Pharmacokinetics of Alternative Administration Routes of Melatonin: A Systematic Review

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Abstract
Background: Melatonin is traditionally administered orally but has a poor and variable bioavailability. This study aims to present an overview of studies investigating the pharmacokinetics of alternative administration routes of melatonin.

Methods: A systematic literature search was performed and included experimental or clinical studies, investigating pharmacokinetics of alternative administration routes of melatonin in vivo. Alternative administration routes were defined as all administration routes except oral and intravenous.

Results: 10 studies were included in the review. Intranasal administration exhibited a quick absorption rate and high bioavailability. Transdermal administration displayed a variable absorption rate and possible deposition of melatonin in the skin. Oral transmucosal administration of melatonin exhibited a high plasma concentration compared to oral administration. Subcutaneous injection of melatonin displayed a rapid absorption rate compared to oral administration.

Conclusion: Intranasal administration of melatonin has a large potential, and more research in humans is warranted. Transdermal application of melatonin has a possible use in a local application, due to slow absorption and deposition in the skin. Oral transmucosal administration may potentially be a clinically relevant due to avoiding first-pass metabolism. Subcutaneous injection of melatonin did not document any advantages compared to other administration routes.

Introduction
Melatonin is a hormone produced by the pineal gland, regulating the circadian rhythm in mammals [1]. Exogenous administration of melatonin improves sleep quality [2], reduces jet lag [3], and possesses analgesic [4, 5], anti-oxidative [6, 7] and anti-inflammatory effects [6]. Melatonin is traditionally administered orally, but the drug displays a poor and variable bioavailability due to an extensive first pass metabolism [8–11]. In order to optimize tissue delivery of melatonin, alternative administration routes, other than oral and intravenous formulations, may be required. The aim of this study was to present an overview of studies investigating the pharmacokinetics of alternative administration routes of melatonin in animals and in humans.

Materials and Methods
This systematic review was conducted in accordance to the PRISMA and PRISMA-P guidelines [12,13] (PROSPERO register, registration number: CRD42015017042). The literature search was performed on February 25th 2015 in PubMed and Embase databases. The review included experimental or clinical studies written in English, investigating pharmacokinetics of alternative administration routes of melatonin in vivo. Alternative administration routes were defined as all administration routes except oral and intravenous. Studies were identified using the search terms (((pharmacokinetic) OR pharmacokinetics) OR bioavailability)) AND melatonin) AND (((human) OR humans) OR animal) OR animals). The “all fields” setting was applied for all search terms. Furthermore, a manual “snowball” search was performed in the reference lists of the studies included.
2 authors (DZ, LPHA) individually assessed records found in the primary literature search. Disagreements were resolved by discussion. Full-text studies were obtained, evaluated, and included on the basis of the inclusion criteria. Study design, number of subjects, administration route, control/comparison and pharmacokinetic outcomes were evaluated for each study. The pharmacokinetic outcomes studied in this review were; dose, peak plasma concentration ($C_{\text{max}}$), time to maximal concentration ($T_{\text{max}}$), volume of distribution ($V_d$), elimination half-life ($T_{1/2}$), clearance (CL) and absolute bioavailability. Only studies presenting one or more of these outcomes calculated from plasma concentrations were included. Data from each study are referred with no transformation or interpretation. The results presented in the review are median or mean values as reported in the studies, without safety intervals.

### Results

The primary search identified 990 records (Fig. 1), whereof 128 duplicates were removed. We screened 862 records on title and abstract. A total of 36 full-text studies were assessed for eligibility, of which 10 studies were included in the final review. The included studies administered melatonin intranasally (I.N.) [14–17], transdermally [18–21], oral transmucosally [20, 22] and subcutaneously [23] (Table 1).

#### Intranasal administration

In humans, a cross-over study in 3 volunteers administered either 0.4 mg melatonin I.N. or 0.2 mg intravenously (I.V.) on 2 separate study days [15]. The study reported a $T_{\text{max}}$ of 5 min for I.N. administration and 10 min for I.V. administration. No other outcomes for plasma values were reported.

![Flow diagram displaying literature search according to PRISMA guidelines.](image)

#### Table 1 Overview of included studies.

<table>
<thead>
<tr>
<th>Study reference</th>
<th>Study design</th>
<th>Species (n)</th>
<th>Dose of melatonin</th>
<th>Administration route</th>
<th>Comparison</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>[14]</td>
<td>Crossover</td>
<td>Human (3)</td>
<td>0.4 mg</td>
<td>Intranasal</td>
<td>I.V. melatonin</td>
<td>$T_{\text{max}}$</td>
</tr>
<tr>
<td>[15]</td>
<td>Case-control</td>
<td>Rabbit (6)</td>
<td>1.5 mg</td>
<td>Intranasal</td>
<td>I.V. melatonin, L.N. melatonin + GC</td>
<td>$T_{\text{max}}$, $T_{1/2}$, Bioavailability</td>
</tr>
<tr>
<td>[16]</td>
<td>Case-control</td>
<td>Rabbit (12)</td>
<td>0.1 mg/kg</td>
<td>Intranasal</td>
<td>L.V. melatonin, L.N. SMS w/melatonin</td>
<td>$T_{\text{max}}$, $T_{1/2}$, Bioavailability</td>
</tr>
<tr>
<td>[13]</td>
<td>Crossover</td>
<td>Rat (8)</td>
<td>0.04 mg</td>
<td>Intranasal</td>
<td>I.V. melatonin</td>
<td>$T_{\text{max}}$</td>
</tr>
<tr>
<td>[17]</td>
<td>Crossover</td>
<td>Human (8)</td>
<td>2.1 mg</td>
<td>Transdermal</td>
<td>Placebo</td>
<td>$T_{\text{max}}$</td>
</tr>
<tr>
<td>[18]</td>
<td>Crossover</td>
<td>Human (2)</td>
<td>3.6 mg</td>
<td>Transdermal</td>
<td>Baseline</td>
<td>$T_{\text{max}}$, $T_{1/2}$, $T_{1/10}$</td>
</tr>
<tr>
<td>[19]</td>
<td>Crossover</td>
<td>Human (12)</td>
<td>0.5 mg</td>
<td>Transmucosal</td>
<td>OCR melatonin</td>
<td>$T_{\text{max}}$</td>
</tr>
<tr>
<td>[20]</td>
<td>Crossover</td>
<td>Human (6)</td>
<td>20 mg, 100 mg</td>
<td>Transdermal</td>
<td>Baseline</td>
<td>$T_{\text{max}}$</td>
</tr>
<tr>
<td>[21]</td>
<td>Crossover</td>
<td>Human (8)</td>
<td>5 mg, 100 mg</td>
<td>Sublingual spray</td>
<td>Oral melatonin</td>
<td>$T_{\text{max}}$, $T_{1/2}$</td>
</tr>
<tr>
<td>[22]</td>
<td>Crossover</td>
<td>Sheep (2)</td>
<td>1 mg, 0.1 mg</td>
<td>Subcutaneous injection</td>
<td>Oral melatonin</td>
<td>$T_{\text{max}}$, $T_{1/2}$</td>
</tr>
</tbody>
</table>

A cross-over study in 6 rabbits investigated bioavailability of intranasal administration of melatonin [16]. The study administered I.V. melatonin, I.N. melatonin and I.N. melatonin with sodium glycocholate. In all 3 administrations, the administered dose was 1.5 mg. The study documented similar T\textsubscript{max} values of 5 min in all 3 administrations routes (first measurement). Mean T\textsubscript{sys} for melatonin was 13 min for I.V. administration and 14 min for both I.N. and I.N.+GC administration. A mean bioavailability of 55 and 94 % was documented for I.N. melatonin and I.N. melatonin with sodium glycocholate, respectively.

A cross-over study including 8 rats studied I.N. administration of melatonin [14]. The study administered 0.04 mg of melatonin I.V. and I.N. T\textsubscript{max} was documented as 2.5 min in both I.V. and I.N. administration (first measurement).

A case-control study investigated I.N. administration of melatonin in 12 rabbits [17]. Melatonin was administered I.V., I.N. or I.N. including starch microspheres in doses of 0.1 mg/kg. T\textsubscript{max} values of 4.70 and 7.80 min were documented for I.N. melatonin and I.N. with starch microspheres with melatonin, respectively. T\textsubscript{sys} values were 5.6 min and 12.3 min in I.N. melatonin and I.N. with starch microspheres with melatonin, respectively. The bioavailability was 69.72 % for I.N. administration and 84.07 % for I.N. with starch microspheres.

Transdermal administration

Transdermal application of melatonin was examined in 8 humans in a randomized, double-blinded, cross-over placebo-controlled trial [18]. Patches containing 2.1 mg melatonin, or a placebo, were applied and followed by a wash-out period of 7–16 days. A mean T\textsubscript{max} of 8.58 h was documented.

A cross-over study in 2 humans investigated transdermal delivery of a nanoparticle gel containing melatonin [19]. The gel, containing 3.6 mg melatonin was applied to a 9 cm\textsuperscript{2} skin area. T\textsubscript{max} was 12.99 and 18.12 h. T\textsubscript{sys} was 5.02 and 10.02 h.

A cross-over study compared transdermal, transmucosal and oral controlled-release administration of 8 mg of melatonin in 12 humans [20]. The study demonstrated a T\textsubscript{max} of 13 h for the transdermal patches. Patches were removed after 10 h, and the plasma concentration of melatonin continued to rise, suggesting a deposition of melatonin in the skin.

Another study examined transdermal application of melatonin in 2 alcoholic solutions in 6 humans [21]. 3 subjects received 20 mg of melatonin (1 % melatonin in a 70% alcohol solution), whereas 3 received 100 mg of melatonin (5 % in a 70% alcoholic solution). The solutions were applied to the scalp of the subjects. The 2 subject groups demonstrated the following T\textsubscript{max}: For the 20 mg melatonin group it was 2, 8 and 8 h, while the 100 mg group was 1, 1 and 6 h, respectively.

Oral transmucosal administration

A cross-over study in humans compared transdermal, transmucosal and oral controlled-release administration of melatonin [20]. They applied a 0.5 cm\textsuperscript{2} mucoadhesive buccal patch containing 0.5 mg melatonin in 12 subjects. They documented a T\textsubscript{max} of 474 min for the buccal patches. Also, 0.23 mg of melatonin was left in the patch after removal, indicating that 0.27 mg of the melatonin had been absorbed.

An open-label, randomized cross-over study in 8 humans compared a sublingual melatonin spray with oral tablets, both containing 5 mg of melatonin [22]. The sublingual administration displayed a mean T\textsubscript{max} of 42.5 min. The study found a significantly higher C\textsubscript{max} for the spray at 17.2 ng/mL compared to oral tablets at 12.4 ng/mL. The mean T\textsubscript{sys} was 54.0 min.

Subcutaneous injection

A cross-over study in 2 sheep investigated subcutaneous injection compared to oral administration of melatonin [23]. The sheep were injected with either 1 mg of melatonin in a saline solution, or 0.1 mg melatonin diluted in peanut oil. Furthermore, oral melatonin was administered after a wash-out period of 2 days. The study demonstrated a T\textsubscript{max} of 15 min and a T\textsubscript{sys} of 30 min in both subcutaneous formulations, and a T\textsubscript{max} of 30 min for the oral melatonin.

Discussion

This systematic review demonstrated that quite limited data on the alternative administration routes of melatonin existed. Studies investigated pharmacokinetic variables following I.N., transdermal, buccal, sublingual and subcutaneous administration. The studies varied extensively in investigated subject, pharmacokinetic outcomes, investigational periods, melatonin doses, and formulations. Our review documented that intranasal administration may have clinical relevance, in circumstances where a systemic effect is wanted, due to rapid T\textsubscript{max} and high bioavailability.

Exogenous melatonin improves sleep quality and reduces jet-lag. Furthermore, recent studies in surgical patients documented analgesic, anti-oxidant and anti-inflammatory effects [1–7]. Traditionally melatonin is administered orally, but due to extensive first pass metabolism melatonin displays a poor and variable bioavailability [8–11]. Furthermore, studies have described a variable absorption of oral melatonin from the gastrointestinal tract [24]. These pharmacokinetic properties may advocate for alternative administration routes of melatonin.

Intranasal administration

The included studies documented a rapid T\textsubscript{max} of intranasal administration, ranging between 2.5 and 7.8 min depending on the subjects (animals and humans) and formulation [14–17]. These properties suggest that melatonin is easily transferred across the nasal mucosa. A study in rabbits demonstrated T\textsubscript{sys} values similar to that of the I.V. administration [16]. Bioavailability was investigated in 2 studies employing rabbits [16, 17], and ranged between 55 and 94 %. These findings indicate that intranasal administration of melatonin provides a significantly higher bioavailability compared to oral melatonin, which is estimated to approximately 15 % [8, 11]. No studies in humans, investigating bioavailability, have been performed yet, but the rapid absorption phase and high bioavailability in rabbits makes I.N. administration of melatonin relevant in future clinical research, where a systemic effect is wanted. Intranasal administration of melatonin could prove relevant in e.g., treatment of jet-lag, due to the ease of administration as a nasal spray.

Transdermal administration

The 4 human studies that investigated transdermal administration of melatonin and documented T\textsubscript{max} ranging between 1 and 18.12 h, with substantial inter individual variation [18–21]. Due to the slow transdermal absorption of the melatonin, just one study was able to estimate T\textsubscript{sys}. Only 2 subjects were included and...
T_{1/2} varied extensively between them [19]. Furthermore, one study demonstrated a deposition of melatonin in the skin, causing the plasma concentration of melatonin to rise after removal of the melatonin-patch [20]. Transdermal administration provides an easy administration route, but so far only a limited number of low volume studies have been performed in humans. Also, the studies used different formulations of melatonin for transdermal delivery, which might contribute to the varying results [18–21]. Development of other formulations should be applied in order to increase absorption rates and provide stable plasma concentrations, if systemic effects of melatonin are intended. If a local effect of melatonin is intended, transdermal administration of melatonin could potentially be used to protect the skin from UV-radiation [25].

Oral transmucosal administration
2 human studies investigated oral transmucosal administration, employing a buccal patch [20] and an oral sublingual spray, respectively [22]. Very variable T_{max} values were demonstrated, documenting an extended absorption phase in the study with the buccal patch [20]. The study administering the sublingual spray also found significantly higher C_{max} values compared to conventional oral administration [22]. The results may be due to lack of first-pass metabolism in oral transmucosal administration. Hence, these collective pharmacokinetic advantages are comparable to i.n. administration. Oral transmucosal administration of melatonin could possibly replace conventional oral administration to improve sleep quality, due to the reliable T_{max} making it easier to predict the time from administration to effect of the melatonin.

Subcutaneous injection
One study in sheep investigated subcutaneous injection, and demonstrated a lower T_{max} compared to oral administration [23]. Currently, no studies in humans have investigated subcutaneous injections. From a clinical point of view view subcutaneous injections may seem unreasonable, due to the variable and low absorption in subcutaneous tissues.

Strengths and limitations
This was the first systematic review of the alternative administration routes of melatonin. The review was performed in accordance to the PRISMA and PRISMA-P guidelines [12, 13]. We documented that only a limited number of studies have investigated this subject. Our review only included 10 studies, and the studies varied extensively in design, subject species, the number of subjects, the formulations of melatonin, and the pharmacokinetic outcomes reported.

Conclusions
This review demonstrated that only a limited number of studies have investigated alternative administration routes of melatonin. The studies varied in both subjects and pharmacokinetic outcomes. I.N. administration demonstrated a higher bioavailability and T_{max} compared to oral melatonin. Transdermal administration of melatonin might be used optimally in a local application, rather than a systemic application, due to slow absorption of melatonin, and deposition of melatonin in the skin. The oral transmucosal route demonstrated higher C_{max} values with similar T_{max} values compared to oral melatonin. Oral transmucosal administration may potentially be a clinically relevant administration route if a systemic effect is wanted. Currently there are no studies investigating subcutaneous injection of melatonin in humans, and studies in animals did not document any advantages compared to other administration routes.

Conflict of Interest
The authors have no affiliations with or involvement in any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this review.

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