasma levels, optimal administration routes, pharmacokinetics and function of melatonin metabolites, and, finally, melatonin administration in patient groups.

First, the studies investigating plasma melatonin levels have applied various methods of analysis, including radioimmunoassay, enzyme-linked immunosorbent assay, and mass spectrometry [16]. Unfortunately, no studies have performed a direct comparison of the individual methods assessing their construct validity in humans.

Second, as mentioned above, plasma melatonin levels varied extensively within studies, even with identical doses. These substantial differences may potentially impact clinical efficacy, with only one clinical study to date correlating clinical effects and actual plasma melatonin concentrations following exogenous administration [25]. In this context, it should be underlined that dosage, subsequent plasma concentrations, and possible clinical effects may very well vary for different indications. As an example, clinical studies demonstrated the antioxidative/anti-inflammatory effects of melatonin following administration of multiple large doses (10 mg/kg × 10 intravenously) [8] compared with the low single doses applied in sleep-aid dosing regimens (approximately 1–10 mg orally) [1]. Therefore, in-depth pharmacokinetic/pharmacodynamic modeling should be performed within the individual indications. Similarly, genetic variation and receptor function has been shown to affect clinical effects in experimental setups [13], although the possible clinical impact in patients is still unknown. However, interestingly, reduced levels of *endogenous* melatonin have been established in various conditions, such as ischemic heart disease, advanced diabetes, and certain types of cancers [26–28].

Nonetheless, these findings originate from cohort studies, and the possible implications are therefore limited by the unestablished causality.

Third, these data could also provide needed answers with regard to optimal administration routes for melatonin. At this moment, pharmacokinetic studies have only investigated oral and intravenous administrations [16]. Alternative routes, such as sublingual, intranasal, or rectal administration may be ideal in a clinical setting by encompassing a rapid t_{max}, a high f, and an uncomplicated administration procedure.

Fourth, to date, studies have assessed either direct plasma melatonin concentrations or urinary levels of the main metabolite, 6-hydroxymelatonin sulphate. Only two preliminary small studies have provided a rough estimate of this metabolite in the plasma of humans [19, 23]. A thorough investigation of this and other metabolites is required in order to further characterize metabolism and elimination of melatonin following its administration, preferably comparing different administration routes. Even more importantly, recent studies provide evidence that melatonin metabolites are physiologically- and possibly also clinically-active compounds [29].

Fifth, only four clinical studies have estimated melatonin pharmacokinetics in critically ill patients [18, 30, 31] and elderly suffering from insomnia [32]. The studies demonstrated that elimination in frail patients was impeded, and a potential risk of extended supraphysiological melatonin plasma levels and potential overdose issues were present. Although no serious adverse effects have been documented from melatonin treatment in patients, the potential risks of, for example, day-time sleepiness and/or unintended sedation should be addressed by dose regulation. These findings may obviously mandate further investigations in other patient groups in order to tailor dosing regimens to specific patient groups and indications.

As a final consideration, now that melatonin is known to be present in edible plants and commercially available meat products [33, 34], consideration should be given to standardizing the diet of subjects being tested for the pharmacokinetic properties when melatonin is administered. Similarly, future studies should also identify patients receiving either fluvoxamine [21] or oral contraceptives [23], and potentially also regulate caffeine intake [22] and smoking [35], which may otherwise introduce bias between investigated subjects.

4 Conclusions

Despite widespread clinical application of melatonin, several unanswered questions remain regarding the pharmacokinetics of this drug. This lack of knowledge may contribute to the inconsistency of results in previous clinical studies. Currently, a t_{max} value of 30–45 min and a $t_{\frac{1}{2}elimination}$ of 45 min are well established. However, several questions relate to what constitutes a clinically effective plasma concentration, the choice of ideal administration route, and the optimal method of analysis. Furthermore, investigations of melatonin metabolites in humans are urgently needed in order to characterize their biological functions and the metabolic fates of these derivatives. Finally, pharmacokinetics in patients should also be investigated further in order to reduce the risk of potential adverse effects, such as daytime sleepiness or unintended sedation.

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